A REVIEW OF ADULT RESUSCITATIVE FLUID PURCHASING AND USAGE TRENDS AT AN ACADEMIC TERTIARY HOSPITAL IN JOHANNESBURG

Dr Kelly Amy Jacobs, MBChB

304941

Supervisor: Dr L Hindle

Co-supervisor: Prof S Omar

A research report submitted to the Faculty of Health Sciences,
University of the Witwatersrand, Johannesburg,
in partial fulfilment of the requirements for the degree of
Master of Medicine in Emergency Medicine

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DECLARATION

I, Dr Kelly Amy Jacobs, hereby declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Emergency Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

Dr Kelly Amy Jacobs

Signed on this 21st day of September 2021.

CONTRIBUTION DECLARATION

Declaration: Student's contribution to article(s) and agreement of co-author(s)

I, Kelly Amy Jacobs, student number 304941, declare that this Thesis/Dissertation/Research Report is my own work and that I contributed adequately towards research findings published in the article(s) stated below which are included in my Thesis/Dissertation/Research Report .

Signature of Student: **Date: 24/06/2021**

Name of Primary Supervisor: Dr Lucy Hindle

Signature of Primary Supervisor ..... **Date** 26/06/2021

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his/her Thesis/Dissertation/Research Report. In cases where the student is not the 1st author of a published article, the primary supervisor must explain (under comments) why the student is entitled to use the paper for his/her degree purposes.

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Authors	Name	Signature	Date
1st author	Dr Kelly Amy Jacobs		24/06/2021
2nd author	Dr Lucy Hindle		26/06/2021
3rd author	Prof Shahed Omar		25 June 2021
4th author			
5th author			
6th author			

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DEDICATION

To my partner Charles, thank you for your unwavering support. I could not have done this without you.

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Dr Hindle and Prof Omar, thank you for walking this journey with me and the constant guidance. Ms Azra Cassim, thank you for all your assistance and being my liaison at the pharmacy.

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DECISION LETTER FROM JOURNAL

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ANAESTHESIOLOGY ANESTEZJOLOGIA
INTENSIVE THERAPY INTENSYWNA TERAPIA

Authors:
Kelly Jacobs, Lucy Hindle, Shahed Omar

Decision letter:
May 31, 2021
AIT-00347-2021-02
A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg

Dear Dr. Kelly Jacobs,

I am pleased to inform you that your manuscript, entitled: A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg, has been accepted for publication in our journal.

Thank you for submitting your work to us.

Yours sincerely,

Prof. Radosław Owczuk
Editor in Chief of Anaesthesiology Intensive Therapy

ait@gumed.edu.pl

ARTICLE AS ACCEPTED BY JOURNAL

A REVIEW OF ADULT RESUSCITATIVE FLUID PURCHASING AND USAGE TRENDS AT AN ACADEMIC TERTIARY HOSPITAL IN JOHANNESBURG

ABSTRACT

Introduction:

Intravenous fluid administration is a vital component in the resuscitation of critically ill patients. In recent years, there have been many studies to help guide which fluids should be used for resuscitation. Currently, it appears the international trend is away from the use of colloids and unbalanced crystalloids and towards the use of balanced crystalloids. The aim of our study was to determine whether evolving international evidence has impacted resuscitative fluid practices in the Emergency Department and the Intensive Care Unit in a tertiary hospital in South Africa.

Material and methods:

Study design was two-fold: a cross-sectional physician survey and a retrospective longitudinal observational study of the pharmacy fluid purchase records from the combined Emergency Department and Intensive Care Unit.

Results:

Cross-sectional survey: In 2020 a doctor was 8.3 times more likely to choose a balanced crystalloid for resuscitation regardless of the clinical scenario over any other fluid (CI 5.0 – 13.8). 55% of doctors surveyed agreed that their resuscitation fluid of choice had changed for a variety of reasons with the most popular reason cited as post-graduate education. Retrospective Longitudinal Observational Study: Throughout the study period, balanced crystalloids were the majority fluid purchased, although in ED lactated Ringers was the preferred balanced crystalloid and in ICU PlasmaLyte was preferred. Minimal colloids were purchased over the study period in declining amounts.

Conclusions:

Doctors working in a tertiary hospital in South Africa are following the trend of current evidence by using a balanced crystalloid as their resuscitation fluid of choice.

INTRODUCTION

Intravenous fluid administration is a vital component in the resuscitation of critically ill patients [1]. Previously the clinical practice guiding the choice of fluid used in resuscitation has been predominantly governed by the opinion of the treating physician [2]. However, over the past decade there have been a variety of publications on this matter that can assist in guiding the treating physician [3, 4, 5, 6]. In 2012, two landmark studies were published against the use of Hydroxyethyl starches (HES) [3,4]. The 6s study group found that when comparing resuscitation using HES versus resuscitation using acetated Ringers in patients with severe sepsis, those who were resuscitated with HES had an increased risk of death and were more likely to require renal replacement therapy [3]. Similarly, the CHEST study group found that when comparing HES use versus saline in the intensive care patient, those resuscitated with HES were more likely to require renal replacement therapy [4]. During 2017 and 2018, two new studies then brought further advancement in the choice of fluids. SALT-ED and SMART were published reviewing the use of balanced crystalloids versus saline in the non-critically ill and critically ill respectively [5, 6]. Both found some benefit in the use of balanced crystalloids over saline [5, 6]. These studies have therefore led many to believe that balanced crystalloids are the most cost-effective and safer resuscitation fluid when compared to colloids or normal saline [1, 3, 4, 5, 6]. A balanced fluid has previously been defined as one whose strong ion difference is at least 24meq/l and whose chloride level is no more than 110mmol/l e.g. lactated Ringers, PlasmaLyte [7].

Despite this available research, actual integration into clinical practice is often delayed [8]. With the growing amount of medical research available to healthcare professionals the research-practice gap has become more apparent [8]. When studied, findings show it can take even more than a decade for research to be implemented into clinical practice and so despite

the above evidence being available to clinicians, we are unsure how this has translated into clinical practice [8].

The aim of our study was therefore to determine whether evolving international evidence has impacted resuscitative fluid practices in the Emergency Department and the Intensive Care Unit in a tertiary hospital in South Africa.

METHODS

The study design was two-fold: a cross-sectional physician survey and a retrospective longitudinal observational study of the pharmacy fluid purchase records. The study took place at a tertiary academic hospital in Johannesburg, South Africa. Ethics clearance was obtained from the Human Research Ethics Committee (Medical) at the University of the Witwatersrand (M190869), the requirement for written informed consent to partake in the study survey was waived by the ethics committee.

Cross-sectional Physician Survey

A prospective, anonymous survey was circulated amongst consultants, registrars and medical officers with four years' work experience reviewing resuscitative fluid choices in four clinical scenarios over two different time periods, their opinion on whether their choices had changed and possible reasons for the change. The four different clinical scenarios were: hypovolaemic shock, haemorrhagic shock, septic shock and shock of unknown origin. Physicians were asked their current resuscitative fluid choice and what they would have chosen 4 years prior.

The departments surveyed were the general Intensive Care Unit (ICU) and the Medical Emergency Unit (MEU), the Surgical Emergency Unit (SEU) and the Trauma Emergency Unit (TEU) which together formed the combined Emergency Department (ED). The ICU is a multi-disciplinary ICU accepting patients from all the Emergency Units included in the study.

Retrospective Longitudinal Observational Study: Fluid Purchase Records

Data was extracted from the pharmacy departments purchase data base from November 2014 until November 2018 for the ED and the ICU.

The following periods were used; 2015: 01 November 2014 - 31 October 2015; 2017: 01 November 2016 – 31 October 2017;2018: 01 November 2017 – 31 October 2018

2016: 01 November 2015 – 31 October 2016 was removed due to missing data

The following fluids were chosen for review:

500ml starch-based colloid (Voluven, Fresenius Kabi, South Africa), 500ml gelatine-based colloid (Gelofusine, B Braun, South Africa), 1000ml 0.9% Sodium Chloride 1000ml (Sodium Chloride 0.9%, Adcock Ingram, South Africa) (NS), 1000ml lactated Ringers (Ringer-Lactate Adcocare, Adcock Ingram, South Africa) (RL), 1000ml PlasmaLyte (SABAX Plasmalyte B, Adcock Ingram, South Africa)(PlasmB).

In our setting the administration of 20% albumin is a specialist led decision requiring motivation and seldom prescribed outside of the ICU. Given these conditions we opted to exclude Albumin from our study.

Fluid amounts for crystalloids refers to litre bags and to colloids refers to half litre bags.

All comparisons were between 2015 and 2018 except for cost where the most recent period (2018) was compared with an average of the earlier periods (2015/2017). All costs are noted in South African Rand 1000’s and taken to the first decimal place.

OUTCOMES

PRIMARY:

Describe the amounts, proportions and annual costs of the resuscitative fluids ordered by the ED and ICU. Determine the resuscitative fluid of choice and possible reasons for any changes in choice over the study period.

SECONDARY

Compare the proportion of colloid and crystalloid orders between 2015 and 2018. Compare the proportion of balanced crystalloid and 0.9% sodium chloride orders between 2015 and 2018. Compare the proportion of lactated Ringers and PlasmaLyte orders between 2015 and 2018.

STATISTICAL ANALYSIS

All percentages and proportions were compared using the Chi square test. When necessary percentages were taken to the second decimal point to ensure statistical completeness. The estimated number of doctors eligible to take the survey was 110 for a 95% Confidence Interval, with a 5% margin of error ideally 86 surveys were to be completed.

RESULTS

81 doctors completed the survey: 61 from the ED and 20 from the ICU. 69 met the inclusion criteria, 51 from the ED and 18 from the ICU. The reasons for exclusion in all cases were doctors that had less than four years' work experience.

PRIMARY OUTCOME: Cross-sectional Physician Survey

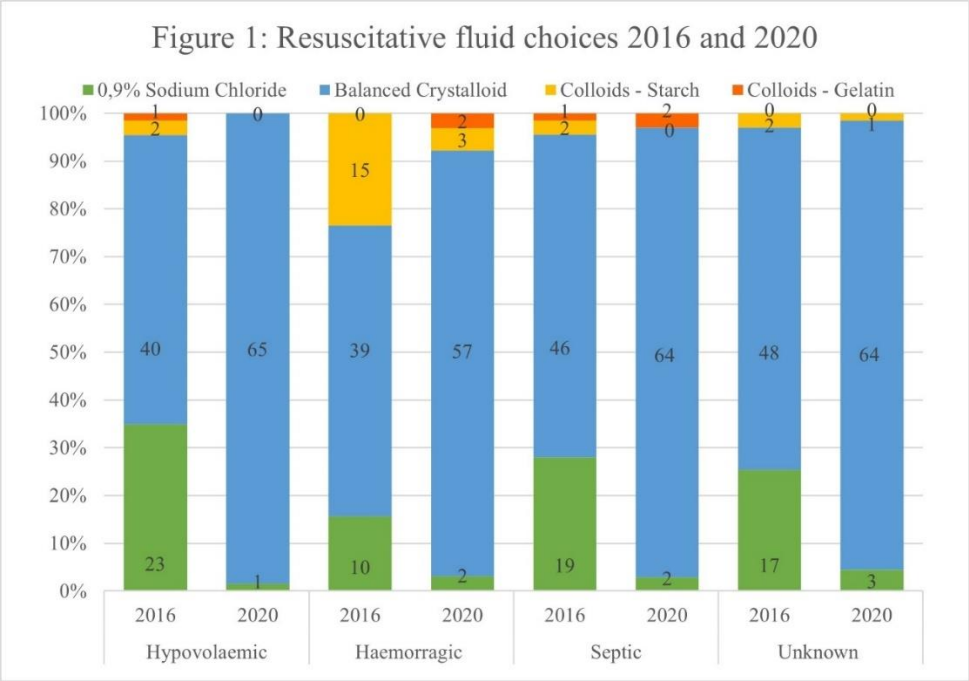
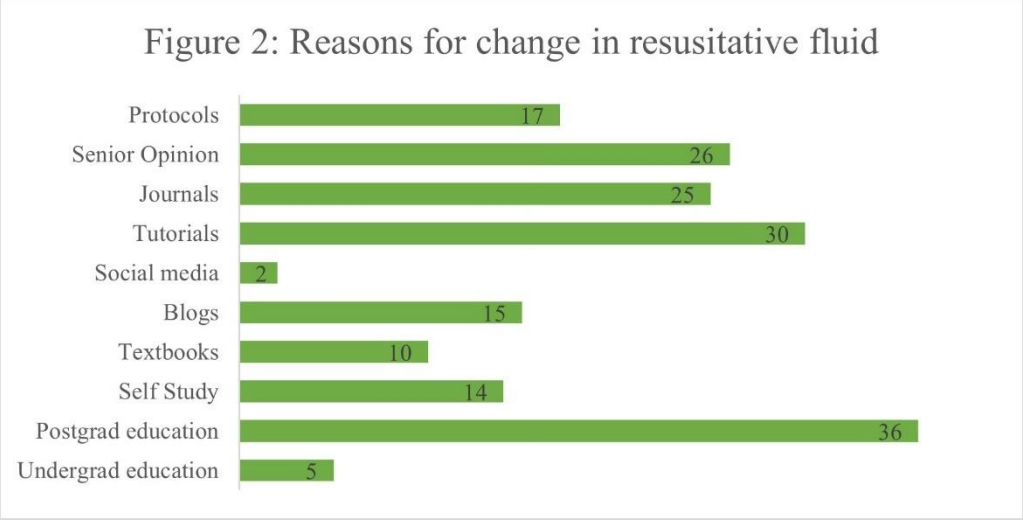


Figure 1 describes the resuscitative fluid choices doctors made over the different time periods in the different hypothetical scenarios.

In 2020 a doctor was 8.3 times more likely to choose a balanced crystalloid for resuscitation regardless of the clinical scenario over any other fluid (CI 5.0 – 13.8).

55% of doctors surveyed agreed that their resuscitation fluid of choice had changed for a variety of reasons as seen in Figure 2.



PRIMARY OUTCOME: Retrospective Longitudinal Observational Study

Table 1 represents the amount and costs of fluids purchased by the ED and the ICU, while Figure 3 represents the proportions of fluids purchased by both departments.

Table 1: Resuscitative fluid bags (Rand costs in 1000's) purchased by ED and ICU

	ED			**ICU**		
	2015	**2017**	**2018**	**2015**	**2017**	**2018**
NS	5104 (39,0)	5652 (41,9)	4896 (39,5)	1800 (13,7)	2400 (17,4)	3435 (27,8)
RL	19228 (150,9)	23700 (185,1)	21720 (183,5)	4380 (35,0)	312 (2,4)	240 (2,0)
PlasmB	5304 (118,4)	4284 (97,8)	5560 (119,6)	7236 (163,1)	10172 (232,2)	13675 (297,9)
Gelofusine	80 (6,7)	420 (34,9)	0 (0)	0 (0)	0 (0)	0 (0)
Voluven	288 (16,8)	40 (2,1)	140 (7,1)	0 (0)	60 (3,4)	0 (0)
Total	30004 (331,8)	34096 (361,8)	32316 (349,7)	13416 (211,8)	12944 (255,4)	17350 (327,7)

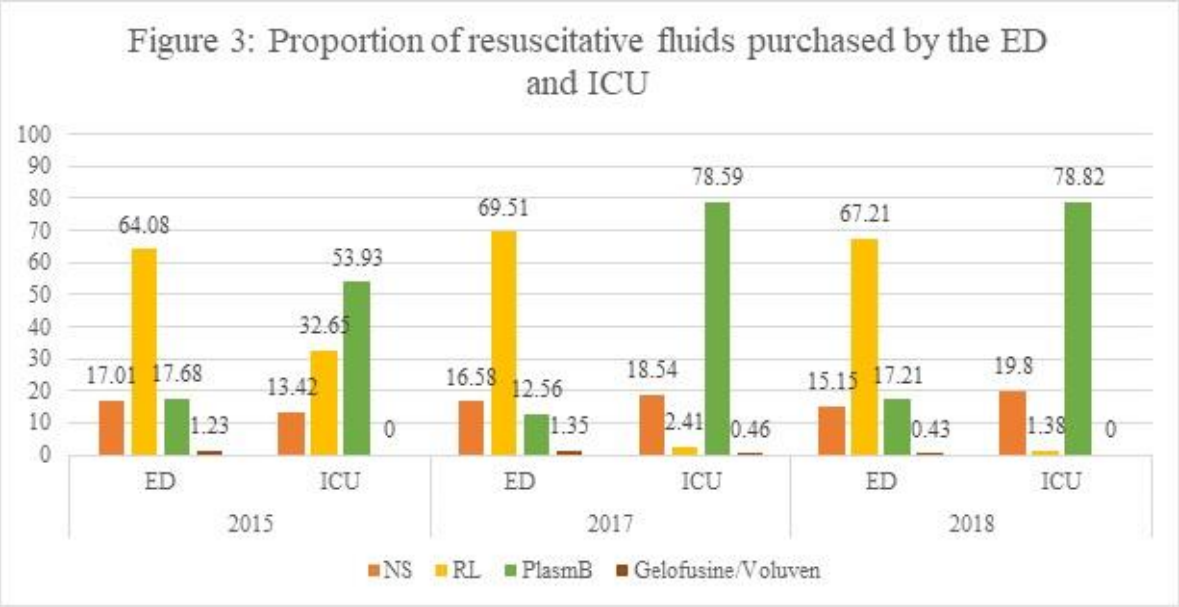


Table 2 compares the annual spend on resuscitative fluids by the ED and the ICU from 2018 to the average of the earlier two periods.

Table 2: Annual cost comparison ED and ICU in Rand 1000's (%)				
	ED		**ICU**	
	Av 2015/2017	**2018**	**Av 2015/2017**	**2018**
Crystalloids	316,5 (91,27)	342,6 (97,96)	231,9 (99,28)	327,7 (100)
Colloids	30,2 (8.73)	7,1 (2,04)	1,6 (0,72)	0 (0)
Total	346,7	349,7	233,5	327,7

SECONDARY OUTCOMES

When comparing the proportion of colloid and crystalloid orders in the Emergency Department, there was a statistically significant reduction in colloid orders from 368 units in 2015 to 140 units in 2018 ($p<0.0001$, chi coefficient 121.1). ICU had no colloid orders for the same period.

When comparing the proportion of unbalanced and balanced crystalloid to total crystalloid orders, baseline levels of balanced crystalloids was already 83% in the ED in 2015. The percentage increased to 85% in 2018. Normal saline levels dropped from 17% to 15% ($p<0.0001$, chi co-efficient 45.78). Lactated Ringers was the main balanced crystalloid ordered by the ED in 2015 and 2018 with levels staying mostly constant throughout the two periods ($p=0.0005$, chi co-efficient 11.89).

In ICU however, the proportion of Normal Saline was seen to increase from 13% in 2015 to 20% in 2018 ($p<0.0001$, chi co-efficient 218.2). When reviewing the balanced crystalloids, PlasmaLyte was already the favoured ICU balanced crystalloid in 2015 at 62% which rose to 98% in 2018 ($p<0.0001$, chi co-efficient 5530).

DISCUSSION

The main finding of our survey is that a doctor was 8 times more likely to choose a balanced crystalloid for resuscitation in 2020 compared to four years prior, irrespective of the clinical scenario faced. This is following almost a decade of emerging research in balanced fluids [5, 6, 9]. In all patient scenarios, the use of saline was markedly reduced by 2020 with the most notable change found in the hypovolaemic shock scenario. More than 30% of doctors would have chosen to resuscitate a hypovolaemic shocked patient with saline in 2016, while less than 2% would still make that choice in 2020. Resuscitation with colloids was already an unpopular choice in the 2016 scenario. The largest use of colloids at that time was in the scenario of haemorrhagic shock where just over 20% of doctors would have chosen to resuscitate with a colloid. By 2020 however, less than 8% of doctors would still make the same choice.

In 2016, an international study was published in which doctors were surveyed on their fluid choices [10, 11]. A BMJ article surveyed Emergency Medicine Physicians and Intensive Care Physicians on their fluid choices in a septic shock patient [10]. As found in our survey, crystalloids were the most popular choice overall. 53.1% chose saline often/always as their first line of fluid while lactated Ringers was chosen 60.5% [10]. In comparison to our septic shock scenario in 2016, where just over 70% of doctors chose to resuscitate with a balanced crystalloid while 25% chose to use saline. This indicates a possible more rapid uptake of balanced crystalloid use locally compared to the countries in the BMJ survey (Canada, UK, Scandinavia, Saudi Arabia). Possible reasons could be that our study took place at a single tertiary centre while they had multiple international centres. With regards to the utilisation of a starch-based colloid in septic shock, 3% of our cohort chose this option compared to only 1% in the BMJ group [10].

We noted that education played a major role in the change of fluid choices from unbalanced crystalloids and colloids to balanced crystalloid with almost all doctors (96%) citing post-graduate teaching and or tutorials as their reason for change. This highlights the importance of ongoing practical education in the medical field. Conversely, undergraduate teaching was one of the least common reasons for change. Kristensen et al [8] found when reviewing the experience of healthcare professionals on implementing research into clinical practice, that the healthcare professionals experienced no formalised procedures or established workflows in the implementation of research. The actual implementation of research was experienced to be at random as senior physicians "passed it on" to junior doctors [8]. This may account for the findings in our study with post-graduate teaching and tutorials forming the majority reason for change.

The use of clinical guidelines is described as an important method in implementing research into clinical practice [11]. In our study the use of protocols was ranked 5th behind post-graduate teaching, tutorials, senior opinion, and journal articles. This may indicate that there is an opportunity to implement medical research through the greater use of integration into clinical guidelines.

Changes in fluid utilisation may be represented by what fluids we are purchasing for resuscitation. From our pharmacy purchase order data, we found that balanced crystalloids were by far the most popular fluid purchased. We can see that already from 2015 the majority type of fluid purchased was a balanced crystalloid in both the combined Emergency Department (82%) and the Intensive Care Unit (87%) reflecting the survey findings above. In the combined Emergency Department, lactated Ringers was the favoured balanced crystalloid purchased, while in the ICU it was PlasmaLyte. Among balanced fluids the benefit of one buffer over another (bicarbonate and lactate) has not been studied. Possible reasons for the differing utilisation rates between ED and ICU could be explained by the higher cost of

PlasmaLyte. The comparison of the exact composition of the balanced crystalloids used in our study can be found under Appendix A. Noticeably they have very similar concentrations of sodium, chloride and potassium. Subtle difference do exist between the two. Lactated Ringers contains calcium where as PlasmaLyte contains magnesium. The pH of the lactated Ringers used is lower than that of PlasmaLyte at 6.5 versus 7.4 although the calculated strong ion difference (SID) of these fluids is, for practical purposes the same (25.8 vs 25.5). However, lactate is a strong ion and anion and therefore, if it accumulates it will have an effect of the patient's metabolic state and the strong ion difference will drop to below zero [12, 13]. Patients in which this accumulation could occur include those suffering from severe liver failure, septic shock, treatment of septic shock with adrenaline and shock with ischaemic hepatitis [13, 14, 15]. If the SID of fluid is less than that of plasma then that will cause a drop in pH which will be proportional to the SID and the volume administered [12].

It is also clear that by 2015 the colloid use in the ICU had already declined with no gelatine-based colloids ordered throughout the study period and only one order of starch-based colloid in 2017, forming less than half a percent of the total fluids ordered. This suggests that the critical care physicians were already following the recommendations published by the European Medical Agency in 2013, that Hydroxyethyl starches not be used in the critically ill patients due to growing safety concerns [16]. In comparison, there were more colloids purchased by the combined Emergency Department although in declining amounts with only 1.23% of fluids ordered in 2015. This could possibly be explained by use in the acute trauma patient subset. A local study published out of Cape Town found that there was improved lactate clearance in patients suffering from penetrating trauma when resuscitated with a Hydroxyethyl starch compared to Normal Saline [17]. This may account for the persistent utilisation of the colloids in the ED, although by 2018 the proportion of colloids purchased had fell to less than 1% following the trend of the international research [3,4].

The amount of normal saline purchased by the Intensive Care Unit was seen to increase over the study period under review. This goes against international data showing increased harm with normal saline infusion versus balanced crystalloid infusion in the critically ill as well as the findings in our survey [6]. After investigation, it was found that due to lack of commercial dialysate availability, normal saline had been used as part of a dialysate in the unit and therefore increased utilisation may be linked to use during renal replacement therapy of patients and not as an intravenous therapy.

South Africa is currently classed as a middle-income country with just over half the population living below the poverty line [18]. Therefore, cost-effective spending is an important consideration in the South African health sector. In the annual cost comparison of fluid spend from the ED, the annual amounts stayed mostly stable despite an increase in crystalloid purchase. This is most likely due to the declining amounts of colloids purchased as the cost per unit of colloid is much higher than that of the crystalloids. In the ICU however, the increased purchase of PlasmaLyte over time, was responsible for a marked increase in annual spend despite no colloid orders, as the cost of PlasmaLyte is almost three times that of lactated Ringers.

We did not adjust colloid cost for bag size in our study data. There is a wide variation on the quoted effect of colloid to cause intravascular expansion when compared to a crystalloid ranging from 1.3 to 1.12 [2, 3]. Regardless of the actual number, in all texts it is believed that less colloid is required to cause the same clinical effect when compared to a crystalloid [1, 2, 3]. For this reason and for simplicity we did not adjust absolute cost and we may have therefore underestimated the cost of colloid use.

LIMITATIONS

Despite multiple attempts to gather data there were only 69 surveys received that met inclusion criteria, meeting the 95% confidence interval with a less than 8% margin of error. The number of doctors working less than 4 years in the departments was underestimated and therefore the number of doctors eligible to take the survey over-estimated. Additionally, once the COVID-19 pandemic gained traction in South Africa, all Academic Meetings by the departments involved were moved to an online platform which was not accounted for in the initial study design.

Additionally, there were surveys in which the participants chose more than one answer when only one was required. For analysis, those questions were excluded, although other correctly answered questions in the survey were still analysed therefore reflecting the different total tallies in the scenario's questions.

Purchase data was used as a surrogate for actual fluid utilisation and may not correlate although previous research shows that purchase data may mirror international utilisation trends [19].

Although patient profiles would be very useful, we were unable to comment on specific clinical characteristics as our study only evaluated the pharmaceutical purchase records. Due to the way in which the fluids were ordered for the combined Emergency Department we were unable to review the separate amounts of fluids by each Emergency Department subsection and therefore were unable to make correlations with the type of patients seen.

As mentioned previously the use of intravenous Albumin is rarely prescribed outside of the Intensive Care Unit and therefore was excluded from our study and we were unable to comment on the change in Albumin utilization.

CONCLUSIONS

Our study showed that doctors working the in a tertiary hospital in South Africa are following the trend of current evidence by using a balanced crystalloid as their resuscitation fluid of choice. Due to the research-practice gap, variations in the uptake of balanced crystalloid utilisation occur globally. Changes in fluid utilisation may have significant cost implications which need consideration.

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AUTHORSHIP:

Conception: K.J, S.O, Design: K.J, S.O, Execution: K.J, Interpretation of data being published: K.J, L.H, S.O, Writing of Paper: K.J, Editing of paper: KJ, L.H, S.O

K.J 75%, L.H 10%, S.O 15%

APPENDIX A: Balanced crystalloid composition

	Lactated Ringer (Ringer-Lactate Adcocare, Adcock Ingram, South Africa)	PlasmaLyte (SABAX Plasmalyte B, Adcock, South Africa)
Sodium	131	130
Potassium	5	4
Chloride	112	110
Calcium	1.8	0
Magnesium	0	1.5
Buffer	29 Lactate	27 Bicarbonate
pH	6.5	7.4
Calculated SID	25.8	25.5

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APPENDIX A:

FINAL RESEARCH PROTOCOL WITH EXTENDED LITERATURE REVIEW

A REVIEW OF ADULT RESUSCITATIVE FLUID PURCHASING AND USAGE TRENDS AT AN ACADEMIC TERTIARY HOSPITAL IN JOHANNESBURG

INTRODUCTION

Intravenous fluid administration is a vital component in the resuscitation of critically ill patients (1). In the past, the clinical practice guiding the use of specific fluids has been governed predominately by the preference of the treating physician (2). With evolving evidence, we now recognise that different fluids carry different risks and benefits (2).

The role of intravenous fluids is to assist with improved cardiac output and tissue perfusion through expansion of intravascular volume (2). An ideal resuscitation fluid should therefore provide a reliable and sustained increase in intravascular volume, have a chemical composition close to blood plasma, not accumulate in tissues, be as cost effective as possible and cause no metabolic or systemic side effects (2). Currently no such fluid exists. Recently more effort has been invested into the study of fluid resuscitation with regards to the type of fluid that should be used in the critically ill.

There are two broad categories of fluids, namely, crystalloids and colloids. Crystalloids are solutions that contain ions that are freely permeable to the body's different fluid compartments (2). Broadly the crystalloids can be categorised as unbalanced and balanced fluids. An example of an unbalanced solution is 0.9% sodium chloride also known as normal saline. This is a misnomer because the concentration of sodium and chloride in this fluid is much higher than the corresponding concentrations in the extracellular fluid, so there is nothing normal about it (3). In contrast, balanced crystalloids have an ion concentration closer to the physiological

levels found in extra-cellular fluid (3). They also contain a buffer in the form of lactate, acetate, malate or gluconate. A balanced fluid has previously been defined as one whose strong ion difference is at least 24meq/l and whose chloride level is no more than 110mmol/l (4). There are a growing number of these fluids available, and examples include Ringer's Lactate, PlasmaLyte and Balsol.

The second category of fluids are the colloids. Colloids are fluids that contain a suspension of macromolecules (3). These macromolecules can be natural or synthetic (3). The only natural colloid currently available is human albumin. There are three main groups of synthetic colloids: the hydroxyethyl starches, the gelatins and the dextrans. Of this group the hydroxyethyl starches have been studied the most (3).

The hydroxyethyl starches come in varying concentrations, the most well-known concentration being 6% Hydroxyethyl starch 130/0.4 also known as Voluven. Some of the adverse effects associated with colloids include allergic reactions and accumulation in the reticuloendothelial system (2). Due to the nature of the macromolecules in colloids they remain predominantly in the intravascular space (2). Previously it was thought that because of this characteristic the colloids were 3 to 4 times more effective than the crystalloids for intravenous resuscitation but in reality, the ratio of efficacy of colloids to crystalloids in resuscitation is closer to 1:1.2 (3). Apart from having these different physiological properties, the different fluids also carry different costs.

Colloids are generally more expensive when compared to crystalloids. In a National Essential Medicine List report published in 2017 the cost of 1 litre Ringer's Lactate was R11.65 compared to a 500ml bag of Hydroxyethyl starch costing R 217.40 (5). Therefore, even if less fluid is used during resuscitation with a colloid solution, they carry a substantially higher cost. In comparison crystalloids are generally very cost effective and readily available in most

institutions. South Africa is currently classed as a middle-income country with just over half the population living below the poverty line (6). Therefore, cost-effective spending is an important consideration in the South African health sector.

As mentioned in the introduction, fluid choice is often based on physician choice and not evidence (2). In 2016 the British Medical Journal published a survey on different fluid resuscitation practices among Emergency Medicine and Critical Care Physicians for patients with early septic shock. A total of 1097 physicians were surveyed (7). This multi-country survey presented the specialists with a scenario involving an adult patient in early septic shock. They were then provided with a choice of different fluids to aid their resuscitation. Among the two groups of physicians crystalloid fluid was the most common first line treatment chosen for resuscitation (7). Only 1% of the group surveyed chose a colloid as their first line resuscitation fluid (7). The Emergency Medicine Physicians chose 0.9% sodium chloride as their preferred crystalloid 83.9% of the time. In comparison, the preferred crystalloid chosen by the Critical Care Physicians was Ringer's Lactate in 81% of those surveyed (7). Interestingly, when presented with the option to choose the ideal fluid regardless of what was available, the use of Ringer's Lactate increased amongst the Emergency Physicians from 35.1% to 45.1% (7). This suggests that limitations in the availability of balanced crystalloids influenced the choice of fluid among the Emergency Physicians. There is now a growing body of evidence available to assist with the choice of fluids in critically ill patients.

In 2012, two landmark studies were published against the use of Hydroxyethyl starches (HES) (8,9). The 6s study group found that when comparing resuscitation using HES versus resuscitation using Ringer's acetate in patients with severe sepsis, those who were resuscitated with HES colloids had an increased risk of death and were more likely to require renal replacement therapy (8). Similarly, the CHEST study group found that when comparing HES use versus saline in the intensive care patient, those resuscitated with HES were more likely to

require renal replacement therapy (9). There is, however, some debate surrounding colloid use in surgical patients.

The FIRST trial conducted in Cape Town found that there was improved lactate clearance in patients with penetrating trauma when resuscitated with hydroxyethyl starch in comparison to resuscitation with 0.9% sodium chloride (10). Although this study only used a small number of patients as a sample it is not the only study looking into the non-septic surgical patient and colloid use specifically. In a sub-group analysis of critically ill surgical patients in the CRISTAL trial, there was no survival benefit noted when comparing crystalloid use to colloid use (11).

However, due to the growing amount of evidence against the use of HES in critically ill patients the European Medical Agency in 2013 released a statement informing that hydroxyethyl starches are not to be used in critically ill patients due to growing safety concerns and lack of supportive data (12). In January 2018 the European Medical Agency further recommended that no Hydroxyethyl starch fluid be used in any patients (13).

In comparison data is lacking on the other fluids in the colloid group. Very few studies have been done on the efficacy of dextrans and they are therefore not supported for use in critically ill patients (3). Similarly, there are few studies on the gelatins with sufficiently powered data to provide evidence-based recommendations (3). There is some data to suggest that when used in the correct clinical scenario Human Albumin use may be beneficial (3).

There have been studies conducted comparing the use of Albumin and crystalloids in critically ill patients. The SAFE study from 2004 found that there were similar outcomes in patients treated with either 0.9% sodium chloride or 4 % human albumin in an intensive care unit (14). Due to the increased price of albumin, limited available stock and lack of evidence it is not currently recommended as a first line resuscitation fluid (3). There is a suggestion that albumin

infusions may be beneficial in the subset of septic patients but more research into this group is required (3). Debate also surrounds the use of different types of crystalloids.

There is no doubt that 0.9% sodium chloride is one of the most widely administered crystalloid fluids (15). There is evolving evidence to suggest that the use of 0.9% sodium chloride over balanced crystalloids is possibly harmful (15–17). Due to the high concentration of chloride and inherent acidic pH of 0.9% sodium chloride, administration tends to cause a hyperchloremic metabolic acidosis (17). In a study performed in healthy subjects receiving either a bolus of 0.9% sodium chloride or PlasmaLyte, subjects given a bolus of saline showed a sustained hyperchloremia associated with reduction in the renal blood flow velocity and renal cortical tissue perfusion (18). During 2017 and 2018, two new studies then brought further advancement in the choice of fluids. SALT-ED and SMART were published reviewing the use of balanced crystalloids versus saline in the non-critically ill and critically ill respectively (15, 16). Both found some benefit in the use of balanced crystalloids over saline (15, 16). These studies have therefore led many to believe that balanced crystalloids are the most cost-effective and safer resuscitation fluid when compared to colloids or normal saline (8, 9, 15, 16).

When reviewing balanced crystalloids, the benefit of one buffer over another (e.g. bicarbonate and lactate) has not been studied. Different balanced fluids have remarkably similar concentrations of sodium, chloride and potassium; however, subtle differences do exist (19). For example, Lactated Ringers contains calcium where as PlasmaLyte contains magnesium and they contain different buffers (19). Lactate is a strong ion and anion and therefore, if it accumulates it will have an effect of the patient's metabolic state and the strong ion difference will drop to below zero (20, 21). Patients in which this accumulation could occur include those suffering from severe liver failure, septic shock, treatment of septic shock with adrenaline and shock with ischaemic hepatitis (21, 22, 23). However, as mentioned previously there is still no current research to guide fluid choices between the different balanced crystalloids.

Despite the available research, actual integration into clinical practice is often delayed (24). With the growing amount of medical research available to healthcare professionals the research-practice gap has become more apparent (24). When studied, findings show it can take even more than a decade for research to be implemented into clinical practice and so despite the above evidence being available to clinicians, we are unsure how this has translated into clinical practice (24). Kristensen et al (24) found when reviewing the experience of healthcare professionals on implementing research into clinical practice, that the healthcare professionals experienced no formalised procedures or established workflows in the implementation of research. The actual implementation of research was experienced to be at random as senior physicians "passed it on" to junior doctors (24).

From the above it is clear that the choice of intravenous fluid should be judged on much more than just an individual physician's opinion and that the physician's opinion does not necessarily conform to the available evidence. In these situations, intravenous fluids should be viewed as a drug. There is growing evidence to suggest that balanced crystalloids are the most cost-effective fluid available with the best risk/benefit profile (8,, 9, 15, 16). This is mirrored in the international trends towards the increased use of balanced crystalloid in critically ill patients and away from the use of 0.9% sodium chloride and colloids (25).

In 2017 a study was published by Hammond et al reviewing the patterns of intravenous fluid resuscitation in 84 intensive care units across 17 countries from 2007 and 2014 (25). Between 2007 and 2014 there was an increase in the proportion of balanced crystalloids used during resuscitation from 30.1% to 69.7% (25). Conversely the proportion of 0.9% sodium chloride resuscitation fell from 65.5% to 26.4% (25). Additionally, colloids were used in fewer patients and in fewer resuscitations falling from 74% to 41.8% (25).

I chose to review the purchasing trends of resuscitative fluids by the combined Emergency Department and the Intensive Care Unit over a 4-year period. While fluid purchasing data is not actual usage, an inference can be made from the purchasing trends. In 2016 an article was published in the Critical Care and Resuscitative Journal reviewing changes in intravenous fluid use patterns in Australia and New Zealand from 2012-2013 to 2013 – 2014 (26). This study was based on national sales of fluids across New Zealand and Australia and was used as a surrogate for fluid consumption (26). Overall crystalloid sales remained mostly constant, but it found that the ratio of balanced to unbalanced crystalloids is decreasing, suggesting a rise in the use of balanced crystalloid (26). The overall sales of colloids dropped by 12% (26). This illustrates that even though purchasing data is not actual usage, patterns that mirror international trends can still be found (25, 26).

I also surveyed physicians working in the Emergency Department and the Intensive Care Unit on their resuscitative fluid practices. As discussed previously often the choice of fluid used in resuscitation is based on treating physician opinion. A study published in 2016, surveyed doctors working in Intensive Care Units across the United States of America (27). The doctors were presented with 3 different clinical scenarios and given a choice of fluids to use in the resuscitation. The scenarios included a septic patient, a bleeding patient and a non-septic, non-bleeding patient requiring volume expansion. Regardless of the clinical scenario the most popular resuscitation fluid chosen was always crystalloids (27). This mirrors the survey findings published in British Medical Journal discussed above (7).

The aim of our study was therefore to determine whether evolving evidence had impacted resuscitative fluid practices in the Emergency Department and the Intensive Care Unit in a tertiary hospital in South Africa.

PRIMARY OBJECTIVES

1. To describe the amounts, proportions and annual costs of 7 different resuscitative fluids ordered annually by the Emergency Department and the Intensive Care Unit at a tertiary hospital in South Africa over a 4-year period.
2. To describe the current and past usage of the above 7 resuscitative fluids by doctors working in the above departments.
3. To describe the possible reasons for change in the use of the above 7 resuscitative fluids.

SECONDARY OBJECTIVES

1. To compare the proportion/percentage of synthetic colloids and crystalloids of total fluid orders between period 1 and period 4.
2. To compare the proportion/percentage of balanced crystalloid and 0.9% saline to total crystalloid fluid orders between period 1 and period 4.
3. To compare the proportion/percentage Ringers Lactate compared to Balsol and PlasmaLyte B of total balanced crystalloids between period 1 and period 4.

METHODOLOGY

The study design will be twofold:

Part 1: A retrospective longitudinal observational study

Part 2: A cross sectional physician survey

Setting

The research will take place at Chris Hani Baragwanath Hospital which is a tertiary hospital in the South of Johannesburg, South Africa which holds 3200 beds (28).

Sample and Variables

Part 1: Retrospective Longitudinal Study

1. The resuscitation fluids to be studied will be:

   Colloids: Voluven 500ml, Volulyte 500ml, Gelofusin 500ml

   Crystalloids:

      Unbalanced crystalloid: Normal Saline 1 litre

      Balanced crystalloid: 1 litre Ringer's Lactate, Balsol and Plasmalyte B

2. The departments to be studied will be:

   The Emergency Department:

      This is a combined department that includes the Medical Emergency Unit (MEU), Surgical Emergency Unit (SEU) and Trauma Emergency Unit (TEU)

   The General Intensive Care Unit (ICU)

3. The retrospective review of fluid purchasing records will be over 4 years and the periods will be defined as:

   Period 1: 01 November 2014 – 31 October 2015

   Period 2: 01 November 2015 – 31 October 2016

   Period 3: 01 November 2016 – 31 October 2017

   Period 4: 01 November 2017 – 31 October 2018

   This sample period represents a time in which there were many changes in international fluid trends.

See Appendix 1: Data collection sheet.

Part 2: Cross-sectional physician survey

1. The doctors to be surveyed include consultants, registrars and medical officers working in the Emergency Department (Medical Emergency Unit (MEU), Surgical Emergency Unit (SEU), Trauma Emergency Unit (TEU)) and the General Intensive Care Unit (ICU):

   Inclusion criteria:

   - Doctors working for more than 4 years (including internship).

     Doctors working for more than 4 years were chosen so that they could be surveyed on their current and previous fluid resuscitative practices over a similar time period to the retrospective fluid purchasing data.

   - Doctors employed full-time by the Department of Health Gauteng

   Exclusion criteria:

   - Anyone answering <4 years in Question 2 of the survey

2. Sample Size:

   Department size is variable between the Emergency Department and the Intensive Care Unit. Below are the estimated number of doctors eligible to take the survey. The total number of possible respondents is estimated to be 110. Ideally all doctors will complete the survey, but a minimum response rate accepted will be 60% per department.

   The Emergency Department: 85

   General Intensive Care Unit: 25

3. The fluids included in the survey are:

   0.9% Sodium Chloride

Balanced Crystalloids: Balsol, PlasmaLyte B, Ringer's Lactate

Colloids – Starch: Voluven, Volulyte

Colloids – Gelatin: Gelofusine

4. The four different clinical scenarios presented in the survey are:

   Non-septic, non-bleeding hypovolemic shock

   Haemorrhagic shock

   Septic shock

   Shock of unknown origin

See Appendix 2: Survey component: Information sheet and Survey.

Methods and Techniques used

Part 1: Retrospective Longitudinal Study

I will review the pharmacy department's purchase order database from November 2014 until November 2018. The monthly records of the volumes and different types of resuscitation fluids purchased for the Emergency Department (Medical Emergency Unit (MEU), Surgical Emergency Unit (SEU), Trauma Emergency Unit (TEU)) and the General Intensive Care Unit (ICU) departments will be captured into an excel document. In addition, I will also capture the individual and total costs for the different fluids. An inflationary adjusted value for period 1 will be calculated based on the actual cost escalation from period 1 to period 4. This adjusted value will be used for comparison with period 4.

Part 2: Cross-sectional physician survey

A cross sectional survey will be circulated to doctors working in the 2 different departments. It will be an anonymous survey reviewing the resuscitative fluid of choice in four different

clinical scenarios, any change in fluid practices over 4 years and possible reasons for this change.

I will distribute the surveys at academic meetings in the different departments as pre-arranged with the respective department heads. If the minimum response rate is not met after attending a single academic meeting, the process will be repeated at another academic meeting as arranged with the department head. The surveys will be circulated with an information sheet detailing the study and contact details for myself, my supervisors and the ethics department at the University of the Witwatersrand. The survey will be completely voluntary and confidential. The completed surveys will be collected by someone other than me and placed in an opaque envelope. These envelopes will be kept in a secure location. I will enter the data from the surveys into a Microsoft Excel document. This information will remain confidential and will only be accessed by myself, my supervisors and a statistician.

Data Analysis

Part 1: Retrospective longitudinal study

Data collected to fulfil the primary objective will be captured using Microsoft Excel and analysed using descriptive statistics for the absolute and proportional amounts of different fluids and their respective costs over the 4-year period. A 4-year period between 2014 and 2018 was chosen for two important reasons; this was a period of emerging international research and awareness of the contribution of different fluid types to the outcome of critically ill patients and it was also a convenience sample due to the availability of pharmacy records. Data collected to fulfil the secondary objectives will be analysed as categorical data using the Chi square test when reviewing the proportion of colloids, crystalloids, balanced crystalloid and normal saline between period 1 to period 4. A significance level of 0.05 will be used. Statistica version 13.2 will be the statistical package utilised and Professor Omar will assist with the

calculation and interpretation of the statistics. If further assistance is required a statistician will be employed.

Part 2: Cross-sectional survey

Information collected from the survey will be recorded in Microsoft Excel and interpreted using descriptive statistics to fulfil the stated objectives. Surveys which are partially completed will still be used in data analysis. Data collected will be categorical and described using frequencies and percentages. Non-parametric data will be described using medians and confidence intervals. As above Statistica version 13.2 will be the package used and Professor Omar or a statistician will assist with calculation and interpretation of the statistics.

ETHICS

An online application will be made to the ethics committee at the University of the Witwatersrand. The application will be done as soon as the protocol for the study has been approved. In addition, permission will be obtained from the CEO of Chris Hani Baragwanath Hospital, the Head of Pharmacy, Surgery, general Intensive Care Unit and Medical Emergency Unit at Chris Hani Baragwanath Hospital.

The survey of the doctors working in the combined Emergency Department and the general Intensive Care Unit will be voluntary and confidential. An information sheet will be attached to the survey and completion of the survey will imply consent.

See Appendix 3: Letters to CEO/Pharmacy and Department Heads

TIMING

	F 18	M	A	M	Jn	Jl	A	S	O	N	D	J 19	F	M	A	M	Jn	Jl	A
Lit Review																			
Protocol																			
DRAG																			
Ethics																			
Data collect																			
Analysis																			
Write up																			

FUNDING

Total budget is expected to be R 1500 and will be funded by myself

R500 to be spent on transport, R1000 on photocopying and stationary required.

If extra assistance from a statistician is required a further R 6000 will be made available by myself to cover the cost.

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APPENDIX 1: Data Collection Sheet template

ED		Amount										Cost									
Month	Period	NS-ED	RL-ED	Bal-ED	PlasmB-E	Tcryst	T Balance	Gelofusir	Volven-E	Volulyte-	Colloid	NS-ED	RL-ED	Bal-ED	PlasmB-E	Tcryst	T Balance	Gelofusir	Voluven-	Volulyte-	TColloid
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ICU		Amount										Cost									
Month	Period	NS-ED	RL-ED	Bal-ED	PlasmB-E	Tcryst	T Balance	Gelofusir	Volven-E	Volulyte-	Colloid	NS-ED	RL-ED	Bal-ED	PlasmB-E	Tcryst	T Balance	Gelofusir	Voluven-	Volulyte-	TColloid
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Key	
Abbreviation	**Description**
ED	Emergency Department
ICU	Intensive Care Unit
NS	Normal Saline
RL	Ringer's Lactate
Bal	Balsol
PlasmB	Plasmalyte B
Gelo	Gelofusin
T	Total
cryst	Crystalloids
balanced	Balanced Crystalloids

APPENDIX 2: Survey Component: Information sheet and Survey

INFORMATION SHEET: SURVEY
A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg

My name is Kelly Jacobs. I am one of the Registrars in Emergency Medicine at the University of the Witwatersrand. To complete my post-graduate degree, I am required to do a MMed research project. The title of my MMed is "A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg"

I am researching the resuscitative fluid practices of the combined Emergency Department and the General Intensive Care Unit at the Chris Hani Baragwanath Academic Hospital. The combined Emergency Department includes the Trauma Emergency Unit, the Surgical Emergency Unit and the Medical Emergency Unit.

Participation in this survey is completely voluntary. The survey that follows will be confidential and anonymous and the data obtained will only be used for my MMed as described above. Included in the survey are 4 clinical scenarios and questions regarding your current and past fluid choices and possible reasons for your choices.

If at any point you no longer wish to partake in the study, please feel free to discard your survey. You may also leave blank any question you do not wish to answer. The surveys are to be distributed in hard copy at the various departmental meetings. If the number of completed surveys are not met, then a repeat session will be arranged. The surveys will be collected by someone other than myself and placed in an opaque envelope to ensure anonymity. All completed surveys will be kept in a secure location and only the researchers will have access to the information. The data will be captured onto a Microsoft Excel document and will only be accessed by myself, my supervisors and a statistician.

If you agree to taking the following survey read through each question and mark your answer in the corresponding tick box. The survey should take no more than 10 minutes of your time. Permission has been granted from the CEO of Chris Hani Baragwanath Academic Hospital and the Head of your respective departments.

Ethics clearance for this study has been obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand, reference M190869.

If you would like any further information regarding my MMed or this survey please feel free to contact me or my supervisors, Dr L Hindle or Professor S Omar. Contact information for the University of the Witwatersrand Human Research Ethics Committee (Medical) is also included. See all contact information below.

Thank you for your time,

Primary Researcher: Dr Kelly Jacobs, 072 140 8396, kellyjacobs24@gmail.com
Supervisor: Dr L Hindle, 082 871 0638, hindle.lucy@gmail.com
Supervisor: Professor S Omar, 083 569 5363, shahedicu@gmail.com

Human Research Ethics Committee (Medical) Research Office, Faculty of Health Sciences, Phillip Tobias Building, Offices 301-304, 3rd Floor, Cnr York Road and 29 Princess of Wales Terrace, Parktown, 2193. Phone: 011 717 1252/2700/1234/2656.

SURVEY

A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg

Please tick in the appropriate block, when more than one answer is required it will be indicated in the question. Please note this survey is **only** looking into resuscitative fluids and **no blood products** are included.

1. Which Department are you currently working in?
   - ☐ Surgery: Non-trauma
   - ☐ Surgery: Trauma
   - ☐ Intensive Care Unit
   - ☐ Medical Emergency Unit

2. How long have you been practising as a doctor (Including internship)?
   - ☐ More than 4 years
   - ☐ Less than 4 years

3. Which **ONE** of the following fluids (not including blood products) will you use for your initial fluid resuscitation in the following scenarios:

   Clinical scenario 1:

   A 50-year-old male patient presenting in hypovolemic shock secondary to acute diarrhoea

   a. Which fluid would you use in your acute resuscitation today (2020)?
      - ☐ 0.9% Sodium Chloride
      - ☐ Balanced Crystalloids: (Balsol, Plasmalyte B, Ringer's Lactate)
      - ☐ Colloids – Starch: (Voluven/Volulyte)
      - ☐ Colloids – Gelatins: (Gelofusin)

   b. Which fluid would you have used 4 years ago?
      - ☐ 0.9% Sodium Chloride
      - ☐ Balanced Crystalloids: (Balsol, Plasmalyte B, Ringer's Lactate)
      - ☐ Colloids – Starch: (Voluven/Volulyte)
      - ☐ Colloids – Gelatins: (Gelofusin)

Clinical scenario 2:

A 34-year-old female involved in a Motor Vehicle Accident with an unstable pelvic fracture presenting with haemorrhagic shock. (Blood products not available)

a. Which fluid would you use in your acute resuscitation today (2020)?
   - ☐ 0.9% Sodium Chloride
   - ☐ Balanced Crystalloid: (Balsol, Plasmalyte B, Ringer's Lactate)
   - ☐ Colloid – Starch: (Voluven/Volulyte)
   - ☐ Colloid – Gelatins: (Gelofusin)

b. Which fluid would you have used 4 years ago?
   - ☐ 0.9% Sodium Chloride
   - ☐ Balanced Crystalloid: (Balsol, Plasmalyte B, Ringer's Lactate)
   - ☐ Colloid – Starch: (Voluven/Volulyte)
   - ☐ Colloid – Gelatins: (Gelofusin)

Clinical scenario 3:

A 47-year-old male presenting with a community acquired pneumonia complicated by septic shock

a. Which fluid would you use in your acute resuscitation today (2020)?
   - ☐ 0.9% Sodium Chloride
   - ☐ Balanced Crystalloid: (Balsol, Plasmalyte B, Ringer's Lactate)
   - ☐ Colloid – Starch: (Voluven/Volulyte)
   - ☐ Colloid – Gelatins: (Gelofusin)

b. Which fluid would you have used 4 years ago?
   - ☐ 0.9% Sodium Chloride
   - ☐ Balanced Crystalloid: (Balsol, Plasmalyte B, Ringer's Lactate)
   - ☐ Colloid – starch: (Voluven/Volulyte)
   - ☐ Colloid – gelatins: (Gelofusin)

Clinical Scenario 4:

A 58-year-old female presenting in shock of unknown cause

a. Which fluid would you use in your acute resuscitation today (2020)?

- ☐ 0.9% Sodium Chloride
- ☐ Balanced Crystalloid: (Balsol, Plasmalyte B, Ringer's Lactate)
- ☐ Colloid – Starch: (Voluven/Volulyte)
- ☐ Colloid – Gelatins: (Gelofusin)

b. Which fluid would you have used 4 years ago?

- ☐ 0.9% Sodium Chloride
- ☐ Balanced Crystalloid: (Balsol, Plasmalyte B, Ringer's Lactate)
- ☐ Colloid – Starch: (Voluven/Volulyte)
- ☐ Colloid – Gelatins: (Gelofusin)

4. Has the type of resuscitative fluid (non-blood product) you use changed in the past 4 years?
   - ☐ Yes
   - ☐ No

5. If yes, what factors have influenced the change in your fluid choice? Tick all that apply

   - ☐ Undergraduate University teaching
   - ☐ Postgraduate University teaching
   - ☐ Self-study:
     - ☐ Textbooks
     - ☐ Online blogs eg Life in the fast lane, EMcrit
     - ☐ Social media eg twitter
   - ☐ In hospital tutorials
   - ☐ Academic Papers/Journals
   - ☐ Senior opinion
   - ☐ Hospital/Unit Protocols

APPENDIX 3: Letters to CEO/Pharmacy/Department Heads

Template of letter to CEO/Department Heads

Dear Dr Lesia/Mr Dikgang/Dr Brown/Prof Smith/Prof Mohammed

Request to conduct research at Chris Hani Baragwanath Hospital

I would like to obtain your permission to conduct a study at Chris Hani Baragwanath Hospital (CHBAH). This research will be used for my MMed in Emergency Medicine at University of the Witwatersrand. The purpose of this is to review whether recent academic papers have influenced the types of fluids bought by acute care departments.

I would like to investigate the resuscitative fluid practices in the acute care departments at CHBAH. This would entail a retrospective review of pharmacy purchase records from November 2014 to November 2018 and a survey of fluid choices made by doctors working in the acute care departments. The fluids to be reviewed are Normal Saline 1l, Ringer's Lactate 1l, Balsol 1l, PlasmaLyte B 1l, Voluven 500ml, Volulyte 500ml and Gelofusine 500ml. The acute care departments to be reviewed are the Medical Emergency Unit (MEU), the Surgical Emergency Unit (SEU), the Trauma Emergency Unit (TEU) and the general Intensive Care Unit (ICU). Please find attached my academic protocol.

I will also seek permission from the Head of Pharmacy, Surgery, Trauma, general ICU and the Emergency Department at CHBAH after your consideration. An application has also been made to the Ethics committee of the University of the Witwatersrand and no research will begin until all the approvals have been obtained. I have been granted provisional ethics approval by the university but require written confirmation of your approval before final clearance can be granted. My ethics protocol reference is M190869. Please see attached for my provisional clearance certificate.

Thank you for your consideration and I look forward to your reply. Please feel free to contact me or my supervisors if you have any questions regarding my research. My supervisors are Dr L Hindle from the Medical Emergency Unit and Professor S Omar from the Intensive Care Unit at CHBAH.

Regards,

Kelly Jacobs
Emergency Medicine Registrar
Student Number: 304941
0721408396
kellyjacobs24@gmail.com

Supervisors:

Dr L Hindle
082 871 0638
hindle.lucy@gmail.com

Professor S Omar
083 569 5363
shahedicu@gmail.com

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 22nd October 2019

TITLE OF PROJECT:

A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr Kelly Jacobs

Department: Emergency Medicine

Supervisor : Dr L Hindle and Prof S Omar

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- **Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.**
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 22/10/2019

Approved/~~Not Approved~~
Hospital Management
Date: 25/10/2019

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Enquiries: Mr. Saul Dikgang
Tel: 011 933-879
Fax: 086 601 899
E-mail:Saul.Dikgang@gauteng.gov.

Dr. Kelly Jacobs – Emergency Medicine Registrar
Chris Hani Baragwanath Academic Hospital

Date: 17 October 2019.

REQUEST FOR PHARMACY RECORDS FOR FLUIDS USED IN VARIOUS ACUTE CARE DEPARTMENTS IN THE HOSPITAL.

Dear Dr. Jacobs.

Your request for purchasing records of certain fluids used by acute care departments at the hospital from the pharmacy bears reference.

Permission for your accessing the records will be subject to your research being approved by the various Heads of the acute care departments as well as approval by the CEO of the hospital.

Once all the abovementioned approvals are in order, you will be expected to work closely with Ms Azraa Paruk, the Supervising Pharmacist who is also in charge of supplying these acute care departments with the fluids mentioned in your request. I would like to use this opportunity to wish you well in your research and studies.

Hoping you find this in order.

Mr. Saul Dikgang
Manager: Pharmaceutical Services
Chris Hani Baragwanath Academic Hospital
Date: 17/10/2019.

health and social development
Department: Health and Social Development
GAUTENG PROVINCE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Intensive Care unit

Dr JM Brown
Jacqui.Brown@wits.ac.za
Tel: 0119381596
Fax:0119381595

10th October 2019

To whom it may concern

Re: Permission to conduct research in Chris Hani Baragwanath Hospital Intensive Care unit

Title of research project:
A Review of Adult Resuscitative Fluid Purchasing and Usage Trends
At an Academic Tertiary Hospital in Johannesburg

Investigator: Dr Kelly Jacobs

Permission is hereby granted for Dr Kelly Jacobs to survey doctors in the ICU for the purpose of data collection. The data collected will be used for her MMed and publication in peer review journals.

The hospital is not liable for any costs related to the study
The study will not disadvantage any Chris Hani Baragwanath patient/staff member

Regards

Dr JM Brown
Deputy Head: Intensive Care Unit
Chris Hani Baragwanath Hospital
Soweto
Affiliated to University of the Witwatersrand

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HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

Directorate: Department of Surgery

☎011 933 8386/8804

🖷011 938 2002

11 October 2019

To whom it may concern

RE: Research request 'A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg'

I hereby grant Dr Kelly Jacobs, an Emergency Medicine Registrar from the University of the Witwatersrand, permission to survey the doctors in my department regarding their resuscitative fluid practices for use in the study 'A review of adult resuscitative fluid purchasing and usage trends at an academic hospital in Johannesburg'.

Regards

Professor Martin Smith

Head of Surgery Department

Chris Hani Baragwanath Academic Hospital

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HEALTH
REPUBLIC OF SOUTH AFRICA

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL
Department of Emergency Medicine
Enquiries: A/Prof Zeyn Mahomed
Tel. #6300 E-mail: zeynmahomed@gmail.com

09 October 2019

To Whom It May Concern

Re: Permission to conduct research

Survey of doctors working in acute care departments in Chris Hani Baragwanath Hospital regarding "Adult resuscitative fluid purchasing and usage"

I hereby grant Dr. Kelly Jacobs permission to conduct her survey in my department.

Yours faithfully

A/Prof Z. Mahomed
Head of the Emergency Department

APPENDIX B:

PROTOCOL ACCEPTANCE LETTER FROM DEPARTMENT RESEARCH COMMITTEE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

Division of Emergency Medicine

Head,
Division of Emergency Medicine
University of the Witwatersrand
Feroza.motara@wits.ac.za

Post Graduate Office

*The protocol of **Dr Kelly Amy Jacobs** titled "A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg" has been approved by the DRAG committee after the appropriate revisions and edits suggested by the committee on 16 May 2019 were made and approved by the committee after electronic re-submission.*

Prof Feroza Motara
Head,
Division of Emergency Medicine
University of the Witwatersrand

Date 18/7/19 **Signature**

Faculty of Health Sciences. School of Clinical Medicine; Division of Emergency medicine; Physical Address: Wits Medical School, 4th floor, Office No: 4B27, 7 York Road, Parktown, Johannesburg· Tel: +27 11 717 2036 E- Mail address: Feroza.motara@wits.ac.za. Website: www.wits.ac.za

APPENDIX C:

ETHICS CLEARANCE FROM HREC (Medical)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr K Jacobs

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M190869

NAME: (Principal Investigator)	Dr K Jacobs
DEPARTMENT:	School of Clinical Medicine Division of Emergency Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg
DATE CONSIDERED:	2019/08/30
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr L Hindle and Professor S Omar
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2019/11/14

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **August** and will therefore reports and re-certification will be due early in the month of **August** each year. Unreported changes to the application may invalidate the clearance given by the **HREC** (Medical).

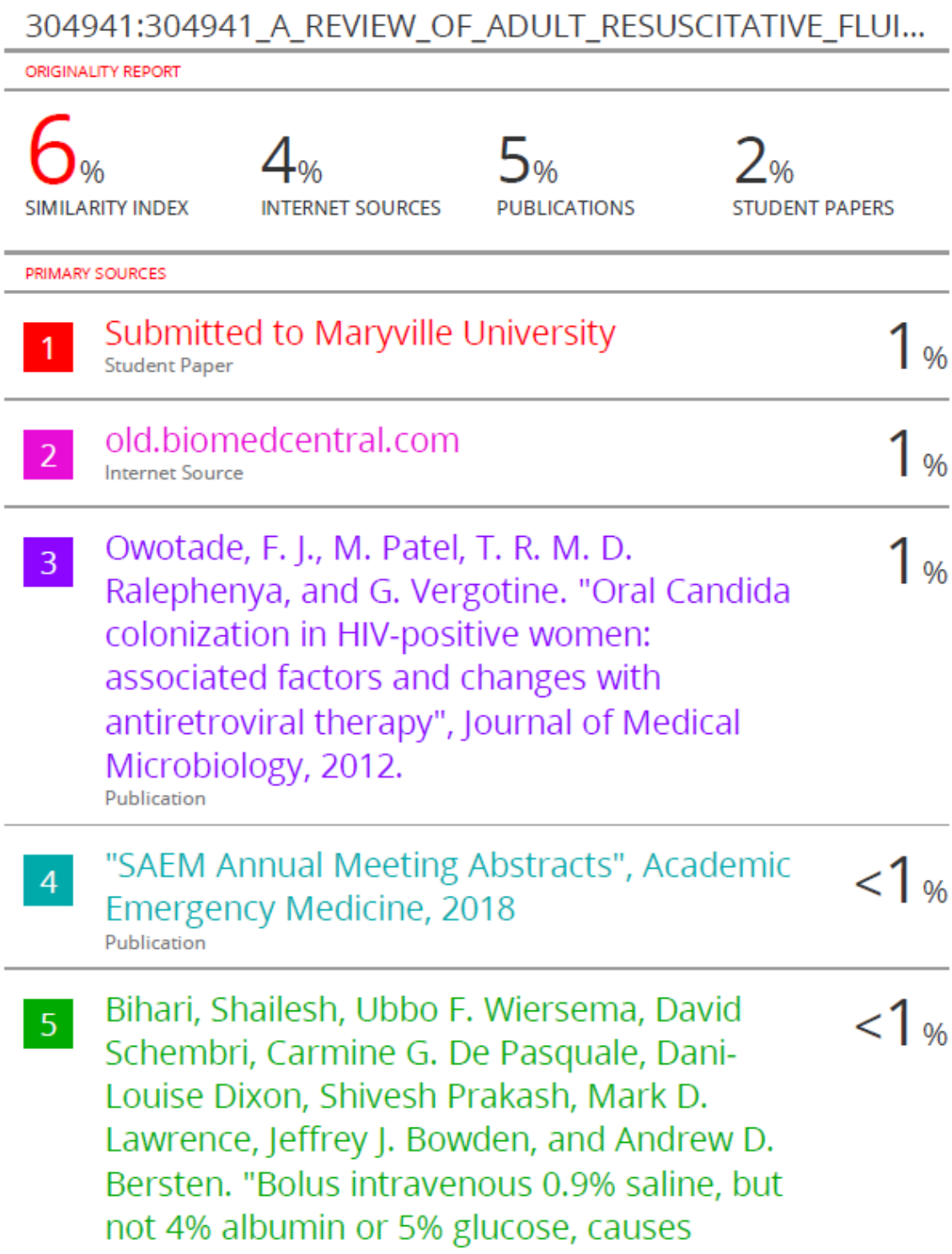
16/11/2019

Principal Investigator Signature — Date

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

APPENDIX D:

TURN-IT-IN PLAGIARISM REPORT



304941:304941_A_REVIEW_OF_ADULT_RESUSCITATIVE_FLUI...

ORIGINALITY REPORT

6%	4%	5%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to Maryville University Student Paper	1%
2	old.biomedcentral.com Internet Source	1%
3	Owotade, F. J., M. Patel, T. R. M. D. Ralephenya, and G. Vergotine. "Oral Candida colonization in HIV-positive women: associated factors and changes with antiretroviral therapy", Journal of Medical Microbiology, 2012. Publication	1%
4	"SAEM Annual Meeting Abstracts", Academic Emergency Medicine, 2018 Publication	<1%
5	Bihari, Shailesh, Ubbo F. Wiersema, David Schembri, Carmine G. De Pasquale, Dani-Louise Dixon, Shivesh Prakash, Mark D. Lawrence, Jeffrey J. Bowden, and Andrew D. Bersten. "Bolus intravenous 0.9% saline, but not 4% albumin or 5% glucose, causes	<1%

	interstitial pulmonary edema in healthy subjects", Journal of Applied Physiology, 2015. Publication	
6	Pietro Caironi, Thomas Langer, Luciano Gattinoni. "Albumin in critically ill patients", Current Opinion in Critical Care, 2015 Publication	<1 %
7	D.J. McLean, A.D. Shaw. "Intravenous fluids: effects on renal outcomes", British Journal of Anaesthesia, 2018 Publication	<1 %
8	academic.oup.com Internet Source	<1 %
9	journals.sagepub.com Internet Source	<1 %
10	Haynes, G. R.. "Risks of Hydroxyethyl Starch 130/0.4 in Cardiac Surgery", Journal of Pharmacy Practice, 2014. Publication	<1 %
11	Piotr F. Czempik, Cezary Kapłan, Monika Krok, Nadia Woźniak. "Effects of introducing a rapid response team in a university teaching hospital – preliminary analysis", Anaesthesiology Intensive Therapy, 2019 Publication	<1 %
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18	Ryan M. Brown, Matthew W. Semler. "Fluid Management in Sepsis", Journal of Intensive Care Medicine, 2018 Publication	<1 %

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

APPENDIX E:

CERTIFICATE OF SUBMISSION SIGNED BY STUDENT

CERTIFICATE OF SUBMISSION FOR EXAMINATION OF MASTERS RESEARCH REPORT / DISSERTATION OR PHD THESIS SIGNED BY HIGHER DEGREES CANDIDATES

Full name	Kelly Amy Jacobs		
Student number	304941		
Title of submitted Research Project: A REVIEW OF ADULT RESUSCITATIVE FLUID PURCHASING AND USAGE TRENDS AT AN ACADEMIC TERTIARY HOSPITAL IN JOHANNESBURG *NB: If this title is different to your previously approved title, no further action can be taken by the Faculty Office until a change of title has been approved.*			
Contact no	0721408396	E-mail	Kellyjacobs24@gmail.com

1. If you are likely to move in the next 6-12 months, please give the anticipated date of move: _____
2. I hereby submit my **Masters (research report)** / ~~**Masters (dissertation)**~~ / ~~**PhD thesis - for examination**~~ (Select whichever is applicable)
3. I have checked all copies of my research report / ~~dissertation / thesis~~ and declare that no pages are missing or poorly reproduced.
4. I have submitted electronically

5. **I confirm that I have:**
   a) A signed declaration indicating my understanding of the concept of plagiarism and a denial of plagiarism in my research document.
   b) A report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document included as an appendix.

6. **I confirm that I have:**
   a) Not used either human or animal tissue or records **~~Yes~~/No**
   b) If yes: I have included the ethics waiver letter pertinent to my research as an appendix **N/A**
   c) Done research using animals **~~Yes~~ / No**
      If yes: I have included a copy of the animal ethics committee clearance certificate as an appendix in this document **N/A**
   d) Done research using human subjects, human tissue or patient records **Yes / ~~No~~**
      If yes: I have included a copy of the human ethics clearance certificate as an appendix to the research document **Yes/~~No~~**

7. I understand that I may not graduate unless my University fees have been paid in full.
8. My Supervisor(s) names, departments, telephone numbers and email addresses are as follows:

Name	Dr Lucy Hindle		
Department	Emergency Medicine, Intensive Care Unit		
Telephone	082 871 0638	E-mail	hindle.lucy@gmail.com
Name	Prof Shahed Omar		
Department	Intensive Care Unit		
Telephone	083 569 5363	E-mail	shahedicu@gmail.com

List all publications, which you have published in peer-reviewed journals from your postgraduate research report/~~dissertation/thesis~~ during the course of your studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

Jacobs K, Hindle L, Omar S. 2021. entitled A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg. Anaesthesiology Intensive Therapy.

Article accepted for publication but not yet published.

Signature of candidate:  Date: 16/08/2021

APPENDIX F:

CERTIFICATE OF SUBMISSION SIGNED BY SUPERVISORS

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

CERTIFICATE OF SUBMISSION FOR EXAMINATION SIGNED BY SUPERVISORS OF HIGHER DEGREES CANDIDATES

Full name	Kelly Amy Jacobs
Student number	304941

Candidate for the degree of: Master of Medicine in Emergency Medicine
has submitted his/her thesis/dissertation/research report

Entitled:

A REVIEW OF ADULT RESUSCITATIVE FLUID PURCHASING AND USAGE TRENDS AT AN ACADEMIC TERTIARY HOSPITAL IN JOHANNESBURG

Contact no	0721408396	E-mail	Kellyjacobs24@gmail.com

Mark with an X on appropriate box	Yes	No
Has this thesis/dissertation/research report been submitted with the acquiescence of the supervisor?	x	
To the best of your knowledge are you able to verify that this is the candidate's work, except as otherwise stated by the candidate?	x	
The substance (nor any part of it) has not been submitted in the past nor is being submitted for a degree in any other university?	x	
The candidate has acknowledged wherever any information used in the thesis, dissertation or other work has been obtained by him/her while employed by, or working under the aegis of, any person or organization other than the University or its associated institutions?	x	
Have examiners been nominated and approved?	x	

I certify that this thesis/dissertation/research report has the approval of the Animal Ethics Committee / Committee for Research on Human Subjects and the Number of the Certificate of Approval is:

M190869

List all publications, which your student has published in peer-reviewed journals from his/her postgraduate research report/dissertation/thesis during the course of his/her studies in the Faculty of Health Sciences (Include authors, year, title of paper, name of journal, volume number and page numbers). This information is mandatory.

Jacobs K, Hindle L, Omar S. 2021. entitled A review of adult resuscitative fluid purchasing and usage trends at an academic tertiary hospital in Johannesburg. Anaesthesiology Intensive Therapy.

Article accepted for publication but not yet published.

Name of Supervisor 1: Dr L Hindle

Telephone: 082 871 0638 Email: hindle.lucy@gmail.com

Signature: _____ Date: _26/06/21_____

1

Name of Supervisor 2: Prof S Omar

Telephone: 083 569 5363 Email: shahedicu@gmail.com

Signature: _____ Date: 25 June 2021

==========

IMPORTANT NOTICE WITH REGARD TO THE SENATE STANDING ORDERS:

A.22 Submission against advice of Supervisor

If the Supervisor is not prepared to agree to the submission of a thesis, the candidate shall still be entitled, if he or she wishes, to submit it for examination. When a thesis is submitted against the advice of the Supervisor, this should be recorded in the minutes of the Faculty Graduate Studies Committee. In such a case, no internal examiners are appointed but a Supervisor's report will still be required. After the examination process, the external examiner(s) will be advised by the Chairperson of the Faculty Graduate Studies Committee that the thesis was submitted against the advice of the Supervisor.

A.24 *Nomination of Examiners*:

Nomination of examiners should take place at least six weeks before submission of the thesis or dissertation. *(The Postgraduate Office will not accept any submission for examination without the confirmed appointment of the nominated examiners.)*

A.25 Confidentiality of names of examiners (both external and internal)

The names of the examiners should be confidential during the examination process and may only be revealed to the candidate with the acquiescence of the examiner once the final version of the thesis has been submitted to the Faculty and the process has been completed.