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Obstetric blood loss quantification.

Thesis presented by

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DECLARATION

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

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This thesis is dedicated to my parents. For their endless love, support and encouragement.

PREFACE

In the field of obstetrics and gynaecology, the monitoring and management of obstetric or maternal blood loss is fundamental to ensuring the well-being of mothers during pregnancy and childbirth. The significance of accurate and timely quantification of maternal blood loss cannot be overstated, as it directly influences clinical decision making and overall patient outcomes. This thesis, focuses on obstetric blood loss quantification, seeking to contribute valuable insights to the ever-evolving landscape of obstetric care.

As a trainee in obstetrics and gynaecology, my professional journey has been characterized by a profound commitment to advancing the understanding of maternal health. The drive to refine our approaches to obstetric blood loss quantification arises from the recognition that obstetric haemorrhage remains a leading cause of maternal morbidity and mortality. The diagnosis of obstetric haemorrhage is difficult and largely retrospective. In the face of this challenge, a comprehensive exploration of the methods used to gauge maternal bleeding in pregnancy and following delivery is necessary. Indeed, it is crucial to identify a blood loss quantification method which promptly detects high blood loss rates and allows for early escalation of care. In theory, this method would reduce the incidence of obstetric haemorrhage and its associated complications.

This thesis examines the strength and limitations of current methods of maternal blood loss quantification. It aspires to furnish healthcare professionals with actionable insights that that can be easily integrated into clinical practice and increase awareness of cognitive bias in the

context of obstetric blood loss quantification. This thesis embraces the spirit of innovation, recognizing that the integration of cutting-edge technologies and methodologies is paramount to advancing obstetric care. We study and develop a novel obstetric blood loss quantifying tool, through lab-based testing and real-world clinical settings. The evolution of obstetric blood loss quantification techniques is not merely a reflection of historical progress, but also a testament to the ongoing commitment to innovation within our field.

The pursuit of excellence in obstetric care requires a relentless commitment to research and the continual refinement of our understanding. It is my sincere hope that the findings presented herein not only contribute to the academic discourse, but also resonate with healthcare professionals and health policymakers alike, fostering a collective dedication to elevating the standard of care for expectant mothers worldwide.

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LIST OF ABBREVIATIONS

aPTT, Activated partial thromboplastin time

ACOG, American College of Obstetricians and Gynecologists

APH, Antepartum haemorrhage

BMI, Body Mass Index

CMQCC, California Maternal Quality Care Collaborative

CUMH, Cork University Maternity Hospital

Hb, Haemoglobin

Hct, Haematocrit

ICSH, International Council for Standardization in Haematology

IVC, Inferior vena cava

MOH, Major or massive obstetric haemorrhage

NPEC, National Perinatal Epidemiology Centre

NWIHP, National Women and Infants Health Programme

PAS, Placenta accreta spectrum

PPH, Postpartum haemorrhage

PT, prothrombin time

RCOG, Royal College of Obstetricians and Gynaecologists

RCPI, Royal College of Physicians of Ireland

SI, Shock Index

SUS, System Usability Scale

SMM, Severe Maternal Morbidity

WHO, World Health Organisation

ACADEMIC ACHIEVEMENTS DURING RESEARCH FELLOWSHIP

Research output related to MD thesis

Publications

I. **Lutfi A**, Eustace D, McKee B, Faul S, Greene RA, Higgins JR. Early feasibility and usability study of a novel obstetric blood loss quantifying device. *Eur J Obstet Gynecol Reprod Biol*. 2024 Sep 14;302:190-195. **doi: 10.1016/j.ejogrb.2024.09.018**. Epub ahead of print. PMID: 39298828.

II. **Lutfi A,** McElroy B, Greene RA, Higgins JR. Cost analysis of care and blood transfusions in patients with Major Obstetric Haemorrhage in Ireland. *Transfus Med*. 2024 Jun;34(3):182-188. **doi: 10.1111/tme.13042**. Epub 2024 Apr 25. PMID: 38664599.

III. **Lutfi A**, Eustace D, Faul S, Greene RA, Higgins JR. Accuracy testing of a novel obstetric blood loss quantifying device: A pilot study. *Int J Gynaecol Obstet.* 2024 Jun;165(3):1290-1292. **doi: 10.1002/ijgo.15385**. Epub 2024 Jan 17. PMID: 38230916.

Research output not related to MD thesis

Publications

I. **Lutfi A**, Hayes-Ryan D, Cottrell E, Greene RA. Systemic methotrexate (MTX) in early pregnancy: a retrospective study of a tertiary maternity hospital. *Ir J Med Sci*. 2024 Jul 9. **doi: 10.1007/s11845-024-03748-9.** Epub ahead of print. PMID: 38980553.

II. **Lutfi A**, O'Rourke E, Crowley M, Craig E, Worrall A, Kevane B, O'Shaughnessy F, Donnelly J, Cleary B, Áinle FN. VTE risk assessment, prevention and diagnosis in pregnancy. *Thromb Res.* 2024 Mar;235:164-174. **doi: 10.1016/j.thromres.2024.01.025**. Epub 2024 Feb 3. PMID: 38350183.

III. **Lutfi A**, Carrion E, Fitzgerald B, Greene R. *AB120. SOH23ABS_057.* Operative management and morbidities of placenta accreta spectrum: a tertiary maternity unit's experience. *Mesentery Peritoneum* 2023;7:AB120. **doi: 10.21037/map-23-ab120**

Manuscripts under review

I. **Lutfi A**, Meyer N, O'Shaughnessy F, Gaffney G, MacMahon P, Byrne P, Cole R, Spring A, Higgins JR, Ní Áinle F, Crowley M. National Clinical Practice Guideline: Prevention and Management of Venous Thromboembolism in Pregnancy.

PRESENTATIONS DURING RESEARCH FELLOWSHIP

Oral

I. **A. Lutfi.** *Clinical testing of a novel obstetric blood loss quantifying device*. Cork University Hospital QI, Audit & Research Symposium. 21 June 2024. Cork, Ireland.

II. **A. Lutfi.** *Obstetric blood loss quantification.* NPEC Research Day. 18 June 2024. . Cork, Ireland.

III. **A. Lutfi** on behalf of the CUMH PPHQII Team. *Our journey to safer care: Tales from the CUMH Postpartum Haemorrhage Quality Improvement Initiative (PPHQII) Team*. UCC Department of Obstetrics and Gynaecology Educational Evening. 24 May 2024. Cork, Ireland.

IV. **A. Lutfi**. *Postpartum haemorrhage and quantifying obstetric blood loss*. Stryker Instruments Innovation Centre. 18 August 2022. Cork, Ireland.

Video

I. **A. Lutfi**, B. McElroy, R.A. Greene, J.R. Higgins. *The economic burden of Major Obstetric Haemorrhage*. NPEC Study Day 2024. 19 January 2024. Portlaoise, Ireland.

II. **A. Lutfi.** *Quantifying Obstetric Blood Loss Studies.* Bright Futures Research Day. University College Cork. April 26, 2023. Cork, Ireland.

Posters

I. **A. Lutfi**, B. McElroy, R.A. Greene, J.R. Higgins. *The economic burden of Major Obstetric Haemorrhage*. British Maternal-Fetal Medicine Society (BMFMS). 25-26 April 2024. Liverpool, UK.

II. **A. Lutfi**, D. Eustace, S. Faul, R.A. Greene and J.R. Higgins. *Accuracy testing of a novel obstetric blood loss quantifying device and its future implications.* JOGS. 23 February 2024. Dublin, Ireland.

III. E. Pons Carrion, **A. Lutfi**, B. Fitzgerald and R.A. Greene. *Neonatal outcomes following placenta accreta spectrum: A single unit cross-sectional study.* JOGS. 23 February 2024. Dublin, Ireland.

IV. **A. Lutfi**, D. Eustace, S. Faul, R.A. Greene and J.R. Higgins. *A pilot study on novel obstetric blood loss quantification technology.* Spark Summit - Innovation in Action. 15 June 2023. Dublin, Ireland.

V. **A. Lutfi**, R.A. Greene and J.R. Higgins. *Evaluating blood loss at Caesarean section: a haemorrhage risk-based prospective study*. Royal College of Obstetricians and Gynaecologists World Congress. 12-14 June 2023. London, United Kingdom.

VI. **A. Lutfi**, S. Faul, D. Eustace, R.A. Greene and J.R. Higgins. *Using blood products to develop obstetric blood loss quantification technology.* Blood Donation, Haematology, Infection and Transfusion Conference (BlooDHIT). 10-11 November 2022. Dublin, Ireland.

VII. **A. Lutfi**, D. Hayes-Ryan, E. Cottrell and R.A. Greene. *Systemic methotrexate therapy in early pregnancy: a retrospective review of a tertiary maternity hospital.* The Association of Early Pregnancy Units (AEPU) Annual Scientific Meeting. 17-18 November 2022. Bristol, UK.

AWARDS AND PRIZES DURING RESEARCH FELLOWSHIP

I. **HSE Library Open Access Research Award.** Dr Steevens' Hospital. 5 December 2024. Dublin, Ireland.

II. **Cillian Twomey Research Medal.** Cork University Hospital QI, Audit & Research Symposium. 21 June 2024. Cork, Ireland.

III. **HSE Bright Spark Award.** Spark Summit - Innovation in Action. 15 June 2023. Dublin, Ireland.

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V. **Second Place Award.** "My Research in a 1min Video" Competition. Bright Futures Research Day. University College Cork. April 26, 2023. Cork, Ireland.

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ABSTRACT

Background

The research undertaken for this thesis focuses on the quantification of obstetric blood loss. Obstetric haemorrhage contributes to rising worldwide maternal morbidity and mortality rates. In Ireland, obstetric haemorrhage is the leading cause of Severe Maternal Morbidity (SMM). Accurate and rapid assessment of maternal bleeding status is essential to the diagnosis of obstetric haemorrhage. Obstetric blood loss quantification needs to be standardised as a varying approach to measuring maternal blood loss may lead to a missed or delayed diagnosis. It is possible that currently utilised quantitative methods, namely volumetry and gravimetry, produce inconsistent measurements of maternal blood loss and that an alternative method may be more reliable. The aim of this research was to identify the limitations of currently utilised quantitative methods and to explore novel blood loss quantifying technology. We also aimed to identify the cost of obstetric haemorrhage to aid in future cost-effectiveness studies on novel blood loss quantifying technology.

Methods

We used a mixed methods approach, utilizing both qualitative and quantitative research methods, to provide a deeper understanding of the cost of obstetric haemorrhage and to study obstetric blood loss quantification. Micro-costing, a research methodology from the social sciences, was used to estimate the cost of obstetric haemorrhage and the cost contribution of blood transfusions used in the management of obstetric haemorrhage in Ireland. In this study, we used a dataset generated from a nationwide cross-sectional study

of obstetric haemorrhage from the National Perinatal Epidemiology Centre (NPEC) in Ireland. An observational study of Caesarean births was performed to assess current blood loss quantification practices in Cork University Maternity Hospital (CUMH), which is a tertiary maternity hospital. Through laboratory testing, we compared the blood detecting accuracy of a novel blood loss quantifying device (the Stryker® System), developed by Stryker Instruments Innovation Centre, against a reference haematology analyser. In this study, unwanted human whole blood provided by the Irish Blood Transfusion Service was diluted with normal saline to simulate birth waste. We transitioned to clinical testing of the device in Caesarean section patients delivering in CUMH where we compared the device against standard volumetry performed by hospital staff members. The haemoglobin content of the birth waste as measured by a haemoglobinometer was assigned as the standard for the purpose of comparison. Hospital staff feedback of the device was gathered to guide future device modifications and improvements.

Results

A cost-analysis of obstetric haemorrhage in Ireland estimates that obstetric haemorrhage adds an additional 140% to maternity care costs with blood transfusions contributing to one third to half of this additional cost. We identified that assessments of maternal blood loss following Caesarean birth varied with hospital staff members applying both subjective and objective methods (a hybrid approach) in the majority of cases (84%). Patients classified as high risk of haemorrhage had more objective methods utilized (40%) when compared to patients classified as low or medium risk (19% and 7% respectively). A pilot study evaluating the accuracy the Stryker® System against a reference haematology analyser showed that the

device is accurate in measuring haemoglobin concentrations (g/dL) of fluid mixtures. Bland-Altman analysis in this study demonstrated 95% limits of agreement of –0.96 to 1.03 g/dL. An early feasibility study of the Stryker® System's performance in Caesarean section births showed that the device offered more accurate measurements of maternal blood loss when compared with volumetry done by hospital staff. Bland-Altman analysis produced mean biases of 0.236 $\pm$ 1.213 g/dL and -0.661 $\pm$ 1.458 g/dL for the device and staff measurements respectively when compared against the haemoglobinometer. The width of the limits of agreement at 95% confidence was narrower for device measurements than staff measurements (4.519 g/dL and 5.715 g/dL respectively). The device's measurements of haemoglobin content correlated more strongly with the haemoglobinometer rather than hospital staff measurements (Spearman correlation coefficients of 0.881 and 0.635 respectively). This suggests that the device is more accurate in determining the blood content of the birth waste than hospital staff volumetric measurements. Lastly, a mean System Usability Scale (SUS) score of 82 $\pm$ 13 suggests that the device is highly usable.

Conclusion

This thesis sheds light on the critical issue of obstetric blood loss quantification. The research highlights the financial burden of obstetric haemorrhage on the healthcare system. Furthermore, it reveals the current inconsistencies and subjectivity in assessing maternal blood loss. This research underscores the necessity for standardized, accurate, and rapid quantification methods to ensure timely diagnosis and management of obstetric haemorrhage. It sets the stage for future advancements in obstetric care, emphasizing the

importance of incorporating novel technologies to enhance patient outcomes and mitigate the global affliction of obstetric haemorrhage.

CHAPTER ONE – INTRODUCTION

Obstetric or maternal haemorrhage is a clinical problem of utmost importance to healthcare professionals and patients. It is abnormal bleeding which can present in early pregnancy and up to 42 days following birth (Figure 1). Commonly, obstetric haemorrhage appears as frank vaginal bleeding, but the condition can also present as intra-abdominal bleeding. Other accompanying symptoms include abdominal pain, nausea and vomiting, diarrhoea, fever or reduced foetal movement[1]. In its most severe forms, obstetric haemorrhage can cause acute circulatory failure which in turn could result in end-organ injury, use of blood transfusions, emergency surgery, psychological morbidity or even death.

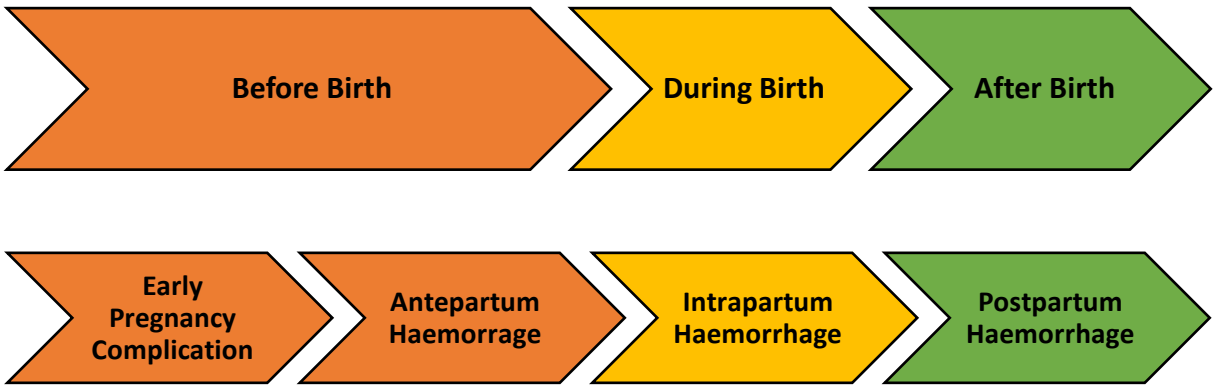

Figure 1 - Obstetric haemorrhage in relation to time in pregnancy.

In early pregnancy, obstetric haemorrhage can present in the context of early pregnancy complications such as miscarriage, ectopic pregnancy or subchorionic haematoma[2,3]. In mid to late pregnancy, obstetric haemorrhage is termed antepartum haemorrhage (APH)[4]. The causes of APH include abnormal placentation such as placental abruption, placenta previa or

placenta accreta spectrum (PAS) disorders[4]. However, the cause of APH is also frequently unexplained[5].

Obstetric haemorrhage during delivery and following birth is termed intrapartum haemorrhage and postpartum haemorrhage (PPH) respectively. PPH is the most common type of obstetric haemorrhage and is further subclassified as primary or secondary PPH. Primary PPH occurs within 24 hours from delivery and can be caused by uterine atony, retained placenta, tissue injury or defects in the haemostasis pathways[6]. Secondary PPH arises more than 24 hours and can present up 42 days following birth and is commonly due to endometritis or retained products of conception[6].

1.1 Defining obstetric haemorrhage

At present, there is no universal definition of what constitutes abnormal bleeding in pregnancy and here we describe the different methods of classifying abnormal bleeding (Figure 2).

1.1.1 Volume-based definitions

A common way of describing abnormal bleeding in pregnancy refers to the perceived volume of blood lost. In the context of PPH, a threshold of 500mL or more was first proposed in 1989 through expert consensus at a World Health Organization (WHO) meeting[7]. In 2011, the WHO added a definition for *Severe* PPH which is defined as greater than 1000mL blood lost[8]. Other similar volume-based definitions are endorsed by professional societies[9]. The Royal College

of Physicians of Ireland (RCPI) defines PPH as *Minor* if blood lost is between 500-1000mL, and *Major* if blood lost in greater than 1000mL[10,11]. The Royal College of Obstetricians and Gynaecologists (RCOG) classify blood lost amounting to 500-1000mL, 1001-2000mL and more than 2000mL as *Minor*, *Moderate* and *Severe* PPH respectively[12]. The American College of Obstetricians and Gynecologists (ACOG) have a higher volume threshold for PPH diagnosis and is described as more than 1000mL blood lost[13].

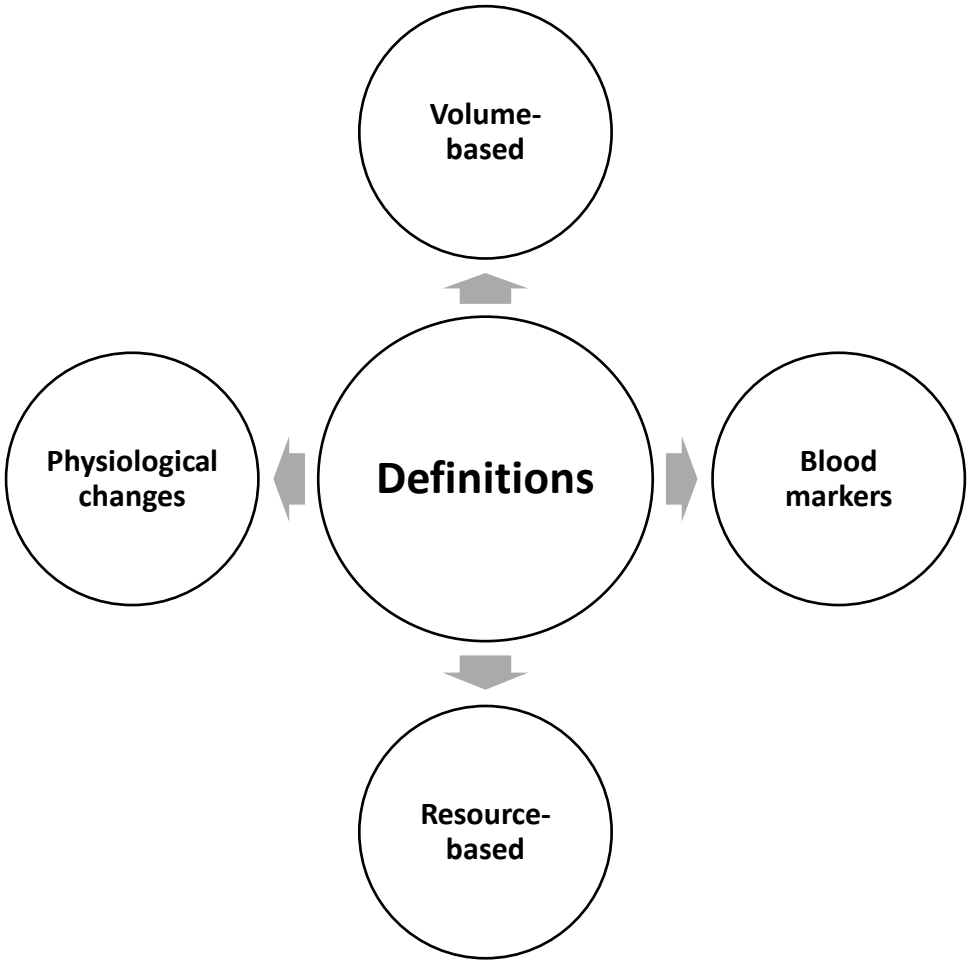

Figure 2 - Types of definitions for obstetric haemorrhage.

With regards to APH, there is no described volume of blood loss needed to make the diagnosis and it could range from streaking or blood spotting noted on underwear or sanitary protection to higher volumes[14]. Subcategories of APH have been used in literature such as significant APH or non-substantial APH[15]. However, it is unclear if these descriptors are used to illustrate a volume of blood loss, or if it is used to highlight the presence or absence of antenatal findings like placental disorders. The RCOG guideline on APH uses blood loss volumes to describe the *severity* of APH as: minor haemorrhage (<50mL), major haemorrhage (50-1000mL) and severe haemorrhage (>1000mL)[14]. When no cause is identified for the APH, the term unexplained APH may be used[14]. Recurrent APH is the term used to describe multiple APH episodes in the same pregnancy[14].

As large volume obstetric haemorrhage could lead to severe illness associated with prolonged hospital stay and high case fatality, it is commonly included among a set of other maternal conditions contributing to Severe Maternal Morbidity (SMM)[16]. For the purpose of national auditing and disease coding, the volume limit for when haemorrhage results in a SMM differs between countries. Ireland adopted the greater than 2500mL blood lost used to classify Major or Massive Obstetric Haemorrhage (MOH) described in the Scottish audit of SMM[17,18]. But, blood loss volume thresholds as low as 1500mL have been used to describe MOH for SMM national reviews like in Pacific Asia[19]. The worldwide differences in the definition of MOH is to due variations in healthcare infrastructure, population characteristics (e.g. prevalence of maternal anaemia), and access to blood transfusion and surgical interventions.

1.1.2 Definitions based on physiological changes

The effects of intravascular volume depletion and loss of red cell mass from haemorrhage results in physiological changes to the host, which presents as changes in vital signs and mental status[20]. This adaptation was included by most professional societies as an important consideration, were any bleeding that results in the signs and symptoms of hypovolemia would diagnose haemorrhage regardless of the perceived volume of bleeding[9-14]. However, in most healthy individuals, these signs and symptoms are subtle, especially with occult and concealed bleeding, as the compensatory response mechanisms to haemorrhage are robust. The American College of Surgeons Committee on Trauma classifications on haemorrhagic shock note that hypotension may not be apparent until more that 30% of the patient's blood volume has been lost[21]. This corresponds to more than 1500mL blood lost in a 70kg (male) patient. However, estimating circulating blood volume and percentage of blood volume lost may be more accurate by using maternal body mass index (BMI) rather than weight[22]. Current linear calculations used to estimate circulating blood volumes based on patient weights leads to overestimation of the percentage of blood lost, as blood volume increases at a disproportional rate to body composition in these models[22]. A curvilinear model based on anthropometric data may limit underestimation of percentage of blood loss in patients with low BMI and prevent overestimation in patients with obesity[22]. For example, a 70kg patient would have an estimated total circulating blood volume of 7000mL in a linear model which does not consider height (assuming 100mL/kg). However; in a curvilinear model, a 70kg tall patient with a BMI of 20 kg/m^2 (healthy BMI) has a total estimated circulating blood volume of 6650mL, while a 70kg short patient with a BMI of $40kg/m^2$ (severe obesity BMI) has a total estimated circulating blood volume of 4900mL[22]. Therefore, the deference in total estimated circulating blood volume between a tall and short 70kg patient is 1750mL.

The ratio of heart rate to systolic blood pressure or Shock Index (SI) has been proposed as an earlier marker of haemodynamic compromise than conventional vital signs[23]. Studies within the non-pregnant population have demonstrated that SI values greater than 0.9 are associated with intensive care management, blood transfusion and a high risk for mortality[23]. Similar SI thresholds have been shown within studies on obstetric patients; however, the optimal SI threshold for when to first alert health professionals is the subject of validation studies on PPH early warning systems[24].

1.1.3 Definitions based on blood markers

Definitions using blood markers compare haemoglobin (Hb) concentration or haematocrit (Hct) levels before and after birth (peripartum change). Though routine Hb level screening following delivery might not be cost-effective, it may prove beneficial when bleeding is concealed or insidious and could account for the inaccuracies of blood loss measurements (see Section 1.3). Studies on undiagnosed or missed PPH suggest that a peripartum Hb level change ≥ 2g/dL corresponds to at least 500mL blood loss; and a peripartum Hct ≥ 10% corresponds to at least 1000mL blood loss[25,26]. The optimal time point for testing of postpartum Hb or Hct levels is controversial as complex haematinic and haemodynamic changes occur normally in the postpartum period, which can take up to seven days for these changes to reach equilibrium[27]. Delaying measurement of Hb or Hct levels also causes logistical challenges as hospital discharge commonly occurs within a few days following vaginal delivery and between three to five days following uncomplicated caesarean delivery. Regardless, the British Society for Haematology recommends that postnatal Hb testing take

place within 48 hours of delivery if blood loss exceeds 500mL or if signs and symptoms of postpartum anaemia are present[28].

Impairments to haemostasis can occur in haemorrhage scenarios and this could be assessed by measuring blood prothrombin time (PT), activated partial thromboplastin time (aPTT), Clauss fibrinogen and platelet counts. Studies suggest that low fibrinogen levels are the earliest predictor of haemorrhage progression[29]. Early coagulopathies in obstetric haemorrhage are associated with cases of placental abruption, severe infection or pre-eclampsia; however, bleeding of any aetiology could lead to coagulopathy where underestimation of volume blood loss or delayed diagnosis of haemorrhage occurs[30]. The presence of coagulation defects following obstetric haemorrhage have been used to define MOH in several national SMM audits worldwide such as thrombocytopenia (platelets < 75 x 10^9/L), prolonged PT/aPTT (ratio > 1.5 x normal) or hypofibrinogenemia (< 2g/L) since treatment for coagulopathy would typically be provided[16,17,31].

1.1.4 Definitions based on resources used

Blood components may be used to replace blood lost or correct coagulation defects due to haemorrhage. In Ireland, receiving five or more units of blood or receiving treatment for coagulopathy (e.g. fresh frozen plasma, platelets or cryoprecipitate) means that the patient experienced MOH. In contrast, Canadian definitions for severe haemorrhage only require the patient to receive a single transfusion[17,32]. In some SMM reports, severe haemorrhage is also defined as whether a procedural intervention was needed to manage bleeding like curettage or hysterectomy[31,32].

1.2 Epidemiology of obstetric haemorrhage

It is important to have a standard definition for obstetric haemorrhage as it allows for better assessment and comparisons of disease incidence worldwide. But irrespective of the definition used, the incidence of obstetric haemorrhage is increasing internationally with PPH rather than APH contributing to the majority of cases[33]. The rate of PPH has increased from 2.7 to 8 cases per 100 deliveries between 2011 and 2018 in Ireland with similar trends reported in other high-income countries such as USA, Canada and Australia[34-37]. Delayed recognition of obstetric haemorrhage could be contributing to growing obstetric haemorrhage rates[38]. As the currently endorsed definition of obstetric haemorrhage in Ireland are volume-based, it is important to have an accurate and standardised approach to measuring maternal blood loss[10,11]. To address rising rates of obstetric haemorrhage in Ireland, the National Women and Infants Health Programme (NWIHP) and the National Perinatal Epidemiology Centre (NPEC), have developed a national quality improvement initiative[39]. This initiative includes the development of a standardised national approach to measuring maternal blood loss[39].

Having a standardised definition for obstetric haemorrhage also allows for better understanding of the risk factors of obstetric haemorrhage. The rise in obstetric haemorrhage and associated morbidity could be due to increasing prevalence of some maternal risk factors for obstetric haemorrhage such as delayed childbearing, conception thought artificial reproductive technology, post-term deliveries and obesity (BMI ≥ 30 kg/m^2)[38]. An Irish audit

considering Robson-Ten Grouping* of obstetric haemorrhage patients with blood loss greater than 2500mL found that patients with multiple pregnancies and preterm births were the largest contributors to obstetric haemorrhage rates[39]. Furthermore, women with obesity were approximately 50% more likely of experiencing obstetric haemorrhage in Ireland[39]. However, one Swedish study found that the distribution of risk factors did not differ significantly among obstetric population subgroups classified according to the Robson Ten-Group criteria[41]. The study identified increasing trends of PPH among all Robson Ten-Groups with the largest contributor to PPH rates surprisingly being nulliparous women with spontaneous labour onset[41]. The definition of PPH in this study was blood loss greater than 1000mL[41]. Intrapartum factors like duration of labour and labour augmentation with oxytocin could be driving PPH rates in this cohort. Therefore, differences in obstetric haemorrhage definitions would impact risk factor interpretation and global comparisons.

Globally, obstetric haemorrhage is a leading cause of SMM in both high and low-income countries; however maternal mortality due to haemorrhage is higher in low-income countries[33]. Again, maternal mortality is mostly the result of PPH rather than APH[33]. Worldwide, it is reported that one woman dies from PPH every seven minutes[6]. More than two-thirds (69%) of global maternal deaths occur in the African region with obstetric haemorrhage as the leading cause (28.8%)[42]. Countries with extremely high maternal mortality rates are South Sudan with 1223 deaths, followed by Chad with 1063 deaths and Nigeria with 1047 deaths per 100 000 live births[42]. Ireland has a maternal mortality rate of 6.3

* Robson Ten-Group Criteria is an obstetric population classification system based on: gestational age, parity, previous caesarean delivery, onset of labour, plurality and foetal presentation[40].

per 100,000 maternities (95% CI 3.2–11.3) with no maternal deaths attributed to obstetric haemorrhage for the triennium 2019 to 2021[43]. The last reported cases of maternal deaths due to haemorrhage in Ireland were in triennium 2009-2012 (two cases)[43].

Maternal deaths due to obstetric haemorrhage in low-income countries could be explained by the "Three Delays" model first described in 1994[44]. Delay one is the delay in seeking care which could be due to the woman's socioeconomic status. Delay two is the delay in reaching healthcare facilities which could be due to poor transport infrastructure especially in remote locations. Delay three is the delay in receiving high quality care at the healthcare facility and could be due to resource shortages or treatment by inexperienced healthcare providers. Countries which address obstetric haemorrhage mortality through the Three Delays model may reduce maternal mortality rates to a rate that similar to developed countries. For example, maternal deaths from obstetric haemorrhage in Japan has reduced from 29% to 7% during an eight-year period (2010 to 2017) by improving healthcare quality alone (the third delay) such as improved monitoring of maternal bleeding[45]. This was achieved through annual recommendations and simulation programs aimed at improving the practices of obstetric care providers organised by the Japan Association of Obstetricians and Gynecologists and the Maternal Death Exploratory Committee (JMDEC)[45].

1.3 Conclusion

Obstetric haemorrhage can present at any point in the pregnancy with differing aetiologies. There are multiple ways of defining obstetric haemorrhage and its incidence is rising. It is a major contributor to maternal morbidity and mortality with PPH accounting for the majority of cases. Timely recognition of obstetric haemorrhage is needed to prevent morbidity and mortality; however, other key principles of effective management include: the early identification of at-risk women, prevention measures and a team approach to treatment. We next focus on how obstetric blood loss is diagnosed through maternal blood loss quantification and highlight the importance of a standardised approach to blood loss measurement.

CHAPTER TWO – BLOOD LOSS QUANTIFICATION AND STANDERDISATION

The normal rate of blood flow to the uterus in a nonpregnant patient is approximately 60ml/min and this increases to approximately 600ml/min in the gravid uterus at full term[46]. Therefore, obstetric haemorrhage of uterine origin can progress quickly and critical to the recognition of obstetric haemorrhage is prompt and accurate assessment of blood loss. Several methods have been described to measure and calculate blood loss each with their own strengths and limitations (Table 1).

2.1 The subjective method

A visual assessment of blood loss by the healthcare professional is commonly used and is often referred to as the subjective method[47]. It involves periodic assessment of the field for blood which includes physical examination of the patient and examination of the surrounding area. It is convenient and easy to perform; however, the literature is replete with studies demonstrating the inaccuracies of the visual assessment technique[48,49]. There is also high variability between healthcare professionals in reporting blood loss when using this approach and this is shown in both clinical and simulated scenarios[50]. Healthcare professionals tend to overestimate blood loss when the amount of bleeding is low and underestimate blood loss when the amount of bleeding is high[50]. Training and the use of visual aid guides can enhance the precision of visual assessment; however, this improvement was transient with significant worsening of the accuracy over time[51].

Table 1 - Summary of described methods for quantifying blood loss.

Method	Description	Advantages	Disadvantages
Subjective or clinical judgement	Visual assessment of blood loss.	Free. No resources needed.	Inaccurate. Variance across professionals.
Gravimetry	Compare weight of blood soiled objects with dry weight. Assume grams of weight gained equivalent to blood loss in millilitres.	More accurate than visual estimation.	Resources needed. Time consuming. Cannot distinguish between blood from mixed fluids leading to overestimation.
Volumetry	Measure volume of blood loss through calibrated drapes, trays or canisters.	More accurate than visual estimation. Faster assessment that gravimetry.	Resources needed. Cannot distinguish between blood from mixed fluids leading to overestimation
Assay	Divide haemoglobin (Hb) mass of fluid mixture with the patient's preoperative Hb concentration to determine blood loss. Utilizes spectrometry or colorimetry.	Highly accurate.	Involves laboratory procedures. Time consuming. Impractical. Expensive.

Blood loss formulas	Calculate patient total circulating blood volume and determine blood loss by considering changes in haematocrit (Hct).	Considers Hct changes.	Requires estimation of total circulating blood volume. Requires blood specimens before and after bleeding event. Dependent on accuracy of Hct determination.
Haemoglobin (Hb) or Haematocrit (Hct) monitoring.	Measure patient's Hb or Hct before and after bleeding event. Monitoring can be continuous.	Can be non-invasive and real-time.	Does not consider blood loss. May require blood specimens before and after bleeding event.
Sonography	Measure inferior vena cava diameter (IVC).	Can aid in predicting postpartum anaemia.	Not established. Resources needed. Time consuming.

2.2 Objective methods

In an attempt to improve the accuracy of blood loss assessment, more objective approaches are utilized and here we describe these methods.

2.2.1 Gravimetry and Volumetry

The gravimetric technique involves weighing of blood soiled items such as surgical sponges, towels or drapes and are then compared against their dry weight[52]. Since blood has a similar density to water (1 g/mL), each gram gained after weighing the blood contaminated item corresponds to an equivalent gain of volume of blood in millilitres[53]. The volumetric technique, also known as "direct measurement", uses surgical suction canisters or specialized collection bags/drapes that collect fluid volume[47]. The accuracy of the volumetric approach is improved when these fluid receptacles are graduated or have calibrated markings corresponding to volume[54,55]. During vaginal delivery, a collector bag or tray is placed under the woman's buttocks which collects all mixed liquids. In the setting of a caesarean delivery, at uterine incision the canister volume is recorded (V_1). After all amniotic fluid or irrigation fluid is aspirated, as second measurement of the canister volume is recorded (V_2). A third and final measurement of the canister volume is recorded at the end of the procedure which corresponds to the total fluid collected (V_3). The amount of blood is then calculated by: Blood Volume = $(V_3 – V_2) + (V_2 – V_1)$.

Several studies have demonstrated that gravimetry and volumetry are more accurate than visual assessment in determining blood loss[55,57]. Both gravimetry and volumetry can be combined for a full assessment of blood loss and this is commonly referred as the

"quantitative method"[58]. The quantitative method is currently the recommended approach to determining blood loss by multiple organizations[10-13,58]. The quantitative method however is time consuming and the presence of non-sanguineous fluids like amniotic fluid, ascites or irrigation fluids can decrease its accuracy.

2.2.2 Assay methods

Assay methods could be used to filter or separate the blood components of fluid mixtures. Haemoglobin (Hb), a protein unique to blood cells, is commonly used to identify blood in fluid mixtures with the assay approach[59]. The assay method requires that the patient's pre-delivery Hb concentration is known and this could be determined using any lab-based or point-of-care haematology analyser.

A photometer or spectrometer could be used to determine the Hb content of the fluid mixture[47]. If the fluid mixture is collected in canisters, the canister Hb concentration (g/dL) is determined with the photometer/spectrometer and then canister Hb mass is calculated by multiplying the canister Hb concentration with the canister volume. Finally, the volume of blood in the canister is determined by dividing the canister Hb mass by the patient's pre-delivery Hb concentration. If the fluid mixture is collected in sponges rather than canisters, the sponges are first rinsed with saline solution to extract the blood[59,60]. The volume of blood of the rinsed solution is then calculated as previously described with the canisters. The yield rate of Hb from the rinsed sponges varies according to the extraction method used. Up to 90% of blood could be extracted from the sponges through manual compression while up to 99% of blood could be extracted by using a centrifuge[60,61]. The information gained from the canisters and sponges can be summed to obtain the total volume of blood lost.

Another way to determine Hb content of a fluid mixtures utilizes colorimetric or image analysis. An example of this is the smartphone or tablet computer application Triton™ first developed by Gauss Surgical Inc. which calculates blood loss by analysing photographs of used surgical sponges and canisters[61]. The technology is similar to facial recognition technology and software uses machine learning to process the photographs.

The assay methods are more accurate than the quantitative method or visual estimation and are often used in studies as reference standards to study and compare novel approaches to blood loss measurement[47,60-61]. Furthermore, the assay methods are more reproducible and further reduces observer bias[47]. However, it is time consuming and requires more resources and training which could be costly. In addition, it assumes that the patients Hb concentration remains constant during delivery. For example, the patient's Hb concentration can vary at delivery due to intravenous fluid administration, which could progressively dilute the patient's blood. This in turn affect the accuracy of blood loss assessment.

2.2.3 Blood loss formulas

Several mathematical formulas have been described to calculate blood loss by using changes in haematocrit (Hct) levels[62]. These equations initially require the estimation of the patient's total blood volume by using variables like weight (kg), height (cm) and sex in the case of Nadler's formula and the formula described by the International Council for Standardization in Haematology (ICSH)[63,64]. Moore's formula uses "build" rather than height and has values

assigned for obese, thin, normal and muscular body types to estimate the patient's total blood volume[65]. Following total blood volume estimation, blood loss is estimated by factoring in the difference in Hct following a bleeding event. Formulas described by Bourke and Gross use the initial Hct, final Hct and mean Hct their calculations[62,66]. The Mercuriali equation specifies that the final Hct level be measured on day 5 following a bleeding event[67]. Some formulas include adjustments for blood transfusion as in the Mercuriali and Casamara equations[67,68]. Unfortunately, there is no gold standard formula for total blood volume estimation or blood loss estimation; and these calculations would be impractical and challenging to perform promptly in acute heavy bleeding situations.

2.2.4 Using other clinical surrogates for blood loss

The subjective and objective methods described above aim to provide the healthcare professional a blood loss *volume* measurement as the endorsed definitions of haemorrhage are commonly volume-based. However, there are other clinical surrogates for blood loss which consider the other non-volume definitions of haemorrhage.

2.2.4.1 Hb or Hct monitoring

Rather than quantifying blood loss volume, it may be more useful to monitor changes in Hb or Hct during a bleeding event through patient blood sample testing. For example, blood transfusion triggers were based on Hb or Hct thresholds (or the presence of symptoms of anaemia). Traditionally, the rule of "10/30" was followed in surgical patients, were a Hb level less that 10g/dL or Hct level below 30% would suggest the need for red blood cell

transfusion[69]. Measuring of Hb or Hct values could be done through point-of-care haematology analysers[70]. However, there would be a delay in obtaining test results and repeated testing would be required in situations where bleeding is uncontrolled and ongoing. Continuous non-invasive Hb monitoring (SpHb) have been described, which provided real-time information of the patient's Hb status through spectrophotometry[71]. Studies within nonpregnant patients have shown that SpHb can reduce delays in decisions to transfuse and decrease the number of blood transfusions received[72]. A study in postpartum patients however demonstrated that SpHb was poorly associated with the quantity of blood loss within 30min since delivery, but there was an association with blood loss over longer time periods (60 and 120 min)[73]. Physiological redistribution of blood volume could account for this delay. It is also possible that SpHb could be influenced by haemodilution caused by intravenous fluid administration. Improvements to SpHb monitoring could provide better live information on the patient's Hb status and could be a promising method of assisting decisions for blood transfusions.

2.2.4.2 Sonography

Use of ultrasound have been illustrated in several studies on obstetric haemorrhage. Ultrasound measurement of the inferior vena cava (IVC) diameter has been described as a method of predicting severe postpartum anaemia[74]. This involves visualizing the IVC at its hepatic portion in the sagittal plane by placing the ultrasound transducer at the upper abdomen. The maximum inner diameter of the IVC during inspiration and expiration is then recorded. Diameters of 5.3mm during inspiration and 7mm at expiration were identified as good thresholds for predicting Hb less than 7g/dL (sensitivity: 71-71.4%, positive predictive

value: 35.7-38.4%, negative predictive value: 97.1%)[75]. A Japanese study using contrast-enhanced ultrasound of the uterine cavity found a correlation between the time until leaking of contrast agents into the uterine cavity with the amount of bleeding[76]. However, ultrasound assessment for the rapid diagnosis of obstetric haemorrhage (rather than assisting in identifying the cause of haemorrhage, like retained products of conception) is not currently established in clinical practice and is the subject of further testing.

2.3 The "ideal" method

As described above, the literature presents us with multiple approaches to blood loss quantification. An ideal method should not only be accurate in evaluating blood loss, but also allow for the prompt diagnosis of obstetric haemorrhage and provide real-time information of the patient's condition by alerting healthcare professionals of haemorrhage progression or clinical deterioration. This may possibly be achieved through blood loss quantifying technology. Novel blood quantification technology should be minimally invasive, user friendly and require minimal training for use. New instruments should allow for patient individualization by considering the patients total blood volume, Hb levels and factor the effects haemodilution or blood transfusion. As much of the morbidity and mortality associated with maternal haemorrhage is experienced in low-income countries, new blood quantification tools should also be cost-effective. Ultimately, the implementation of new blood quantification strategies should translate to a reduction in obstetric haemorrhage rates and its associated complications.

2.4 Standardisation of obstetric blood loss quantification

Objective maternal blood loss quantification could allow for earlier detection of obstetric haemorrhage[77]. Methods for quantifying obstetric blood loss objectively includes volumetry, gravimetry, colorimetry or combined approaches and are summarised in Table 1. Standardisation refers to the establishment of and adherence to a set of uniform healthcare protocols or methods (in the context of health policy, management and administration)[78]. Standardisation can reduce error and unnecessary variation[78,79]. We explore how standardisation to the detection of obstetric haemorrhage reduces haemorrhagic morbidity rates.

2.4.1 Checklists and bundles

Standardisation is an intuitive solution to many challenges to quality and safety in healthcare. Lack of a standardised process of blood loss measurement and communication can lead to delays in the response to acute haemorrhage[80]. The implementation of obstetric haemorrhage safety checklists and bundles in maternity care is seen as an effort to standardise the recognition and management of obstetric haemorrhage[80]. Checklists and bundles can help with the adherence to the established healthcare standards[81]. *Checklists* were first developed by World War II pilots to improve adherence to guidelines and reduce human error under stressful circumstances which reduced aviation related accidents[82]. In healthcare, checklists can serve as memory aids and ensure that essential steps in care are not overlooked[82]. *Bundles* are sets of individual evidence-based practices that, when grouped together, improve patient outcomes[81].

Standardisation of obstetric blood loss quantification was part of a PPH quality improvement programme in Wales which has reduced the incidence of MOH from 6.4 to 4.9 per 1000 maternities[84,85]. In the Welsh initiative, obstetric blood loss was measured through both volumetry and gravimetry[84,85]. The programme also included obstetric blood loss risk assessment, prompt escalation to senior clinicians and use of point-of-care testing for targeted blood component therapy[84,85]. The E-MOTIVE study was international, cluster randomised trial, with approximately 100,000 patients per study group, demonstrated a 60% reduction in risk of the composite of three clinical outcomes following vaginal birth (severe PPH, laparotomy or maternal death for bleeding) when a PPH bundle was used compared with usual care[85]. The method of blood loss quantification used in this trial was a volumetric, using a calibrated blood-collection drape[86]. Like the E-MOTIVE trial, the recently published recommendations on PPH bundles by the WHO advocates for routine objective measurement of postpartum blood loss through for calibrated drapes in vaginal delivery to improve the detection of PPH[87]. In contrast, an obstetric haemorrhage bundle developed by The National Partnership for Maternity Safety, Council on Patient Safety in Women's Health Care in the United States advises that cumulative blood loss measurements should be formal and quantitative and recommends using gravimetry after vaginal delivery instead[88,89].

2.4.2 Standardisation barriers

Though objective measurement of maternal blood loss is a necessary part of these bundles, barriers to the standardised use of these methods exist in obstetric care[90]. We classify barriers to standardized obstetric blood loss quantification into two categories: system-level and human-level (Figure 3). System level factors refers to the division and lack of coordination among different components of the healthcare system. In fragmented systems, achieving

consensus and adherence to standards can be difficult, as different providers may have varying practices and priorities. Human related factors refer to barriers at the level of the health provider that prevent them from adhering to standardised obstetric blood loss quantification.

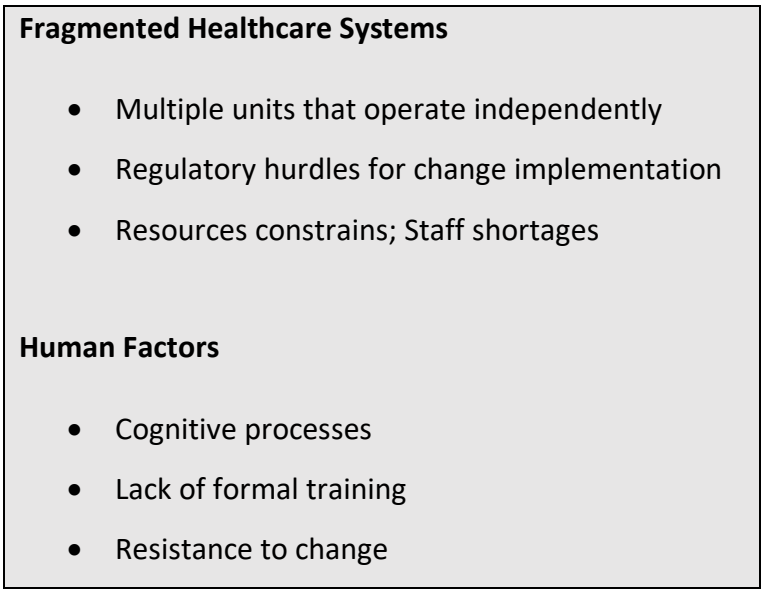

Figure 3 - Barriers to standardised objective obstetric blood loss quantification.

2.4.2.1 Fragmented healthcare systems

In fragmented healthcare systems, patients often receive care from units or providers each with their own definition of what obstetric blood loss measurement entails. A survey of all Irish maternity units done by the National Perinatal Epidemiology Centre (NPEC) showed national variations in the measurement of maternal blood loss following delivery (Table 2). This could be due to a lack of a national description for the requirements of objective obstetric blood loss quantification. Furthermore, healthcare training in Ireland may require persons to

relocate to different hospitals which could allow flawed practices from one unit to appear in another unit.

Table 2 - Percentage of Irish maternity units and their method of maternal blood loss quantification according to mode of delivery (with permission from the National Perinatal Epidemiology Centre, Ireland).

Method of maternal blood loss quantification	Mode of delivery	
	Vaginal delivery	Caesarean delivery
Combined volumetry and gravimetry	63% (12/19)	74% (14/19)
Volumetry and visual estimation	11% (2/19)	11% (2/19)
Visual estimation only	26% (5/19)	15% (3/19)

Standardizing care in such an environment is challenging because it requires aligning practices and processes across various networks. The process of implementing national change in this setting may be delayed due to regulatory hurdles. Regulatory hurdles, while essential for ensuring patient safety and quality of care, can sometimes create challenges for standardization efforts. For instance, regulations may require specific documentation or meetings prior to the implementation of standard practices. This can lead to a compliance burden for providers and discourage the adoption of standardized practices.

2.4.2.2 Human factors

Multiple training programmes in Ireland exist for the safe provision of care such as hand hygiene and haemovigilance education, yet there is no formal training programme for objective maternal blood loss quantification. Obstetric emergency training like the PRactical Obstetric Multi-Professional Training (PROMPT) for PPH focus more on the standardised management of PPH rather than objective maternal blood loss quantification. A formal training programme on objective maternal blood loss quantification may translate to standardised assessment of maternal bleeding status across the country. Healthcare professionals may resist standardization efforts due to concerns about autonomy, workflow disruptions, or the perception that one-size-fits-all approaches may not meet the unique needs of their patients[79]. In this context, efforts to protect the status quo may delay the implementation of standardized obstetric blood loss quantification. Implementing standardized care often requires significant investments in training, technology, process redesign and adequate staffing[90]. Units may be hesitant to allocate resources to these endeavours, especially if they perceive potential disruptions to their daily operations. Resistance may also stem from organizational inertia, where longstanding practices and traditions are difficult to modify, and there may be a preference to avoid upheaval. Additionally, leaders within healthcare organizations may be resistant to change if they are not convinced of the benefits or if they perceive it as a high-risk endeavour.

2.5 Possible solutions

Firstly, a national consensus defining objective blood loss measurement is needed. At present, it is the opinion of the author to utilize both volumetry and gravimetry in all deliveries to measure maternal blood loss. A suggested approach is detailed on Appendix 1 and 2 for vaginal deliveries.

Secondly, a national consensus on the frequency of measurement following birth is needed. If healthcare professionals focus on achieving an "accurate" blood loss measurement value rather than a "timely" measurement value, it can result in failed recognition of acute haemorrhage. Poorly utilizing objective measurements may paradoxically delay rather than prompt an emergency response as healthcare providers may wait until a certain proven value of blood loss has occurred. An accurate measurement that does not facilitate the early escalation of care is not useful. Therefore, we suggest five interval assessments around the time of delivery: prior to delivery, immediately following delivery, following delivery of the placenta, at 5min and 10min following delivery. Another assessment is warranted prior to discharging the woman from the delivery suite followed by daily assessments until hospital discharge. Any change in haemodynamic status should also prompt an assessment of bleeding status.

Until a novel blood loss quantifying tool is available, regular formal training and education in objective blood loss measurement will ensure that this clinical skill is maintained and remains consistent. Hospital managers and administrators should also ensure appropriate staffing and resources are available to minimise practice modification. Lastly, exploring and studying novel

blood loss quantifying technology may help identify innovative methods which may further address human related factors impairing standardised and objective maternal blood loss measurement.

2.6 Conclusion

Quantification of blood loss is an important part of obstetric practice and the current supported approach to blood loss evaluation is the quantitative method. Other techniques have been described which report better accuracy in quantifying blood loss and improved detection of obstetric haemorrhage but are limited by clinical practicality especially during acute and rapid bleeding situations. We described possible barriers to standardised and objective maternal blood loss quantification and suggest possible solutions. Recognizing and understanding these barriers can help support future efforts focused on reducing maternal morbidity and mortality due to haemorrhage and improve the overall quality of maternity care.

CHAPTER FOUR – OBSERVATIONAL STUDY ON OBSTETRIC BLOOD LOSS QUANTIFICATION

To demonstrate barriers to standardised maternal blood loss measurement in real-time clinical practice, we describe a prospective observational study on Caesarean births. Caesarean births provide a controlled environment where healthcare providers can closely monitor maternal blood loss due to the surgical setting and need for meticulous record-keeping. This makes it an ideal scenario to study the nuances of obstetric blood loss quantification. This project focuses on developing our understanding of blood loss evaluation from the perspective of those involved in the process.

4.1 Methods

4.1.1 Study design and setting

This study was a single institution prospective study performed at Cork Maternity University Hospital, Cork, Ireland. Data was collected by a single investigator over the study period through direct observation of theatre activities. We studied Caesarean deliveries occurring on Mondays and Wednesdays from August 1st to October 31st, 2022, to reflect weekday working hours. The data collector had no involvement in the scheduling of elective Caesarean deliveries or decisions for emergency Caesarean deliveries. The data collector did not allocate the surgeons, anaesthetists, midwifery or nursing staff to the obstetric theatre lists. Cases requiring respiratory or contact isolation were excluded for infection control precautions and to avoid a lengthy decontamination process. Caesarean section patients routinely receive oxytocin intravenously for the prevention of PPH. Theatre staff were blinded to the data

collected. Ethical approval for the study was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (Ref: ECM 5 (4) 02/12/2021 and ECM 4 (h) 19/10/2021).

4.1.2 Data collection

Patients were categorised into low, medium and high risk for PPH according to the California Maternal Quality Care Collaborative (CMQCC) risk assessment tool[58]. We used the patients' medical records to record demographic data including patients' age, gravida, parity, gestation, body mass index (kg/m^2) and type of pregnancy (singleton vs multiple). The urgency of the Caesarean section delivery was classified as elective or emergency. We documented the type of anaesthesia received. Years of experience of the primary surgeon in obstetrics (<3 years, 3-9 years or >9 years) and the number of surgical assistants needed were recorded (excluding the scrub nurse).

The operating time (minutes) was defined as the time between start of skin incision to complete skin closure. To study staff and theatre utilization in measuring obstetric blood loss, we recorded the number of surgical swabs and the volume of fluid waste (mL) obtained through suctioning. The time spent (seconds) swabbing and suctioning blood loss were recorded as percentages of operating time. We recorded whether swabs soiled with blood were weighed to assist in calculating blood loss. Swabs used for packing the abdomen to obtain better surgical exposure were not considered for the analyses. The number of staff involved in calculating blood loss, the number of revisions to blood loss measurements and

time spent documenting blood loss (minutes) were documented. We recorded the final cumulative blood loss (mL) using the sum of estimated blood volume in canisters and swabs.

4.1.3 Data analysis

Data was recorded using Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA). All statistical analysis was performed using SPSS 28 (IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk Test was used to study the normal distribution of the data. Parametric data is presented as mean $\pm$ standard deviation and nonparametric data is presented as median with range.

4.2 Results

4.2.1 Demographic information

During the three-month study period, we studied 100 Caesarean deliveries. A total of 27 patients were classified as low risk for obstetrics haemorrhage according to the CMQCC assessment tool, while 54 patients and 19 patients were classified as medium and high risk respectively. Patients who are medium and high risk tended to be multiparous but there were no significant differences between groups with regards to patient age, delivery gestation, BMI and total delivery weights (Table 5). Multiple pregnancies were found in 2% (1) of patients classified as medium risk and 32% (6) of patients classified as high risk.

Table 5 - Patient demographics and Caesarean delivery indication according to obstetric haemorrhage risk category. Data presented as mean ± standard deviation or median (range).

	Obstetric Haemorrhage Risk Category		
	Low (n=27)	**Medium (n=54)**	**High (n=19)**
Age (Years)	35 ± 5	36 ± 4	35 ± 4
Gravida (n)	1 (1 – 6)	3 (1 – 6)	3 (1 – 6)
Parity (n)	0 (0 – 2)	1 (0 – 4)	1 (0 – 4)
BMI (kg/m^2)	28 (22 – 40)	27 (19 – 47)	29 (20 – 44)
Gestation (Week^{+Day})	38^{+5} (37^{+0} – 41^{+3})	38^{+5} (37^{+0} – 41^{+0})	38^{+0} (32^{+3} – 41^{+3})
Multiple Gestation (n)	0	1	6
Total Delivery Weight (kg)	3.52 (2.28 – 4.16)	3.44 (2.86 – 4.86)	3.70 (2.32 – 5.38)
Delivery Indication (n)			
Elective	17	51	14
Emergency	10	3	5

The reason for Caesarean delivery was elective in the majority (82%) of cases reflecting daytime working hours, while 18% of patients had emergency Caesarean deliveries. All patients received a spinal anaesthetic and only one patient was converted to general anaesthesia. The primary surgeon's experience was <9 years in approximately half (57%) of patients. One surgical assistant was needed in most (86%) cases. In addition to the Caesarean sections, four patients had tubal sterilization procedures, one patient had adhesiolysis of bowel adhesions, one patient had an ovarian cystectomy, and one patient needed Caesarean

hysterectomy to manage antenatally diagnosed placenta accreta spectrum (PAS) disease and major obstetric haemorrhage.

4.2.2 Blood loss evaluation

The median estimated blood loss was 450mL (300 – 2000), 400mL (300 – 850) and 500mL (400 – 5700) in low, medium and high-risk patients respectively (Figure 5). Approximately one third (39%) of patients had >500mL blood loss and only one patient had >2500mL blood loss and required intraoperative blood transfusion. To measure blood loss, both subjective and objective methods were used. A median number of two persons (in addition to the primary surgeon) were involved in measuring and calculating blood loss across all risk categories. In all cases, blood volume was estimated from calibrated suction canisters containing fluid waste; however, only 16% of patients had blood soiled surgical swabs weighed. A higher percentage of patients in the high-risk group (40%) had swab weighing compared to the low risk (19%) and medium risk (7%) groups. The number of surgical swabs used and fluid waste suction volume across all risk categories were similar.

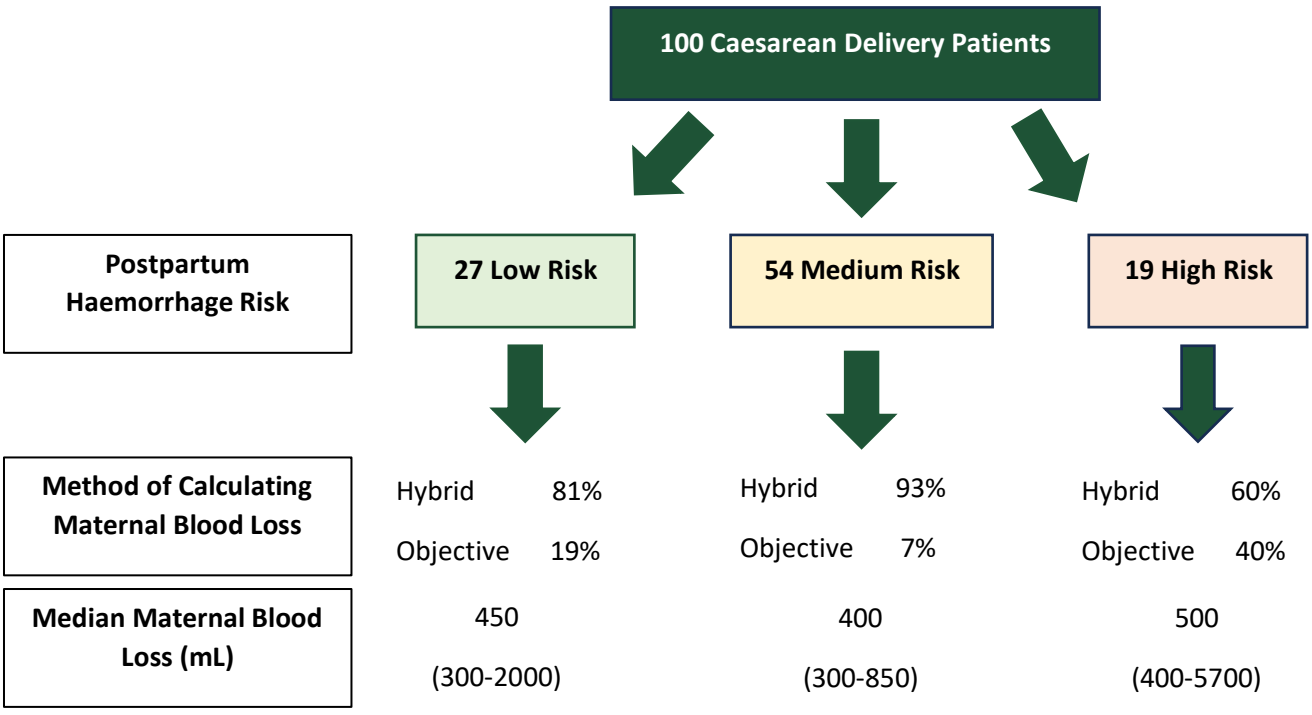

Figure 5 - Methods of calculating and median maternal blood loss according to postpartum haemorrhage (PPH) risk.

The median operating time was 37 minutes (16 – 59), 44 minutes (18 – 105) and 42 minutes (21 – 72) in low, medium and high-risk patients respectively (Table 6). In terms of blood loss collecting activities, time spent suctioning blood and fluid waste increased from a median of 35 seconds to 67 seconds; and time spent swabbing increased from 41 seconds to 53 second from low to high-risk patients respectively. However, this relationship was similar relative to operating time. Revisions to the final measurement was done in three cases and was due to ongoing bleeding in one patient and disagreements with calculated blood loss on two occasions. Less than one minute was required to document blood loss in almost all cases (99%).

Table 6 - Caesarean delivery blood loss evaluation activities according to obstetric haemorrhage risk category. Data presented as mean ± standard deviation or median (range).

	Obstetric Haemorrhage Risk Category		
	Low (n=27)	**Medium (n=54)**	**High (n=19)**
Estimated Blood Loss (mL)	450 (300 – 2000)	400 (300 – 850)	500 (400 – 5700)
Primary Surgeon Experience			
< 3 Years	8	16	8
3 to 9 Years	7	13	5
> 9 Years	12	25	6
Assistant(s)	1 (1 – 1)	1 (1 – 2)	1 (1 – 3)
Surgical Swabs Used (n)	7 (4 – 15)	7 (5 – 15)	9 (5 – 31)
Swabs Weighed (%)	19 (5)	7 (4)	40 (7)
Suction Volume (mL)	500 (50 – 1750)	500 (50 – 1600)	900 (300 – 5200)
Operating Time (min)	37 (16 – 59)	44 (18 – 105)	42 (21 – 72)
Swabbing Time (sec)	41 (10 – 112)	52 (21 – 134)	53 (16 – 237)
Swabbing Time (%)	2.21 (0.33 – 5.19)	1.86 (0.85 – 6.30)	1.91 (1.01 – 5.49)
Suction Time (sec)	35 (8 – 93)	44 (9 – 120)	67 (19 – 536)
Suction Time (%)	1.86 (0.36 – 6.46)	1.5 (0.19 – 10.83)	2.44 (0.62 – 12.4)
Staff Calculating Blood Loss (n)	2 (2 – 3)	2 (2 – 3)	2 (2 – 6)
Revisions to Blood Loss (%)	7 (2)	0 (0)	5 (1)

4.3 Discussion

We studied obstetric blood loss evaluation at Caesarean section according to the patients' risk of PPH with a particular focus on the activities in measuring, calculating and documenting blood loss. Despite a higher proportion of patients at high-risk of PPH had objective blood loss quantification, our results show that evaluation of blood loss at Caesarean sections was not uniform across PPH risk groups. The most frequent encountered approach to obstetric blood loss evaluation was a hybrid method of both subjective and objective techniques (84%). This involved estimating blood loss volume from calibrated suction canisters and estimating blood volume in blood soiled surgical swabs without swab weighing. A higher percentage of patients in the high-risk group (40%) had swab weighing compared to the low risk (19%) and medium risk (7%) groups. Between the three obstetric haemorrhage risk groups in our study, time spent swabbing and suctioning when compared to operating time were similar. The median utilization of swabs and canisters was also similar between groups. Blood loss evaluation at Caesarean section encompassed approximately 5% of operating time in most cases in our study.

4.3.1 Possible factors influencing blood loss quantification.

In our study, different methods for quantifying blood loss were observed between PPH risk groups. Multiple PPH risk assessment tools have been described, such as the California Maternal Quality Care Collaborative (CMQCC) risk assessment tool, which allow healthcare professionals to anticipate and plan for PPH before delivery[58,113]. The CMQCC risk assessment tool stratifies patients into three haemorrhage risk categories (low, medium and high risk) based on patient-level risk factors[58]. However, PPH risk assessment tools have, at best,

moderate accuracy in predicting PPH as demonstrated by a large obstetric population study showing that over 40% of PPH events occurred in patients classified as low risk[114]. This, undoubtedly, would have implications on the appropriate selection of patients for pretransfusion testing and blood bank resource utilization. Could the low predictive valve of these PPH risk assessment tools be the result of *how* blood loss is evaluated at delivery?

Patients at high-risk for PPH had more objective methods utilized than patients with low or medium risk. Though weighing of blood soiled surgical swabs to aid in blood loss calculation is required for more accurate measurement, only a small portion of cases had weighing of swabs. Staff decision-making regarding weighing swabs is likely to be complex. Possible explanations include a mismatch between staff training and what is feasible in the facility. A study on the barriers to PPH detection has shown that high workloads and staff shortages may require staff to adapt their practice[115]. It is also possible that staff experience and intuition plays a role, where the perception of a "normal" amount of blood loss does not necessitate a need for precise measurement. It is likely that the initial diagnosis of PPH is made by clinical impression rather than blood volume lost as demonstrated on behavioural studies on the PPH recognition[116,117]. Therefore, staff cognitive bias factors in obstetric blood loss evaluation and new methods at blood loss qualification should minimize this bias in an attempt to standardise care. Standardising blood loss evaluation may improve the prediction and usefulness of PPH risk assessment tools. This calls for minimally invasive technology that provides automated and objective measurement of blood loss. A greater emphasis on blood suction volume was used to determine blood loss in our study. Perhaps the activity of suctioning blood contaminated fluid could be paired with real-time assessment of

haemoglobin content of the waste and this measurement could be used to predict haemoglobin changes following delivery.

4.3.2 Observational study strengths and limitations

We highlighted the importance of studying how blood loss is evaluated and identified possible barriers to standardized blood loss assessment in a tertiary maternity hospital. Sample size selection was limited by the lack of similar published studies for comparison. We recognise that theatre staff behaviour may have been influenced by the presence of the researcher in theatre. A further limitation is that some patients had other procedures in addition to the Caesarean section. Interviewing those involved in measuring maternal blood loss may further identify the reasons for utilizing different approaches to bloods loss measurement in PPH risk groups.

4.4 Conclusion

We showed that evaluation of blood loss at Caesarean sections was not uniform across PPH risk groups through real-time observation of hospital staff blood loss quantifying activities. Novel tools aimed at better quantifying blood loss could reduce the cognitive bias associated with blood loss evaluation, ensure standardised practice and support decision-making. This in turn may reduce maternal morbidity and mortality associated with postpartum haemorrhage.

CHAPTER SEVEN – GENERAL DISCUSSION AND CONCLUSION

The diagnosis of obstetric haemorrhage is dependent on the accurate and prompt assessment of maternal bleeding status. However, even current objective obstetric blood loss quantification practices involve human mental processes (which are influenced and affected by the working environment). The human factor contributes to missed or delayed diagnosis of obstetric haemorrhage (Figure 12). To address this human component, health systems would traditionally focus on re-training and re-education on obstetric blood loss quantification, provision of resources, standardization efforts, obstetric haemorrhage risk prediction and situational awareness. However, we propose that the human element should be removed all together and suggest that obstetric haemorrhage should be diagnosed by a machine or novel technology. We hypothesize that a device-made diagnosis would be more standardized, automated and real-time, which may promote early management of obstetrics haemorrhage, reducing severe maternal morbidity and mortality.

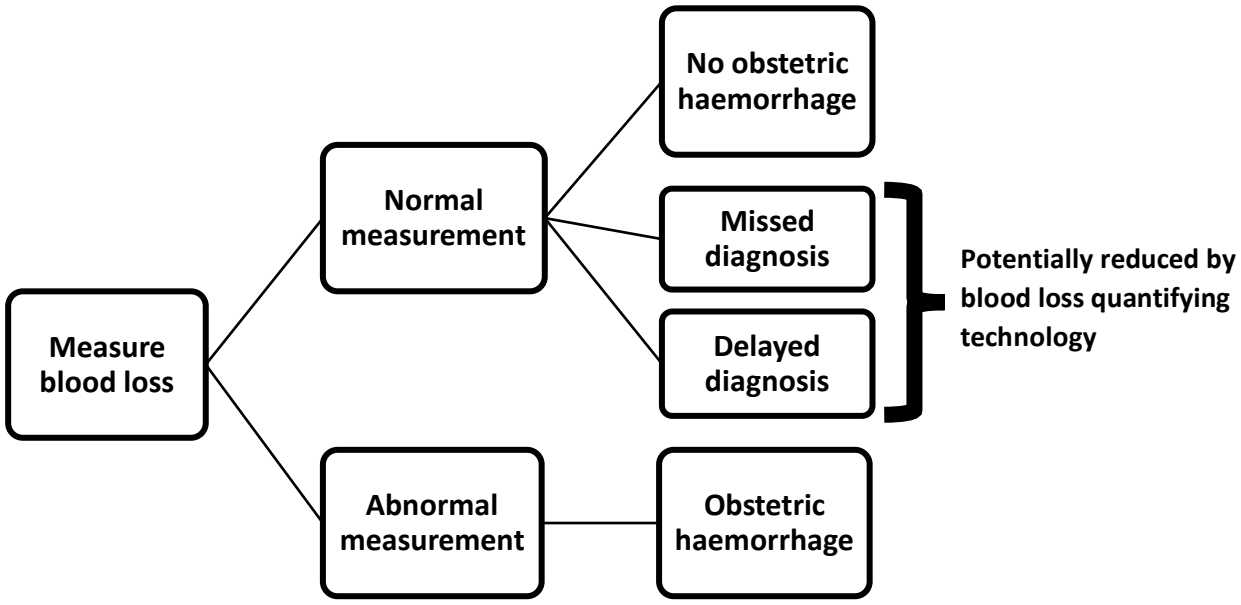

Figure 12 - Potential impact of obstetric blood loss quantifying technology.

7.1 Summary of thesis questions and answers

7.1.1 Is quantitative obstetric blood loss assessment standard practice?

To explore this question, we observed obstetric blood loss quantification practices in Cork University Maternity Hospital at Caesarean births and found inconsistencies in the choice of method of assessing blood loss. A hybrid method of quantification combining both subjective and objective approaches was the predominate method of blood loss measurement. Measurement of maternal blood loss was also not standardised according to a nationwide survey by NPEC.

Blood loss quantification was more objective in patients at high risk of haemorrhage. This raises the question of whether labelling the patient as high-risk haemorrhage would translate to objective blood loss evaluation and whether all patients should be categorised as high risk in order to achieve routine objective blood loss of quantification. This question is rhetorical as the purpose of risk stratification is to coordinate resources and expert care; and that objective blood loss quantification should be standard care. The human element possibly contributes to deviation from standard care especially if the task at hand is too cumbersome or time consuming. Qualitative studies exploring healthcare professionals' opinions of current quantification methods may help identify why healthcare professionals deviate from purely objective quantification practices. A limitation of this study is that it observed practices of single unit and that other centres may be more consistent. Despite this, one would have assumed that the presence of the study observer would have acted as a quality check and promoted healthcare professionals to abide by good practice. Again, the inconsistences in quantification between haemorrhage risk groups suggests that healthcare professionals pick

and choose when they adhere to standard practice regardless of the study observer's attendance.

7.1.2 Could standardised measurements of maternal blood loss be achieved with novel blood loss quantifying technology?

Blood loss quantifying technology may promote consistent and standard practice. We developed a blood loss quantifying device, the Stryker® System, in collaboration with Stryker Instruments Innovation Centre. We used unwanted human whole blood provided by the Irish Blood Transfusion service to assess the ability of the device in detecting blood through haemoglobin protein levels (a protein unique to blood). We compared the device against a reference haematology analyser through Bland-Altman analysis and identified that the device is accurate in detecting haemoglobin levels. This evidence supported testing the device in clinical settings and we then upgraded the device for clinical testing. We compared the updated device with volumetric blood loss quantification and found that the device was more accurate in blood loss measurement. This evidence supports studying this novel device as an alternative to volumetry. Furthermore, hospital staff found the device highly usable.

7.1.3 What is the cost of obstetric haemorrhage to the Irish healthcare system?

The severe maternal morbidity and mortality associated obstetric haemorrhage is well recognised worldwide and in Ireland. Although, the economic burden of obstetric haemorrhage has never been described in Ireland. Understanding the economic impact of obstetric haemorrhage allows for future cost effectiveness studies on new prevention and

care strategies such as the introduction of novel blood loss quantifying technology. Reasonably, obstetric haemorrhage patients would require more recourses and consequently this would add to care costs (up to 140% additional costs). However, through a cross-sectional study, we found that blood products contributed approximately one third to half of the care costs. Based our study, reducing blood transfusion rates would be a key marker for improvement in the care of obstetric haemorrhage patients and blood transfusion rates should be used as a metric to assess the impact of novel blood loss quantifying technology.

7.2 Implications on research

7.2.1 An alternative to typical gravimetry

The success in demonstrating that the Stryker® System was more accurate than typical volumetric measurements encourages us to explore whether similar technology can be developed to determine the blood content of soiled items like surgical swabs. This technology should provide automated and real-time information to users too and should be studied in tandem with the Stryker® system.

7.2.2 A cluster randomised controlled trial.

For novel blood loss quantifying technology to replace current practice, it must demonstrate that it reduces severe morbidity and mortality associated with obstetric haemorrhage. Following sample size analysis and power testing, a cluster randomised controlled trial would randomly allocate participating maternity services to either current obstetric blood loss quantifying practices or to a blood loss quantification though the device. The primary

outcome of the study would be national and maternity unit specific Major Obstetric Haemorrhage (MOH) rates which could be compared with previous MOH rates. The secondary outcomes would include blood transfusion rates, postnatal anaemia rates, hospital stay durations, intensive care unit admission rates and rates of surgeries or procedures to treat refractory bleeding.

7.2.3 A personalised obstetric haemorrhage alarm

Following the results of the cluster randomised controlled trial, a follow-up study may assess whether the incorporation of patient personalisation to the device(s) might further improve on the previously mentioned primary and secondary outcomes. For example, device customization could consider the patient's obstetric haemorrhage risk, BMI, pre-delivery haemoglobin levels and biophysical parameters. This device software would adjust the threshold for obstetric haemorrhage treatment initiation and escalation and allow for more individualised care (which may prevent severe morbidity and mortality). This tailored alert system could present as an audio-visual alarm which the healthcare professional must interact with to silence. The alarm system in this context would not the alert healthcare professional to a specific blood loss volume, but possibly an obstetric haemorrhage level (for example PPH Level 1, PPH Level 2, etc), were each level is associated with the chance of a morbidity (for example risk of blood transfusion).

7.3 Implications on clinical practice and policy

With a novel blood loss quantifying tool available, the need to invest into training to standardise measurements of maternal blood loss through current volumetry or gravimetry may be curtailed. As per professional societies, the current definitions of obstetric haemorrhage take in to account blood loss measurements. However, a blood loss quantifying device which utilises the alarm system described above may change how we define obstetric haemorrhage provided that it demonstrates reduced morbidity and mortality. With this perspective, the diagnosis of obstetric haemorrhage would be determined by the device and the healthcare professional would merely respond to the device rather than a specific blood loss measurement. If the supporting research is favourable, this would be a significant change to clinical practice and to the definitions currently endorsed by professional societies.

7.4 Conclusion

Obstetric haemorrhage is a long-standing clinical problem to maternity services. We learn through this thesis the deferent approaches of diagnosing obstetric haemorrhage and discuss how currently utilised blood loss measurement methods are fickle due to human decision making. Through this thesis, we present the preliminary work needed to support further research on the innovative approaches to obstetric blood loss quantification.

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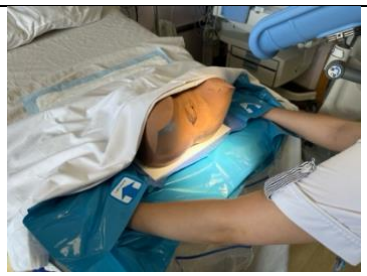
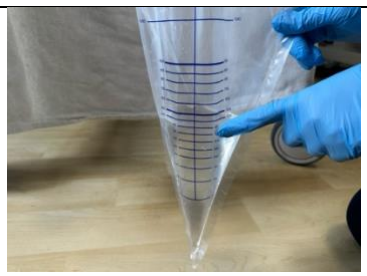
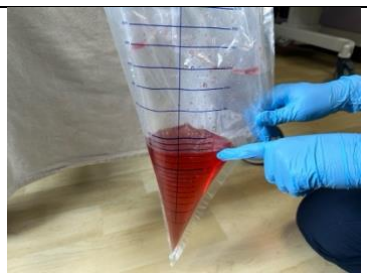
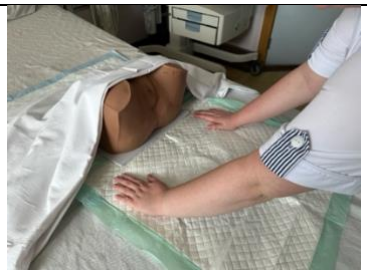
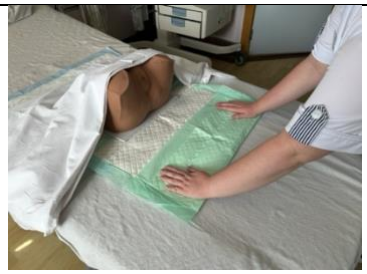
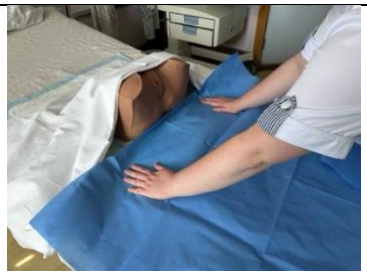
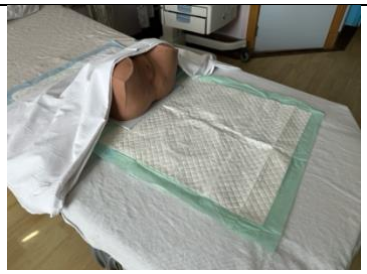
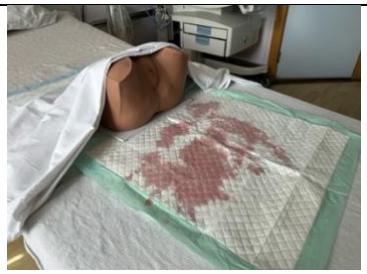
APPENDICES

Appendix 1 - Volumetric maternal blood loss measurements at vaginal delivery.

Volumetric method	
1. Use calibrated under-buttock drape	
2. Place drape under maternal buttock prior to delivery	
3. Measure amniotic fluid volume after delivery	
4. Perform interval assessments of the drape and subtract amniotic volume from final volume to obtain blood loss measurement.	

Appendix 2 - Gravimetric maternal blood loss measurements at vaginal delivery.

Gravimetric method	
1. Measure dry weight of swabs and absorbent pads	 
2. Place absorbent pad under maternal buttock and roll it prior to delivery	 
3. Place non-absorbent sheet for delivery	
4. Remove non-absorbent sheet after umbilical cord is clamped and cut, and unravel absorbent pad. Perform interval assessments of the absorbent pad.	 
5. Weigh blood soiled items and compare against dry weight (assuming 1g gained in weight is equivalent to 1ml of blood).	 

Appendix 3 - Inpatient inlier costs according to Diagnostic Related Groups (DRG) for Major Obstetric Haemorrhage (MOH) and control groups.

Study Group	DRG Code	DRG Description	Cost (€)[a]
MOH	O01A	Caesarean delivery, major complexity	11,158
	O01B	Caesarean delivery, intermediate complexity	5,353
	O02A	Vaginal delivery in operating theatre, major complexity	8,055
	O03A	Ectopic pregnancy, major complexity	5,977
	O04A	Postpartum and post abortion in operating theatre, major complexity	10,534
	O04B	Postpartum and post abortion in operating theatre, minor complexity	3,560
	O60A	Vaginal delivery, major complexity	5,276
Control	O01C	Caesarean delivery, minor complexity	3,934
	O03B	Ectopic pregnancy, minor complexity	3,561
	O60C	Vaginal delivery, minor complexity	2,584
	O61B	Postpartum and post abortion, minor complexity	1,373

[a]Healthcare Pricing Office activity-based funding admitted patient price list, 2022

Appendix 4 - Ethical approval for thesis projects.

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

University College Cork
Tel: +353-21-4901901 Lancaster Hall
Email: crec@ucc.ie Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 5 (4) 02/12/2021
& ECM 4 (h) 19/10/2021

Date: 3rd December 2021

Professor John Higgins
Consultant Obstetrician & Gynaecologist
Cork University Maternity Hospital
Wilton
Cork

Study Title: Quantification of obstetric blood loss studies.

Dear Professor Higgins

The committee reviewed the above application at its recent meeting.

Approval may be granted to carry out the above study at:

Cork University Maternity Hospital

subject to receipt and approval of the following:

Revised Consent Form	(a) If the chief investigator will not obtain consent from all study participants change "Chief Investigator Signature" to "Researcher Signature" (b) Change "Cork Research Ethics Committee.." to "Clinical Research Ethics.."

You must ensure that changes to previously submitted documents are clearly highlighted and that the revised documents contain a new version number and date. The version and date must be included on the document and not just on the file name. It should be visible when the document is printed. The revisions must be submitted by email along with a copy of this letter.

The following documents have been approved:

Document	Approved	Version	Date
Application Form			10th August 2021
Evidence of Insurance	Yes (CIS)		
CV for Chief Investigator	Yes		
Study Protocol	Yes		
Patient Information Leaflet	Yes		
Data Collection Sheet	Yes.		

We note that the co-investigator(s) involved in this project will be:

Name	Appointment Details
Dr Ahmed Lutfi	Registrar
Professor Richard Greene	Consultant Obstetrics/Gynaecology.

Please note that permission is not yet granted to begin this study. When the document/documents required above have been submitted and approved by CREC, you will receive a full approval letter You cannot begin this study until you have received that letter. Original signed approval letters/conditional approval letters from CREC must be kept in your study master file for audit purposes.

Applications for this meeting were reviewed by:

Professor David Kerins (Chairman)
Professor Brendan Buckley
Dr Mark James
Dr Mairead O'Riordan
Dr John Bourke
Aoiffe Lowe
Justin Condon (Solicitor).

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 5 (4) 02/12/2021
& ECM 4 (h) 19/10/2021 & ECM 3 (mmm) 11/01/2022

Date: 23rd December 2021

Professor John Higgins
Consultant Obstetrician & Gynaecologist
Cork University Maternity Hospital
Wilton
Cork

Study Title: Quantification of obstetric blood loss studies.

Dear Professor Higgins

The following document has been approved:

- Consent Form Version 2 dated 19th December 2021.

The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018/2021.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

University College Cork
Tel: +353-21-4901901 Lancaster Hall
Email: crec@ucc.ie Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (q) 12/09//2023

Date: 13th September 2023

Professor John R Higgins
Consultant in Obstetrics and Gynaecology
Cork University Maternity Hospital
Wilton
Cork

Study Title: Quantification of Obstetric Blood Loss Studies.

Dear Professor Higgins

Approval may be granted to carry out the above study at:

Cork University maternity Hospital

subject to receipt and approval of the following:

Information Leaflet for User Feedback Questionnaire	(a) Not included for review.

You must submit the following by email to crec@ucc.ie:

(a) Only the document listed above.
(b) A copy of this letter.

No changes, other than those listed above, must be made to the documents. Should you wish to make further changes you must submit an amendment application. The amendment must only be submitted once full approval to carry out the study has been granted.

The following documents have been approved:

Document	Approved	Version	Date
Application Form	Yes		Signed: 9th August 2023
CV for Chief Investigator	Yes		
Proof of Insurance (CIS)	Yes		
Study Protocol	Yes	1	8th August 2023
Patient Information Leaflet	Yes		
Consent Form	Yes	1	8th August 2023
Data Collection Sheet	Yes		
User Feedback Questionnaire	Yes.		

We note that the co-investigator(s) involved in this project will be:

Name	Appointment Details
Dr Ahmed Lutfi	Registrar and Research Assistant Obstetrics/Gynaecology, UCC
David Eustace	Research Engineer, Stryker
Stephen Faul	Senior Principal Research Engineer, Stryker
Professor Richard Greene	Consultant Obstetrics/Gynaecology, UCC.

Please note that permission is not yet granted to begin this study. When the document/documents required above have been submitted and approved by the CREC, you will receive a full approval letter. You cannot begin the study until you have received that letter. Original signed approval letters/conditional approval letters from the CREC must be kept in your study master file for audit purposes.

COISTE EITICE UM THAIGHDE CLINICIÚIL

Clinical Research Ethics Committee of the Cork Teaching Hospitals

Tel: +353-21-4901901
Email: crec@ucc.ie

University College Cork
Lancaster Hall
6 Little Hanover Street
Cork
Ireland

CREC Review Reference Number: ECM 4 (q) 12/09//2023
& ECM 3 (r) 24/10/2023

Date: 25th September 2023

Professor John R Higgins
Consultant in Obstetrics and Gynaecology
Cork University Maternity Hospital
Wilton
Cork

Study Title: Quantification of Obstetric Blood Loss Studies.

Dear Professor Higgins

The following document has been approved:

User Feedback Questionnaire Information Leaflet

Full approval is now granted to carry out the above study. The date of this letter is the date of authorization of the study.

Please keep a copy of this signed approval letter in your study master file for audit purposes. The study must be carried out in accordance with General Data Protection Regulation and Health Research Regulation 2018/2021.

You should note that ethical approval will lapse if you do not adhere to the following conditions:

1. Submission of an Annual Progress Report/Annual Renewal Survey (due annually from the date of this approval letter). **We would encourage you to keep note of this date as the CREC will not issue a reminder.**
2. Report unexpected adverse events, serious adverse events or any event that may affect ethical acceptability of the study
3. Submit any change to study documentation (minor or major) to CREC for review and approval. Amendments must be submitted on an amendment application form and revised study documents must clearly highlight the changes and contain a new version number and date. Amendments cannot be implemented without written approval from CREC.
4. Notify CREC of discontinuation of the study
5. Submit an End of Trial Declaration Form and Final Study Report/Study Synopsis when the study has been completed.

Yours sincerely

Professor David Kerins
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix 5 - Study participant consent forms and information leaflets.

VERSION 2 (19th DECEMBER 2021)

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH STUDY

PATIENT NAME:

STUDY TITLE: Quantification of Obstetric Blood Loss Studies

NAME OF CHIEF INVESTIGATOR: Professor John R Higgins

CONTACT NUMBER FOR CHIEF INVESTIGATOR: 021 492 0500

You are being asked to participate in a research study. The doctors at ***Cork University Maternity Hospital (CUMH)*** study the nature of disease and attempt to develop improved methods of diagnosis and treatment. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form gives detailed information about the research study. The Chief Investigator will also discuss the study with you in detail. When you are sure you understand the study and what will be expected of you, you will be asked to sign this form if you wish to participate.

NATURE AND DURATION OF PROCEDURE(S):

Postpartum haemorrhage (PPH) is heavy bleeding after birth. If heavy bleeding does occur, it is important that it is recognized very quickly so that a minor haemorrhage doesn't become a ***Massive/Major Obstetric Hemorrhage (MOH)***, which can be life-threatening.

To prevent PPH and MOH, it is important to measure blood loss very quickly and accurately following birth. In association with the ***Stryker Instruments Innovation Centre*** in Cork, we are developing a machine to assist doctors in measuring blood loss rapidly and accurately.

To test this machine, we will need to measure your liquid waste for blood content following your planned caesarean section delivery.

This will mean that at the end of your procedure a member of the research team will collect the liquid waste to be analyzed using this machine in an onsite hospital laboratory.

No part of the machine system will come into direct contact with you. This study will not require off-site analysis and under no circumstance will any samples be retained by the investigators.

Once the measurements are collected, the surgical waste and accompanying waste containers/tubes will be returned for disposal in the standard manner.

We will compare the current method of measuring bleeding after birth in CUMH against this machine.

POTENTIAL RISKS AND BENEFITS:

Your delivery and care will continue as standard and will not be affected by participating in the study.

Information gathered from this study can be potentially useful to preventing PPH and MOH.

All data will be anonymized and all research data would be kept on a secure password protected hospital computer available only to the investigators. Anonymous data required for analysis and training of the system will be kept on a secure, password protected, Stryker computer available only to the investigators. Once system training and testing is complete, the data will be deleted from the Stryker computer. The hospital computer is located in a hospital office with ID card access security.

Data reported will be GDPR compliant with no patient identifiers. Data collected will be stored on computers at CUMH for up to 10 years.

POSSIBLE ALTERNATIVES:

Your participation is voluntary.

VERSION 2 (19th December 2021)

AGREEMENT TO CONSENT

The research project and the treatment procedures associated with it have been fully explained to me. All experimental procedures have been identified and no guarantee has been given about the possible results. I have had the opportunity to ask questions concerning all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above-described project conducted at Cork University Maternity Hospital I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the Chief Investigator listed above. I understand that the study has been approved by the Clinical Research Ethics of the Cork Teaching Hospitals (CREC) and if I have further queries concerning my rights in connection with the research, I can contact CREC at Lancaster Hall, 6 Little Hanover Street, Cork, 021 4901901 or email crec@ucc.ie.

Please circle YES or NO:

I have read and understand the study:	YES	NO
I grant permission for the data collected to be used in this research only:	YES	NO
I understand that my anonymized data will be stored at Cork University Maternity Hospital (CUMH) for 10 years:	YES	NO

RESEARCHER SIGNATURE: _____

SIGNATURE OF STUDY PARTICIPANT: _____

DATE: _____

PATIENT INFORMATION LEAFLET

What is Postpartum Haemorrhage (PPH) and Massive/Major Obstetric Haemorrhage (MOH?

Postpartum haemorrhage (PPH) is heavy bleeding after birth. If heavy bleeding does occur, it is important that it is recognized very quickly so that a minor haemorrhage doesn't become a *Massive/Major Obstetric Hemorrhage (MOH)*, which can be life-threatening.

How is PPH and MOH identified?

PPH and MOH is identified by measuring how much blood is lost following delivery and this is recorded in millilitres. Blood loss can be estimated visually but this can be inaccurate. In our institution, we measure the volume of blood lost through surgical canisters, graduated drapes and weighing surgical swabs.

What is the study title?

Quantification of Obstetric Blood Loss Studies

Where will the study take place?

Cork University Maternity Hospital, Wilton, Cork

What will be required of the participants?

In association with the ***Stryker Instruments Innovation Centre*** in Cork, we are developing a machine to assist doctors in measuring blood loss rapidly and accurately.

To test this machine, we will need to measure your liquid waste for blood content following your planned caesarean section delivery.

This will mean that at the end of your procedure a member of the research team will collect the liquid waste to be analyzed using this machine in an onsite hospital laboratory.

Your delivery and care will continue as standard and will not be affected by participating in the study.

Where will data be stored and who will have access to it?

All data will be anonymized and all research data would be kept on a secure password protected hospital computer available only to the investigators. Anonymous data required for analysis and training of the system will be kept on a secure, password protected, Stryker computer available only to the investigators. Once system training and testing is complete, the data will be deleted from the Stryker computer. The hospital computer is located in a hospital office with ID card access security.

Data reported will be GDPR compliant with no patient identifiers.

How long will data be stored?

Data collected will be stored on computers at CUMH for up to 10 years.

Are there any risks?

Your delivery and care will continue as standard and will not be affected by participating in the study.

Data security measures will be in place to protect patient information.

What are the benefits?

Information gathered from this study can be potentially useful to preventing PPH and MOH.

Who can I contact for more information?

Name of Chief Investigator:	Professor John R Higgins
Contact Number for Chief Investigator:	021 492 0500

USER FEEDBACK QUESIONNAIRE
INFORMATION LEAFLET

What is Postpartum Haemorrhage (PPH) and Massive/Major Obstetric Haemorrhage (MOH?

Postpartum haemorrhage (PPH) is heavy bleeding after birth. If heavy bleeding does occur, it is important that it is recognized very quickly so that a minor haemorrhage doesn't become a *Massive/Major Obstetric Hemorrhage (MOH)*, which can be life-threatening.

How is PPH and MOH identified?

PPH and MOH is identified by measuring how much blood is lost following delivery and this is recorded in millilitres. Blood loss can be estimated visually but this can be inaccurate. In our institution, we measure the volume of blood lost through surgical canisters, graduated drapes and weighing surgical swabs.

What is the study title?

Quantification of Obstetric Blood Loss Studies

Where will the study take place?

Cork University Maternity Hospital, Wilton, Cork

What will be required of the User?

In association with the ***Stryker Instruments Innovation Centre*** in Cork, we are developing a machine to assist midwives or doctors in measuring blood loss rapidly and accurately.

We would like you to use the device and complete an anonymous feedback questionnaire.

Where will data be stored and who will have access to it?

All data will be anonymized and all research data would be kept on a secure password protected hospital computer available only to the investigators. Anonymous data required for analysis and training of the system will be kept on a secure, password protected, Stryker computer available only to the investigators. Once system training and testing is complete, the data will be deleted from the Stryker computer. The hospital computer is located in a hospital office with ID card access security.

Data reported will be GDPR compliant with no patient identifiers.

How long will data be stored?

Data collected will be stored on computers at CUMH for up to 10 years.

Are there any risks?

Care will continue as standard and will not be affected by participating in the study.

Data security measures will be in place to protect user information.

What are the benefits?

Information gathered from this study can be potentially useful to further developing the device.

Who can I contact for more information?

Name of Chief Investigator:	Professor John R Higgins
Contact Number for Chief Investigator:	021 492 0500

Appendix 6 - Approvals to use blood components for research from the Irish Blood Transfusion Service.

Irish Blood Transfusion Service
Seirbhís Fuilaistriúcháin na hÉireann

IBTS Research & Development

BLOOD COMPONENT REQUEST & INDEMNITY FORM

Institution name:	Cork University Maternity Hospital
Researcher:	Dr Ahmed Lutfi
Principal Investigator:	Professor John Higgins
Brief description of Research Project:	Quantification of obstetric blood loos studies
Blood component requirements:	**Component type:** Packed red cells
	Frequency: Once weekly
	Volume: 5 units
Purpose for which blood component will be used:	Calibrating novel blood loss quantification tool.
How will the blood component be stored?	Secure onsite hospital laboratory
How will the blood component be disposed?	Hospital waste management disposal
Have you previously received blood components for this purpose?	☐ YES ☒ NO If yes, was it from your current institution? ☐ YES ☐ NO If no, please provide name of previous institution Click here to enter text. N/A

SUPPLY AGREEMENT

- The Irish Blood Transfusion Service provides pro bono, blood, blood components, blood samples or portions thereof to research partners including Irish third level educational facilities or health care facilities solely for the purposes of research, education or quality control.
- The blood provided is from voluntary non-remunerated donors donated primarily for therapeutic application to patients, but that for various reasons would not otherwise be used for therapeutic purposes, or which has been collected or assigned specifically for the stated purposes of research, education or quality control.
- The blood, blood components and blood samples are not made available for commercial purposes, and consent by donors for such commercial purposes is neither explicit nor implied. However the IBTS understands that research purposes for which the blood is used by the receiving institution may ultimately find commercial applications and such use is not precluded by this agreement.
- This agreement specifically excludes onward supply of the blood etc. to 3rd parties for any purpose without explicit consent from the IBTS Medical & Scientific Director or Research & Development Lead Facilitator. This consent must be documented in writing.
- The IBTS has no means of controlling how the blood is used after release by the IBTS; as a result it does not have any responsibility for any consequences (whether direct, indirect or consequential, physical, economic or otherwise) that arise out of provision of such material.
- Please note: Persons at the receiving institution handling such blood etc. may be exposed to an infectious hazard either through
  - Diseases which may be transmissible but for which there is no current test or
  - Failure of the testing procedures to identify an infection for which a test has been performed.
- The material is provided to the recipient institution entirely on the basis that the IBTS will be indemnified by that institution in respect of any claim arising for its provision or use.
- **N.B.** The IBTS does not undertake to recall blood etc. issued for research purposes in the event of it becoming aware at a later date that the blood may have been infectious or otherwise unsuitable for issue for research purposes.

Irish Blood Transfusion Service
Seirbhís Fuilaistriúcháin na hÉireann

IBTS Research & Development

BLOOD COMPONENT REQUEST & INDEMNITY FORM

The signatures below indicate awareness and acceptance of the above conditions.

Researcher Signature

Name: Dr Ahmed Lutfi
Title: Registrar Obstetrics/Gynae
Address: Cork University Maternity Hospital
Signature: Click here to enter text.
Date: 17/01/2022
Institution Stamp: Click here to enter text.

Cork University Maternity Hospital
17 JAN 2022
GYNAE SECRETARY

Principal Investigator

Name: Professor John Higgins
Title: Consultant Obstetrics/Gynae
Address: Cork University Maternity Hospital
Signature: Click here to enter text.
Date: 17/01/2022
Institution Stamp: Click here to enter text.

Professor John R. Higgins
17 JAN 2022
Clinical Director Approved

For IBTS office use only	
Institution code:	Click here to enter text. 035-003-22
eProgesa Code (PI):	Click here to enter text. RES 507
eProgesa Code (Researcher):	Click here to enter text. RES 507
Date approved:	Click here to enter a date. 18-01-2022
Renewal Date:	Click here to enter a date. 31.01.23
Approved by (RDLF / MSD / MRTC consultant)	**Print Name:** Click here to enter text. Dr. Allison Waters **Title:** Click here to enter text. R&D Lead Facilitator **Signature:** Click here to enter text.

APPROVED

Professor John R. Higgins
17 JAN 2022
Clinical Director Approved

Irish Blood Transfusion Service
Seirbhís Fuilaistriúcháin na hÉireann

Lárionad Náisiúnta Fola
Sráid Shéamais
Baile Atha Cliath 8
National Blood Centre
James's Street
Dublin 8
D08 NH5R

Tel: +353 1 432 2800
Fax: +353 1 432 2930
www.giveblood.ie

RCN: 2000 6280

31/01/2023

RESEARCHER IS APPROVED TO ACCESS ANONYMOUS BLOOD COMPONENTS FROM THE IRISH BLOOD TRANSFUSION SERVICE

Dear Ahmed,

We have reviewed your application and you are now approved to access our blood components to progress your research.

- Researcher code: 0000RES508
- Expiry date: 31/01/2024

Please note the following:

- Approval is subject to all agreed terms and conditions on the initial application and the associated clinical indemnity
- Approval is granted for a maximum of 12 months, and must be re-sought in January of every year, as required.
- Please quote your Researcher Code on all product requests.
- Call 01 432 2998 to place an order.
- We retain a unique identifier for all products issued to research in case follow-up is required.
- Information on our donor declaration at donation, donor information booklet and Research & Development information booklet can be downloaded directly from our website.
- We require all research using our products to have been granted the appropriate ethical approval from a Research Ethics committee prior to commencement.

All blood components and samples are produced from non-remunerated blood and platelet donors and we have duty-of-care to maximise the utility of their donation. We are delighted to enable your research and ask that you place a true value on the contribution of our donors to your work.

Kind regards,

Dr. Allison Waters, Research & Development Lead Facilitator Email: research@ibts.ie

Appendix 7 - Biosafety course certificates from UCC.

Certificate of Training

To Certify That

Lutfi, Ahmed

Has Completed Course Requirements for

Biosafety in UCC - Introduction

On July 20, 2022

Issued by BioRAFT

On behalf of University College Cork

#18946841658309043-102984910251145007

Certificate of Training

To Certify That

Lutfi, Ahmed

Has Completed Course Requirements for

Biological Risk Assessments

On July 20, 2022

Issued by BioRAFT

On behalf of University College Cork

#18946831658307311-50985110253145007


Certificate of Training
To Certify That
Lutfi, Ahmed
Has Completed Course Requirements for
Working with Potential Pathogens (including clinical samples, and human or primate cell lines)
On July 20, 2022
Issued by BioRAFT
On behalf of University College Cork
#18946871658310188-98995010254145007