Institution: Cardiff University

Unit of Assessment: Clinical medicine (1)

Title of case study: Changes to international clinical practice guidelines for postpartum haemorrhage and reduction in massive bleeding and transfusion after childbirth throughout Wales

Period when the underpinning research was undertaken: 2008 – 2018

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Collins, Peter	Professor	01/10/2001 – present
Hood, Kerenza	Professor	01/10/1996 – present
Townson, Julia	Research Fellow	11/03/1996 – present
Cannings-John, Rebecca	Senior statistician	30/09/2002 – present
Sanders, Julia	Professor	01/04/2010 – present

Period when the claimed impact occurred: 01/01/2017 – 31/12/2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide and is associated with low levels of the clotting factor fibrinogen. The Cardiff team validated a clinical algorithm to rapidly replace fibrinogen based on point-of-care testing. This research led to a new 4-stage PPH care package now implemented across Wales. The package involves risk assessment and blood loss monitoring, alongside use of the point-of-care fibrinogen algorithm. This new treatment approach reduced progression to massive PPH by 29% and use of blood transfusion by 23%. The Cardiff research findings also influenced clinical guidelines, and in turn, clinical practice in Europe, Australia and New Zealand.

2. Underpinning research (indicative maximum 500 words)

Massive bleeding during childbirth (postpartum haemorrhage, PPH) has doubled in the UK in the last 15 years, affecting approximately 5,300 women a year, resulting in >750 ITU admissions. Between 2014 and 2016, it caused 31 UK maternal deaths. PPH is defined as bleeding >500mL in the first 24 hours after childbirth, whilst massive PPH is defined as bleeding >2,500mL. The bleeding is caused by obstetric complications exacerbated by blood clotting abnormalities.

Management of blood clotting during PPH, including the Royal College of Obstetricians and Gynaecologists' (RCOG) 2009 Green-top Guideline, was based on major trauma protocols (e.g., the 2006 British Committee for Standards in Haematology Guidelines). These protocols emphasised early replacement of clotting factors with infusion of fresh frozen plasma (FFP) and platelets, with fibrinogen only recommended if bleeding continued.

Between 2008 and 2018, joint Cardiff University and NHS research challenged this treatment approach as follows:

2.1 Accurate quantification of blood loss during delivery

During PPH, national guidelines recommend escalation of care to senior clinicians after specific volumes of blood loss. Cardiff research showed that standard visual estimation of blood loss resulted in errors of up to 1,500mL, even by senior staff. The Cardiff team validated a method combining gravimetric and volumetric techniques (e.g., comparing wet and dry weights of standard delivery suite materials) as a more accurate measure of blood loss during PPH. This was evaluated through an observational study of 875 deliveries where PPH was identified **[3.1]**. The study found that accurate quantification of blood loss using this method could be carried out in real time by junior staff, such as maternity care assistants **[3.1]**.

2.2 Rapid point-of-care testing for bleeding biomarkers

Low laboratory-measured fibrinogen, recorded early during PPH, is a predictive biomarker for progression from moderate to massive PPH **[3.2]**. Fibrinogen testing, however, takes between 60-90 minutes to return results, making testing too slow to be clinically useful in an obstetric emergency. In a prospective cohort study **[3.2]**, the Cardiff team found that a surrogate point-of-care test for fibrinogen (FIBTEM), generating diagnostic results within 10 minutes using a ROTEM machine, was an effective predictive biomarker for progression to massive PPH, identifying women who would need blood transfusion and surgical procedures to control bleeding **[3.2]**.

2.3 Appropriate use of fibrinogen and clotting factors

Cardiff research showed that during PPH fibrinogen falls to critically low levels earlier than other clotting factors **[3.3]**. In the absence of point-of-care fibrinogen testing, previous guidelines recommended empirical, early transfusion with clotting factors in the form of fresh frozen plasma (FFP), which resulted in many women receiving unnecessary transfusions.

Through a prospective, double-blind, randomised controlled Cardiff-led study **[G3.1]**, using the point-of-care FIBTEM test to guide targeted early fibrinogen replacement, the Cardiff team showed for the first time that a **fibrinogen level >2g/L (or FIBTEM >11mm) equivalent to standard non-pregnant physiological levels** was adequate to control bleeding during severe PPH. This established for the first time an appropriate intervention trigger for blood product treatment during PPH **[3.4]**.

Cardiff's research also showed that during severe PPH it is unusual for deficiencies of other clotting factors **[3.3]** or platelets **[3.5]** to develop, with over 90% of women having normal blood clotting, in contrast to trauma-induced bleeds. Subsequently, findings from the randomised controlled study **[G3.1]** demonstrated that it was safe to withhold FFP infusions based on rapidly available ROTEM assays avoiding unnecessary infusions in many cases **[3.6]**.

Based on these findings, the Cardiff team designed a new integrated care package for PPH management which included more accurate identification of abnormal bleeding with timely escalation to more senior clinicians, and early, targeted, correction of fibrinogen using point-of-care FIBTEM testing (see section 4).

3. References to the research (indicative maximum of six references)

[3.1] Powell E, James D, Collis R, **Collins PW**, Pallman P, Bell S (2020) Introduction of standardised, cumulative quantitative measurement of blood loss into routine maternity care. *The Journal of Maternal-Fetal & Neonatal Medicine*. https://doi.org/10.1080/14767058.2020.1759534

[3.2] Collins PW, Lilley G, Bruynseels D. *et al*. (2014) Fibrin-based clot formation as an early and rapid biomarker for progression of postpartum hemorrhage: a prospective study. *Blood* 124:1727-36. http://dx.doi.org/10.1182/blood-2014-04-567891

[3.3] De Lloyd L, **Bovington R**, **Kaye A**, **Collis RE**, **Rayment R**, **Sanders J**, **Rees A**, **Collins PW**. (2011) Standard haemostatic tests following major obstetric haemorrhage. *International Journal of Obstetric Anesthesia* 20:135-4. http://dx.doi.org/10.1016/j.ijoa.2010.12.002

[3.4] Collins PW, **Cannings-John R**, Bruynseels D, *et al.* (2017) Viscoelastometric-guided fibrinogen concentrate replacement during postpartum haemorrhage: OBS2 a double blind randomised controlled trial. *Br J Anaes* 119:411-421. https://doi.org/10.1093/bja/aex181

[3.5] Jones RM, De Lloyd L, Kealaher EJ, Lilley GJ, Precious E, Burckett St Laurent D, Hamlyn VE, Collis RE, **Collins PW**. (2016) Platelet count and transfusion requirements in moderate and severe postpartum haemorrhage. *Anaesthesia* 71:648-656. https://doi.org/10.1111/anae.13448

[3.6] Collins PW, **Cannings-John R**, Bruynseels D, *et al*. (2017) Viscoelastometic guided fresh frozen plasma infusion for postpartum haemorrhage: OBS2, an observational study. *Br Anaes* 119:422-434. https://doi.org/10.1093/bja/aex245

Selected grant:

[G3.1] Collins PW, **Cannings-John R**, **Hood K**, **Paranjothy S**, **Sanders J**. *Fibrinogen concentrate versus placebo for treatment of postpartum haemorrhage: A Multicentre, prospective, double blind randomised controlled trial*. CSL Behring GmbH 01/12/2012-30/06/2017 £863,375

4. Details of the impact (indicative maximum 750 words)

The Cardiff team designed and implemented a new comprehensive care package for PPH. This was initially developed in Cardiff, then rolled out across Wales in a national quality improvement programme called the Obstetric Bleeding Strategy for Wales (OBS Cymru). It is now being integrated into clinical practice in Scotland and England. The research also changed international clinical guidelines on PPH.

The new Cardiff-designed PPH care package, developed at the University Hospital of Wales, Cardiff and Cardiff University between 2013 and 2015 **[5.1]**, involves the following 4 stages:

1. risk assessment of all cases on arrival on delivery suite;
2. quantitative measurement of blood loss during childbirth using volumetric and gravimetric techniques **[3.1]**;
3. escalation of care to senior clinicians at specified volumes of blood loss, with a senior midwife informed at 500mL, an obstetrician and anaesthetist required to attend at 1,000mL and a consultant obstetrician and anaesthetist informed at 1,500mL;
4. point-of-care FIBTEM testing and targeted, early replacement of fibrinogen and conservative use of FFP based on application of a standardised and validated algorithm **[3.4, 3.6, 5.2]**.

4.1 All-Wales implementation: OBS Cymru

The implementation of the PPH care package in Cardiff resulted in an **83% reduction in massive PPH** (bleeds ≥2,500mL). In addition, the number of mothers **requiring a blood transfusion fell by 32%, and transfusion of ≥5 units of blood and FFP transfusion both fell by 86% [5.1]**. Eighteen months after the end of the pilot, the overall incidence of massive PPH, blood transfusion ≥5 units or FFP transfusion was 2.8/1,000, compared to 6/1,000 elsewhere in the UK **[5.1]**.

Following the positive health outcomes seen with the care package, it was rolled out across Wales (between January 2017-December 2018) in a national quality improvement programme (OBS Cymru) **[5.2]**. The programme included all maternity units in Wales, covering hospitals varying in size, complexity of cases, and staffing levels, and introduced point-of-care testing into every obstetric unit in Wales **[5.2, 5.3]**. The OBS Cymru care package led to major clinical health benefits in Wales as follows:

- By December 2017, the care package had been adopted by all maternity units with quantitative measurement of blood loss being used for 98% of deliveries **[5.4]**.
- Incidence of massive haemorrhage fell by 23% with a 29% reduction in women progressing from early to massive bleeding. This equates to 46 fewer women a year experiencing massive haemorrhage after childbirth **[5.4]**.
- The number of women requiring a blood transfusion fell by 23%; equating to 164 women avoiding transfusion each year, a reduction of 390 units in total blood transfused **[5.4]**. Further, massive blood transfusions (≥5 units) fell by 30% **[5.4]**.
- 42% reduction in the number of women receiving FFP compared to standard guidelines, with no adverse effects on blood clotting **[5.4]**.
- 29 senior clinicians noted that OBS Cymru had changed both individual and unit level management of PPH, including “awareness of ongoing blood loss” and “consistent management” **[5.4]**.
- Feedback showed that 95% of women felt well supported during bleeding **[5.4]**

- Although hospital stays were sometimes marginally longer (1-2hrs on average), the care package itself was cost neutral across Wales **[5.5]**.

Following the success of OBS Cymru, the Welsh Government issued a Health Circular in 2019 (WHC/2019/012) requiring **all hospitals in Wales to embed the OBS Cymru care package into routine clinical practice [5.6]**.

The importance of OBS Cymru was recognised by the MediWales Innovation awards Efficiency through Technology Programme (December 2017), the NHS Wales Awards for Promoting Clinical Research and Application to Practice (September 2018), the NHS Wales Midwifery and Maternity awards for OBS Cymru champion midwives (2019) and the British Medical Journal Innovation in Quality Improvement Category awards (June 2019).

4.2 Implementation of OBS Cymru practice across the UK

Following the positive outcomes observed in Wales, the care package was implemented across Scotland as part of the Scottish Patient Safety Programme **[5.7]**. The OBS Cymru approach is also part of a larger package of changes being implemented by NHS England to "*improve the early recognition and management of deterioration of either mother or baby during or soon after birth*", via NHS Improvement in England **[5.7**, p.1**]**, the quality improvement body for NHS England. The package document lists key aspects of the OBS Cymru programme, for example, targeting clinical training "to promote 4-stage PPH protocol" **[5.7**, p.4**]**, and implementing "*the use of cumulative gravimetric measurement of blood loss"* **[5.7**, p.6**].** The package was implemented through the Maternity and Neonatal Safety Improvement Programme launched in July 2019. NHS England Trusts were split into three annual waves, with 44 trusts being supported to implement change in 2019, and a further 43 being supported in 2020; this schedule is currently under review as a result of COVID-19 **[5.7]**.

4.3 Changing national and international guidelines on PPH

Cardiff research additionally led to the following changes in guidelines and consensus statements:

- The British Society of Haematology guideline on point-of-care clotting tests, co-authored by Collins, recommends using the OBS Cymru blood product treatment algorithm for bleeding after childbirth **[5.8]**. This is the gold standard care recommendation in this area of medicine throughout the UK.
- Royal College of Obstetrics and Gynaecology (RCOG) guidelines on the *Prevention and Management of Postpartum Haemorrhage* (2016 update), which Collins assisted in developing, now state that **"***A plasma fibrinogen level of greater than 2g/l should be maintained during ongoing PPH*" **[3.2, 5.9]**. Previous RCOG guidelines had recommended maintaining fibrinogen >1g/L during major PPH.
- Citing the RCOG guidelines, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) 2017 guidelines on the Management of Postpartum Haemorrhage (PPH) recommend giving "*particular*" attention to fibrinogen testing by using point-of-care tests and providing cryoprecipitate or fibrinogen concentrate where the fibrinogen is <1.5-2g/L **[5.10a]**.
- The International Society on Thrombosis and Haemostasis (ISTH), a leading international organisation, recommended a more conservative use of FFP and platelets **[3.2, 3.4]** in its *Guideline on Management of Coagulopathy Associated with Postpartum Haemorrhage,* authored by Collins **[5.10b]**.
- The 2017 German PPH guidelines, compiled by the German, Austrian and Swiss Societies of Gynaecology and Obstetrics, cite Cardiff research **[3.2]** in their recommendation that: "*a fibrinogen concentration <2g/l may identify those at increased risk for severe bleeding {consensus of the committee}*" **[5.10c]**.

Through their research into measured blood loss and rapid point-of-care fibrinogen testing for PPH management, the Cardiff team created an integrated new care package which provided clearer, standardised methods for monitoring blood loss, aligned to the provision of more

timely and effective treatment. This reduced the incidence of massive and life-threatening PPH and the need for blood transfusion whilst preventing infusion of unnecessary blood products. The new care package was implemented across Wales, and more recently Scotland and England. The research findings also underpinned changes to international guidelines used to inform clinical management of maternal bleeding globally.

5. Sources to corroborate the impact (indicative maximum of 10 references)

[5.1] Collins PW, Bell SF, de Lloyd L, Collis RE. (2019) Management of postpartum haemorrhage: from research into practice, a narrative review of the literature and the Cardiff experience. *Int J Obst Anaesth* 37:106-117. doi: 10.1016/j.ijoa.2018.08.008

[5.2] Bell SF, Kitchen T, M. J, *et al*. (2020) Designing and Implementing an All Wales Postpartum Haemorrhage Quality Improvement Project: OBS Cymru (The Obstetric Bleeding Strategy for Wales). *BMJ Open Quality* 9:e000854

[5.3] OBS Cyrmu tools and resources, 1,000 Lives webpages

[5.4] Bell S, Collis R, Pallmann P, Bailey C, James K, John M, Kelly K, Kitchen T, Scarr C, Watkins A, Edey T, Macgillivray E, Greaves K, Volikas I, Tozer J, Sengupta N, Roberts I, Francis C, and Collins, P. Reduction in massive postpartum haemorrhage and red blood cell transfusion during a national quality improvement project, Obstetric Bleeding Strategy for Wales, OBS Cymru: an observational study (11 October 2020

[5.5] Dale, M., Bell, S., Scarr, C., Collis, R., James, K., Carolan-Rees, G. & Collins, P. 2020 OBS Cymru: A health economic evaluation, Presentation at the Obstetric Anaesthetist Association Conference 2020.

[5.6] Implementation of OBS Cymru (Obstetric Bleeding Strategy for Wales), a management strategy for Postpartum Haemorrhage (PPH), in Maternity Services. Welsh Health Circular, April 2019, Welsh Government

[5.7] Scottish Patient Safety Programme Postpartum Haemorrhage 4 stage approach. NHS England Improve the early recognition and management of deterioration or either mother or baby during or soon after birth.

[5.8] Curry NS, Davenport R, Pavord S, Mallett SV, Kitchen D, Klein AA, Maybury H, Collins PW, Laffan M. (2018) The use of viscoelastic haemostatic assays in the management of major bleeding. *BJH* 182:789-806. British Society for Haematology guidance

[5.9] Mavrides E, Allard S, Chandraharan E, Collins P, Green L, Hunt BJ, Riris S, Thomson AJ on behalf of the Royal College of Obstetricians and Gynaecologists. (2016) Prevention and management of postpartum haemorrhage. *BJOG* 124:e106–e149

[5.10] International guidelines evidence set: **a**. RANZCOG guidelines, **b.** Collins P, Abdul-Kadir R, Thachil J. (2016) Management of coagulopathy associated with postpartum hemorrhage: guidance from the SSC of the ISTH. *J Thromb Haemost* 14:205–10, **c.** 2017 German PPH Guidelines