Institution: University of Birmingham

Unit of Assessment: UoA 1, Clinical Medicine

Title of case study: Saving the lives of mothers in low-resource countries by reducing bleeding following childbirth

Period when the underpinning research was undertaken: 2015–2020

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:
Arri Coomarasamy	Professor of Gynaecology	2008–present
Dr Ioannis Gallos	Clinical Lecturer in Obs and Gynaecology	2013–2018
	Senior Lecturer in Global Maternal Health	2018–present
Tracy Roberts	Senior Lecturer in Health Economics	1998–2009
	Professor of Health Economics	2009–present
Dr Malcolm Price	Research Fellow in Medical Statistics	2013–2015
	Lecturer in Medical Statistics	2015–present
Jon Deeks	Professor of Biostatistics	2006–present

Period when the claimed impact occurred: 2018 to December 2020

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

1. Summary of the impact

Research from the University of Birmingham has improved the management of life-threatening bleeding following childbirth (postpartum haemorrhage; PPH) for women in low- and lower-middle-income countries (LMIC). Specifically:

(i) **World Health Organization (WHO) public healthcare guidelines have changed** and now recommend the use of carbetocin, a heat-stable drug, for prevention of PPH;
(ii) **Health policies and guidelines in 17 LMIC** have adopted carbetocin for prevention of PPH;
(iii) **Affordable access to carbetocin** has been made possible in 79 LIC/LMIC;
Non-governmental organisations have supported the use of carbetocin in practice in LMIC.

2. Underpinning research

Excessive bleeding after childbirth (postpartum haemorrhage; PPH) is a major concern for every pregnant woman. It can lead to long-term ill health and death. The World Health Organization (WHO) recommends the uterus-contracting ('uterotonic') drug oxytocin for prevention of PPH. In high-income countries, oxytocin is given as standard practice to halve a woman's risk of PPH but in LMIC oxytocin is often ineffective because it is heat labile (i.e. effectiveness reduced at higher temperatures) and facilities for refrigerated storage and transport are generally not available. PPH during childbirth kills around 100,000 mothers and 80,000 babies each year in LMIC. Lack of an effective uterotonic medication is a major contributor to high maternal mortality in these countries. A heat-stable alternative would be more effective and potentially save many lives.

There are at least seven uterotonic medicines for preventing PPH, including the heat-stable drug carbetocin. In 2015, the National Institute for Health Research (NIHR) and Ammalife Charity supported Coomarasamy (principal investigator), Gallos, Roberts, Deeks and Price at the University of Birmingham (UoB) to **identify the most effective uterotonic drug for preventing PPH with the fewest adverse effects, using network meta-analysis (NMA)**; a complex statistical method to analyse data for multiple treatments from multiple studies [R1].

The NMA compared multiple drugs in a single coherent analysis. Gallos was the principal reviewer, and Price and Deeks were statisticians on the study. They designed the NMA methods using a reputable Cochrane protocol and performed the statistical analysis of 140 randomised controlled trials involving 88,947 women. They reported the following key finding in April 2018 [R2]:

KF1: Three uterotonic drugs, including carbetocin, are more effective for the prevention of PPH than oxytocin.

In parallel, between 2015 and 2018, WHO conducted a large randomised controlled trial — The CHAMPION trial — across 23 sites in ten countries to compare the effects of heat-stable carbetocin with those of standard therapy (oxytocin) on PPH after vaginal birth. This trial was funded in order to investigate the effectiveness of carbetocin compared to oxytocin and give justification for agreements to make it available at affordable price in public-sector facilities of high-burden countries. Coomarasamy was the UK lead for this WHO trial. A total of 29,645 women were randomised and the study reported the following key finding [R3]:

KF2: Carbetocin is non-inferior to (i.e. not worse than) oxytocin for preventing blood loss of at least 500ml or need for additional uterotonic medication at the time of vaginal birth.

In 2017, WHO prioritised the update of their existing (2012) recommendations on the use of uterotonics for prevention of PPH. This was in order to inform changes to practice and to work toward reducing global maternal mortality by 2030, in line with target 3.1 of the third Sustainable Development Goal. WHO identified the detailed NMA [R2] in progress in Cochrane Library by the UoB researchers. They invited Gallos to serve on the Evidence Synthesis Group for the recommendations and asked the UoB team to update their NMA to include the new evidence from the CHAMPION trial [R3] and other recent trials relating to other uterotonics [S1, p. 8]. The updated NMA, published in December 2018, included 196 randomised controlled trials conducted across 53 countries (across all income levels) and involving 134,414 women. The study provided effectiveness and safety estimates for each of the uterotonic agents, reported a ranking for each drug and described the following key findings [R4]:

KF3: Carbetocin is superior to oxytocin, preventing for all births (vaginal and caesarean section) one more PPH event out of three (30% reduction) without any greater undesirable effects.

KF4: Using carbetocin as the drug of choice worldwide could save more than 4 million women from suffering PPH each year and reduce related complications, including death, that are a particularly significant risk for women in LMIC.

Heat-stable carbetocin has a higher unit cost than oxytocin (£17.64 vs £0.91). To assess whether carbetocin could be recommended for general healthcare, its cost-effectiveness and affordability compared with other uterotonics had to be considered. Using pooled data from the NMA, Roberts developed a model-based cost-effectiveness analysis to compare, from the perspective of the UK NHS as representative of a high-income country setting, the six different combinations of uterotonic drugs available [R5 and R6]. The study made the following key finding:

KF5: In developed countries, where the cost of PPH is high, carbetocin is the most cost-effective drug for the prevention of PPH.

3. References to the research

R1: Gallos ID, Williams HM, **Price MJ**, Merriel A, Gee H, Lissauer D, Moorthy V, Tunçalp Ö, Gülmezoglu AM, **Deeks JJ**, Hofmeyr GJ, **Coomarasamy A**. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD011689. **doi: 10.1002/14651858.CD011689**

R2: Gallos ID, Williams HM, **Price MJ**, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, **Deeks JJ**, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, **Coomarasamy A**. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database of Systematic Reviews 2018, Issue 4. Art. No.: CD011689. **doi: 10.1002/14651858.CD011689.pub2.**

R3: Widmer M, Piaggio G, Nguyen TMH, Osoti A, Owa OO, Misra S, **Coomarasamy A**, Abdel-Aleem H, Mallapur AA, Qureshi Z, Lumbiganon P, Patel AB, Carroli G, Fawole B, Goudar SS, Pujar YV, Neilson J, Hofmeyr GJ, Su LL, Ferreira de Carvalho J, Pandey U, Mugerwa K, Shiragur SS, Byamugisha J, Giordano D, Gülmezoglu AM; WHO CHAMPION Trial Group. Heat-stable carbetocin versus oxytocin to prevent hemorrhage after vaginal birth. N Engl J Med 2018;379:743-752. **doi: 10.1056/NEJMoa1805489.**

R4: Gallos ID, Papadopoulou A, Man R, Athanasopoulos N, Tobias A, **Price MJ**, Williams MJ, Diaz V, Pasquale J, Chamillard M, Widmer M, Tunçalp Ö, Hofmeyr GJ, Althabe F, Gülmezoglu AM, Vogel JP, Oladapo OT, **Coomarasamy A**. Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis. Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD011689. **doi: 10.1002/14651858.CD011689.pub3**
R5: Pickering K, **Gallos ID**, Williams H, **Price MJ**, Merriel A, Lissauer D, Tobias A, Hofmeyr GJ, **Coomarasamy A**, **Roberts TE**. Uterotonic Drugs for the Prevention of Postpartum Haemorrhage: A Cost-Effectiveness Analysis. Pharmacoecon Open. 2019 Jun;3(2):163-176. **doi: 10.1007/s41669-018-0108-x.**
R6: Gallos I, Williams H, **Price M**, Pickering K, Merriel A, Tobias A, Lissauer D, Gee H, Tunçalp Ö, Gyte G, Moorthy V, **Roberts T**, **Deeks J**, Hofmeyr J, Gülmezoglu M, **Coomarasamy A**. Uterotonic drugs to prevent postpartum haemorrhage: a network meta-analysis. Health Technol Assess. 2019 Feb;23(9):1-356. **doi: 10.3310/hta23090**. PMID: 30821683; PMCID: PMC6421507.

4. Details of the impact

We have **improved the management of life-threatening postpartum haemorrhage** (PPH) after childbirth for women. This is most important for women living in hot, isolated, rural areas in LMIC who are among the world's poorest with limited access to health resources. Specifically, we have:

1. **Changed World Health Organization and national guidelines on the prevention of PPH**

1.i. WHO guidelines have changed with regard to recommended use of uterotonic drugs and their status as essential medicines:

- In 2018, WHO updated their recommendations on the use of uterotonic drugs for prevention of **PPH to include carbetocin**, such that the guidelines now advise:
  - [carbetocin should be used] "in settings where oxytocin is unavailable (or its quality cannot be guaranteed)" [S1, Recommendation 3, p. ix; KF1–KF4];
  - [use of] "carbetocin […] for the prevention of PPH for all births [vaginal and caesarean section] in contexts where its cost is comparable to other effective uterotonics" [S1, Recommendation 1.2, p. ix; KF1–KF4]

That these recommendations are a result of our research is shown by the fact that the WHO cited our research as the "primary source of evidence on the benefits and harms" of the alternative uterotonic drugs available [S1, p. 7; R4]. Likewise our research was used as "evidence on the relative effectiveness and safety of the different uterotonic agents relative to oxytocin" [S2; R2].

- In 2019, **carbetocin was added to The WHO Model List of Essential Medicines** [S3i, p. 47] on account of its significant health and cost-effective benefits [R3–R6; S3ii]. Its use is especially advised in settings such as LMIC where "the cold-chain transport or storage of oxytocin is not possible" [S3iii, p. 418].

1.ii. International bodies have promoted the use of carbetocin:

- **The International Federation of Gynecology and Obstetrics (FIGO) and The International Confederation of Midwives (ICM)** are in the process of aligning with WHO guidance to include carbetocin within updated guidelines on PPH management as they believe that "with new treatment options (including carbetocin) it is possible to save most women (>90% of those currently dying from PPH) from PPH death even at the health center level, in hands of a midwife or other skilled provider" [S4i].
- **The United Nations Fund for Population Activities (UNFPA**) reported giving consideration to carbetocin for addition to the list of maternal health medicines offered by the programme in its 2019 annual report [S4ii].

1.iii. **Guidelines in 17 of the world's 79 LIC/LMIC now recommend carbetocin** to prevent PPH in line with the changes to the WHO recommendations, just seven months after carbetocin obtained market approval from Swissmedic, the Swiss national authorisation and supervisory

authority for drugs and medical products. As of the end of December 2020, the following changes to national guidelines have been achieved:

- Regulatory approval granted in **India (2020)** [S5i, p. 4] and Tanzania (2020) [S5ii];
- Submissions for regulatory approval awaiting outcomes in four countries (**Kenya, Nigeria, Sierra Leone and Uganda**) [S5iii];
- Added to Essential Medicines Lists (EML) in four countries [S5iv] (**Kenya (2019)** [S5v, p. 100], **Nigeria (2020)** [S5vi, p. 19], **Côte d'Ivoire (2020)** [S5vii, p. 15] and The **Philippines (2018)** [S5viii]);
- Applications for addition to EML in progress in 11 countries (**Ethiopia, Rwanda, Uganda, Burkina Faso, Ghana, South Sudan, Liberia, Senegal, Sierra Leone, Burundi and Mali**) [S5iv, S5ix, S5x];
- Guidelines updated in two LIC/LMIC to include heat-stable carbetocin for PPH prevention (**Kenya** (2019) and **Burkina Faso** (2020)) [S5iv];
- Updates to intrapartum guidelines for PPH prevention incorporating use of heat-stable carbetocin in progress in 12 countries (**Ethiopia, Rwanda, South Sudan, Kenya, Uganda, Burkina Faso, Ghana, Liberia, Senegal, Sierra Leone, Burundi and Mali**) [S5iv, S5ix, S5x];
- The **Australian state of Queensland** included carbetocin for prevention of PPH after vaginal birth and caesarean section in their 2020 guidelines on PPH [S5xi, pp. 13 and 15], quoting the effectiveness estimates from R4 as part of their evidence for recommendation.

Swissmedic and Non-governmental organisations (NGOs) helped to achieve this rapid uptake of carbetocin into policy in LIC/LMIC. Swissmedic reduced the time taken for market approval of carbetocin in LIC/LMIC by following the Marketing Authorisation for Global Health Products (MAGHP) procedure even though this had not been done for a medicinal product before [S6]. NGOs (e.g. Concept Foundation and WACI Health) worked with the countries' health authorities to promote the 2018 WHO PPH recommendations and assisted in preparing their applications to integrate carbetocin into national recommendations and obtain regulatory approval [S5iii, iv, ix, x]. These NGOs were and continue to be supported by funding from Merck, Sharp & Dohme (MSD), through 'MSD for Mothers', an initiative of Merck & Co., Inc., NJ, U.S.A.

2. <u>Adopting carbetocin in clinical practice in LMIC</u>

Changing clinical practice in the use of carbetocin involves not just changing recommendations, but also making access to the treatment possible. Our work has contributed to making carbetocin available for **use in clinical practice** in the poorest countries of the world through (i) making it affordable and (ii) removing barriers to take-up.

2.i. The cost of carbetocin was set 30–150 fold lower than market price in public sector facilities of LMIC. Our work [R3, R4], which confirmed the non-inferiority of carbetocin for preventing PPH, triggered an agreement on affordable pricing for carbetocin between WHO and the pharmaceuticals (Ferring and MSD). The price agreed was comparable to the United Nations Population Fund price for oxytocin [S3iii, pp. 419–420].

2.ii. NGOs have supported clinical practice change, by providing the funding, manpower and expertise needed to help remove the barriers to take-up of carbetocin (e.g. through sustainable financing, supply chain management, training of healthcare providers and other stakeholders, and improving the awareness and engagement of expectant mothers). Examples of programmes include:

- **MSD for Mothers' Smiles for Mothers initiative:** A community-level programme operating across **ten counties of Kenya** and **three states of Nigeria** executed on the ground by implementing non-profit consortiums Jhpiego and Solina Center for International Development and Research (SCIDaR) respectively. In total, **40 health facilities across Kenya and 84 across Nigeria** are involved [S5iii].
- **The University of Birmingham's E-MOTIVE implementation program** funded by an $11M grant from the Bill and Melinda Gates Foundation is being rolled out in **80 hospitals across five countries (Tanzania, Kenya, Nigeria, South Africa and Sri Lanka)**,

involving over 400,000 women giving birth. Carbetocin is given in the first response bundle of treatment and in these countries a progressive switch to carbetocin for PPH prevention is taking place enabling E-MOTIVE to monitor the occurrence of PPH with carbetocin and provide evidence-based guidance for the full package of PPH care in LMIC [S7i, ii].

- **Concept Foundation** together with African project partner WACI Health have begun a programme of work to improve access to medicines for management of PPH in 12 sub-Saharan Africa countries. The work started in January 2019 with regional and country-specific workshops. Countries are now working on completing the drafts of their new guidelines and EML including heat-stable carbetocin. The second phase of the program, beginning January 2021, is set out to develop a national clinical protocol in eight countries with pilot implementation in four [S5vii, xi, x].

5. Sources to corroborate the impact

S1 WHO recommendations (2018) Uterotonics for the prevention of postpartum haemorrhage
S2 A systematic review of the cost-effectiveness of uterotonic agents for the prevention of postpartum haemorrhage
S3i World Health Organization Model List of Essential Medicines (2019)
S3ii Proposal for inclusion of Carbetocin in the WHO List of Essential Medicines
S3iii The Selection and Use of Essential Medicines
S4i FIGO statement on the initiation of a collaborative effort to improve PPH control (Jan 2020).
S4ii UNFPA supplies annual report 2019: highlights of key progress.
S5i Carbetocin approval by Indian Drug Regulatory Authorities (2020)
S5ii Carbetocin approval by Tanzanian Drug Regulatory Authorities (2020)
S5iii MSD for Mothers update on activities to support adoption of the 2018 WHO recommendations for prevention of PPH in LIC/LMIC.
S5iv MSD for Mothers review of normative policy change to align with WHO Recommendations on Medicines to Prevent & Treat PPH: Country PPH Guidelines and EML
S5v Kenya Essential Medicines List (2019)
S5vi Nigeria Essential Medicines List (2020)
S5vii Côte d'Ivoire Essential Medicines List (2020)
S5viii Implementation of the approved medicine in the 8th edition of the Philippine National Formulary
S5ix Concept Foundation update on activities to improve access to PPH medicines across Africa.
S5x Concept Foundation's web pages detailing the organisation's initiatives for LIC/LMIC country support. Available from: Concept Foundation initiatives for country support
S5xi Queensland Clinical Guidelines on primary postpartum haemorrhage
S6 Swissmedic authorises a medicinal product under the Marketing Authorisation for Global Health Products (MAGHP) procedure for the first time
S7i EMOTIVE award letter
S7ii EMOTIVE site ISRCTN: NCT04341662