Institution: London School of Hygiene & Tropical Medicine

Unit of Assessment: 1

Title of case study: Repurposing tranexamic acid as a life-saving treatment for severe bleeding

Period when the underpinning research was undertaken: 2005-2012

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

Name(s):	Role(s) (e.g. job title):	Period(s) employed:
Ian Roberts	Professor	10/03/01-present
Haleema Shakur-Still	Associate Professor; Professor	01/11/02-present

Period when the claimed impact occurred: 2013-2020

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

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

Researchers from the Clinical Trials Unit at LSHTM found innovative ways to repurpose an existing drug as a life-saving treatment for major blood loss. Their findings demonstrated that early administration of tranexamic acid in patients with acute traumatic bleeding or post-partum haemorrhage could reduce deaths from bleeding by one third, without adverse effects. This resulted in the drug being included in the World Health Organization Essential Medicines List for both trauma and post-partum haemorrhage and the WHO recommending its use on a global scale. Advocacy campaigns from the lead researchers led to it being used to prevent haemorrhage in the NHS in Britain, the UK and US militaries, and by international health bodies worldwide. The drug was found to be highly cost-effective in high, middle- and low- income settings.

2. Underpinning research (indicative maximum 500 words)

Tranexamic acid (TXA) is a drug that reduces bleeding by inhibiting blood clot breakdown. It has been licensed for use for many years to treat heavy menstrual periods, for dental extraction in people with bleeding disorders, and to reduce blood transfusion in surgical patients. Researchers in the Clinical Trials Unit at LSHTM led two global randomised clinical trials: the CRASH-2 trial (Clinical Randomisation of Antifibrinolytic in Significant Haemorrhage) and the WOMAN (World Maternal Antifibrinolytic) trial, that provided strong evidence that repurposing this drug as a life-saving treatment for major blood loss reduced mortality by one third.

CRASH-2

Worldwide, traumatic bleeding kills around 2 million people each year, with over 90% of the deaths in low- and middle-income countries (LMICs). Because similar haemostatic mechanisms are activated in surgery and trauma, LSHTM researchers hypothesised that TXA might reduce bleeding in trauma patients, up to one third of whom die from haemorrhage. The NIHR-funded CRASH-2 trial was a randomised trial of the effects of the early administration of TXA on death, vascular occlusive events and blood transfusion. A total of 20,211 adults with significant traumatic bleeding attending 247 hospitals in 40 countries from 2005 to 2009 were randomised to TXA or matching placebo, with 99.6% follow-up. The risk of death due to bleeding was significantly reduced with TXA. Importantly, there was no increase in fatal or non-fatal vascular occlusive events. Deaths from all causes were also significantly reduced with TXA. The large numbers of patients studied across a range of health care settings helped these results to be widely relevant. The trial results were published in The Lancet in 2010, winning BMJ Research Paper of the Year (3.1).

The trial's key researchers were Roberts and Shakur-Still from LSHTM, with Professor Tim Coats of the University of Leicester and Dr Beverley Hunt, Consultant in Haematology & Rheumatology, Guy's & St Thomas' Trust. Roberts and Shakur-Still were the lead applicants and principal investigators for the worldwide trial, and LSHTM's Clinical Trials Unit ran the trial.

Subsequent analyses also published in The Lancet (2011) found that early TXA treatment (within 1 hour of injury), was more effective in reducing death due to bleeding than late treatment (3.2). Cost-effectiveness analysis reported that TXA administration was highly cost-effective in high, middle- and low-income countries. The incremental cost per life year gained of administering TXA was USD48, USD66 and USD64 in Tanzania, India and the UK respectively (3.3).

WOMAN

While recruiting participants for CRASH-2, health providers in LMICs highlighted the burden of death by excessive bleeding after birth, or post-partum haemorrhage (PPH). A woman dies from PPH every 6 minutes around the world, amounting to more than 100,000 deaths per year. Most of these women live in LMICs which often lack access to life-saving facilities and resources. The WOMAN trial, led by Shakur-Still and Roberts, tested whether TXA could also reduce deaths from post-partum haemorrhage. Between 2010 and 2016, the LSHTM-coordinated trial enrolled 20,060 women with a clinical diagnosis of PPH from 193 hospitals in 21 collaborating countries. The trial found that death by bleeding was reduced by 31% in women given tranexamic acid compared to the control placebo group, especially if given within three hours of giving birth, and had no adverse effects for mothers or babies. The findings, published in The Lancet in 2017, also demonstrated that TXA reduced the need for urgent surgery to control bleeding (laparotomy) by more than a third (36%) (3.4).

A cost-effectiveness analysis found that treating PPH with TXA was highly cost-effective in the study sites in Nigeria and Pakistan, and was therefore likely to be cost-effective in other countries with a similar baseline risk of maternal mortality due to PPH (3.5).

The Clinical Trials Unit later conducted an individual patient data meta-analysis of randomised trials of TXA in acute severe bleeding showing the importance of urgent treatment and the impact of treatment delay. This study combined the data from the CRASH and WOMAN trials, giving a sample size of over 40,000 (3.6). The results showed that immediate treatment increased survival chances by 70%, decreasing by 10% with every 15-minute delay until 3 hours, after which there was no health benefit.

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

3.1 The CRASH-2 collaborators. 2010. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 3;376(9734):23-32. doi: 10.1016/S0140-6736(10)60835-5

3.2 The CRASH-2 collaborators. 2011. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 trial. *Lancet*. 377(9771):1096-101, 1101.e1-2. doi: 10.1016/S0140-6736(11)60278-X.

3.3 Guerriero C, **Cairns J**, **Perel P, Shakur H, Roberts I.** 2011. Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial. *PLoS ONE* 6(5): e18987. doi:10.1371/journal.pone.0018987.

3.4 The WOMAN trial collaborators. 2017. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. *The Lancet.* 389(10084):2105-2116. doi: 10.1016/S0140-6736(17)30638-4.

3.5 Li B, Miners A, **Shakur-Still H, Roberts I**, et al, on behalf of the WOMAN trial collaborators. 2018. Tranexamic acid for treatment of women with post-partum haemorrhage in Nigeria and Pakistan: a cost-effectiveness analysis of data from the WOMAN trial. *Lancet Global Health.* 6(2):e222-e228. doi: 10.1016/S2214-109X(17)30467-9.

3.6 Gayet-Ageron A, Prieto-Merino D, Ker K, **Shakur-Still H**, Ageron F-X, **Roberts I** for the Anti-fibrinolytic Trials Collaboration. 2017. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40,138 bleeding patients. *Lancet.* 391(10116):125-132. doi: 10.1016/S0140-6736(17)32455-8.

We believe this body of research meets the 'at least 2*' definition given its reach, significance and rigour.

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

CRASH — changing the way bleeding from trauma is treated

The CRASH-2 trial led to a worldwide change in treatment practices, with treatment using TXA now regarded as the standard of care in severe injury. In 2010, LSHTM successfully applied to include tranexamic acid on the World Health Organization (WHO) List of Essential Medicines, and in 2011 and 2012, the British and US Armies included TXA in their combat care treatment protocols. Since 2013, the sustained impact of these protocol changes recommending worldwide use of TXA following severe injury has led to increased use in armed conflict settings and globally, and to reduced mortality. A 2018 paper in BMJ Military Health showed that 93% of military doctors knew the initial dose of TXA, and 91% knew of the CRASH trial and the optimal time for delivery of the drug (5.1).

In 2019, the then UK Defence Secretary Gavin Williamson granted a GBP5 million transformation fund for the development of the TXA auto-injector, which is expected to benefit up to a third of seriously injured soldiers who would otherwise die from their wounds (5.2).

TXA was the first drug to be fast-tracked for use in the NHS under the government's medicines innovation scheme, and was used widely across the NHS. The National Institute for Clinical Excellence (NICE) guideline 2016 for 'Major trauma: assessment and initial management' recommends use of intravenous TXA as soon as possible in patients with major trauma and active bleeding (5.3).

To facilitate the implementation of these protocols and the use of the medicine, LSHTM led efforts with patients, media (winning the 2013 NIHR media competition), clinicians and policy makers (the National Clinical Director, NHS Trusts, the World Health Organization). From 2012 to 2015, the team worked with RoadPeace, the road traffic victims' charity, in monitoring NHS Trust use of TXA via annual Freedom of Information requests to NHS Trusts. The team then worked with Professor Chris Moran, the National Clinical Director for Trauma, to revise the best practice tariff for trauma to incentivise treatment with tranexamic acid at the crash scene and within three hours of injury, with an additional per patient payment (of GBP2,800 in 2017). Payments depended on achieving a series of quality standards, which include TXA administration to severely injured patients (5.4). TXA is now administered under patient group directives by paramedics across UK Ambulance Trusts and London's Air Ambulance (5.5).

Research led by Professor Timothy Coats of the University of Leicester described the use of TXA in trauma care in England and Wales since the publication of the CRASH-2 trial. Their analysis of data from the Trauma Audit and Research Network (TARN) showed that TXA use had increased from near zero in 2010 to 10% in 2016, and 80% of those that received TXA did so within 3 hours of injury. (5.5a)

The administration of TXA in patients with haemorrhage requiring transfusion in Major Trauma Centres increased from near zero in 2010 to 90% in 2016, and in association with wider changes in UK trauma management, the odds of survival have increased by nearly a fifth between 2008 and 2017 (5.5b).

Following Roberts' criticism of the BBC over a 2011 episode of Holby City promoting a trauma drug for which there was no evidence of saving lives, LSHTM trauma experts successfully lobbied the BBC to include TXA in its other emergency care soap, Casualty (2017), advocating for accurate representation and promotion of drugs to prevent bleeding. The BBC's 2014 programme

'An Hour to Save Your Life' highlighted the current use of TXA in UK trauma care implemented as a direct result of CRASH-2 (5.6).

In 2019, Roberts was awarded the first Faculty of Public Health Bazalgette Professorship Champion of Evidence Award, which recognises major contributions to public health policy and/or practice through research translation for the benefit of UK population health (5.7).

WOMAN — making TXA part of maternity care

The life-saving impact of the WOMAN trial has gone further than the vast scale of the trial itself which demonstrated the innovative potential and alternative application of a well-established drug. Safe, effective and affordable PPH treatments are critical to saving the lives of pregnant women globally, and the findings of this trial had important implications for the delivery of high-quality maternity care.

The WHO was given access to the trial results prior to publication and acted quickly to update its guidance, reflecting the urgency of action to prevent maternal deaths in line with the Sustainable Development Goal (SDG) 3 to reduce maternal and newborn mortality. In March 2017, the WHO convened a panel of international experts to review and prioritise the evidence for updating the recommendations in maternal and perinatal health. Recommendations relating to PPH prevention and treatment (including the recommendation on the use of tranexamic acid for PPH treatment) were listed as highest priority for implementation. In April 2017, new WHO guidance was released following the panel review of evidence, strongly recommending early use of TXA within three hours of birth as part of standard care when PPH is diagnosed (5.8a). This was directly informed by the results of the WOMAN trial and also highlighted the need for all health systems, regardless of their level of resources, to recognise that TXA is a life-saving intervention that should be made readily available for PPH management wherever emergency obstetric care is provided. Professional organisations, including the Royal Society for Obstetricians & Gynaecologists, endorsed the results (5.9).

In 2019, the WHO updated its essential medicines list to include TXA specifically for PPH (5.8b). In most countries, the cost per dose of TXA is only GBP2 and it is already available for treating blood loss.

The Wellcome Trust, who funded the trial, undertook further work following the trial results to understand, identify and address country-specific issues and local barriers around TXA use for PPH. Training of 25 practitioners across 10 provinces in Tanzania in 2019 and 2020 was followed up by mentorship to health care professionals. In Nepal, Wellcome worked closely with the Family Welfare Division of the Ministry of Health and clinicians and public health experts at community and regional levels to develop policy guidelines and protocols for TXA for PPH management in 2020. As a result, Nepal's PPH treatment and guidance policy was updated to recommend TXA in line with WHO guidelines (5.10).

The WOMAN Trial results were reported by media in more than 60 countries and generated over 800 pieces of coverage across TV, radio, print and online. This included more than 450 online articles, plus at least 350 TV and radio pieces identified by broadcast monitoring, although this figure is likely to be much higher as stories were syndicated to around 2,500 stations globally. There were in excess of 4,200 posts about the results on social media, with a potential reach of 79 million people (5.11).

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

5.1 Herron JBT, French R, Gilliam AD (2018). Civilian and military knowledge of tranexamic acid (TXA) use in major trauma: a comparison study. BMJ Military Health. 164:170-171

5.2 News story. Lifesaving frontline technology given £5 million funding boost. 2019. Ministry of Defence. Accessed at: https://www.gov.uk/government/news/life-saving-frontline-technology-given-5-million-boost

5.3 National Clinical Guideline Centre. Major trauma: assessment and initial management. NICE Guideline NG39: methods, evidence and recommendations. February 2016.

- Pg 51 recommendation, CRASH-2 trial evidence used pg 130, 134-135, 140, reference 117 & 127

5.4 NHS England and NHS Improvement. Guidance on best practice tariffs, 2017/18 and 2018/19 National Payment Tariff System. 2016.

- Eligibility criteria, pg 28
- Guidance on best practice tariffs, 2017/18 and 2018/19 National Payment Tariff System. NHS England and NHS Improvement. 2016. Annex F, pg 33

5.5a Coats TJ, Fragoso-Iñiguez M, Roberts I. Implementation of tranexamic acid for bleeding trauma patients: a longitudinal and cross-sectional study. *BMJ Emergency Medicine Journal*. 2019;36:78-81.

- shows increasing use of TXA for trauma care

5.5b Moran CG, Lecky F, Bouamra O, Lawrence T, Edwards A, Woodford M, et al. Changing the system – major trauma patients and their outcomes in the NHS (England) 2008-17. *The Lancet.* 2018.

- Findings demonstrate increased use of TXA following publication of CRASH-2

5.6 'Holby City accused of using 'unsafe' drug in storyline.' The Independent. 3 September 2011. Accessed at: https://www.independent.co.uk/arts-entertainment/tv/news/holby-city-accused-using-unsafe-drug-storyline-2348420.html

Tranexamic acid in BBC One's Casualty. Accessed at: https://www.youtube.com/watch?v=YffGc6Dy1-A

BBC2. 'An hour to save your life'. Accessed at: https://www.bbc.co.uk/programmes/b05y19q2/episodes/guide

5.7 Faculty of Public Health Bazalgette Lecture. Ian Roberts awarded Bazalgette professorship for translating research on TXA in the management of acute severe bleeding into practice. Statement accessed at: https://www.fph.org.uk/news-events/events-courses-and-exams/2019/fph-bazalgette-lecture/

5.8a World Health Organization. WHO recommendation on tranexamic acid for the treatment of postpartum haemorrhage. 2017.

5.8b World Health Organization. Executive summary. The Selection and Use of Essential Medicines 2019. Report of the 22nd WHO expert committee on the selection and use of essential medicines.

5.9 Royal College of Obstetricians & Gynaecologists. RCOG statement on drug treatment for excessive blood loss after childbirth. 2017.
Accessed at: https://www.rcog.org.uk/en/news/rcog-statement-on-drug-treatment-for-excessive-blood-loss-after-childbirth

5.10 Testimonial from Olivia Allen, Wellcome Trust Senior Global Policy & Advocacy Officer

5.11 WOMAN trial media coverage book