Institution: London School of Hygiene & Tropical Medicine (LSHTM)

Unit of Assessment: UoA2 – Public Health, Health Services & Primary Care

Title of case study: Identifying and promoting a new trauma treatment which could save over 100,000 lives a year

1. Summary of the impact

Research by LSHTM has alerted international health bodies, the UK and US militaries, politicians and doctors around the world to a new trauma treatment that could save over 100,000 lives each year. A proactive advocacy campaign following the publication of the CRASH-2 trial in *The Lancet* has secured media coverage in major global news outlets, the inclusion of the drug tranexamic acid (TXA) on the WHO List of Essential Medicines and direct endorsements from WHO officials, UK ministers and army figures. TXA was the first drug to be approved under the UK government's Medicines Innovation Scheme.

2. Underpinning research

Traumatic bleeding, mostly from road traffic accidents or violent crime, kills around 2m people worldwide each year, with over 90% of deaths in low- and middle-income countries.

Shosuke and Utako Okamoto discovered in 1962 that TXA is a potent inhibitor of fibrinolysis. Since then it has been used to treat heavy menstrual periods, for dental extraction in people with bleeding disorders, and to reduce blood transfusion in surgical patients. Because similar haemostatic mechanisms are activated in surgery and trauma, researchers from LSHTM hypothesised that TXA might also reduce bleeding in trauma patients, up to one third of whom die from acute haemorrhage.

A group of academics and doctors, led by Professor Ian Roberts (LSHTM since 2001) and Senior Lecturer Haleema Shakur (LSHTM since 2002 then Trial Manager), secured £2.5m in funding from the National Institute of Health Research in 2007 to carry out the CRASH-2 trial – a randomised controlled trial of the effects of the early administration of TXA on death, vascular occlusive events and blood transfusion. Other collaborators were Professor Tim Coats, University of Leicester, and Professor Beverley Hunt, Guy's and St Thomas' Trust. The team also secured around £850,000 in additional funding.

The CRASH-2 trial was designed and coordinated by LSHTM and carried out within a global network of trauma hospitals. A total of 20,211 adult patients with significant traumatic bleeding were recruited from 274 hospitals in 40 countries. They were injected with 1g of TXA or placebo within a few hours of being injured followed by another 1g in a drip over the next eight hours, or a matching placebo. The researchers found that TXA reduced the chances of death from severe blood loss by one third, with no side effects. The results were published in *The Lancet*[3.1] in March 2010 (and subsequently republished in many languages), and the academics recommended the inclusion of TXA on the WHO List of Essential Medicines. They subsequently estimated that TXA could prevent over 100,000 deaths every year across the world[3.2] and in countries like India and China it could save tens of thousands of lives each year.

A subsequent analysis of the CRASH-2 trial published in *The Lancet*[3.3] in 2011 showed strong evidence that the effect of TXA on death due to bleeding varied according to the time from injury to treatment, with early treatment (within an hour from injury) significantly more effective. A second pre-specified analysis, published in the *BMJ*, showed that TXA can be administered safely to a wide spectrum of patients with traumatic bleeding and should not be restricted to the most severely injured.[3.4] A cost effectiveness analysis[3.5] showed that TXA administration is highly cost effective in high-, middle- and low-income countries. A study[3.6] of the effect of TXA in traumatic brain injury – CRASH-2 Intracranial Bleeding Study – concluded that neither moderate benefits nor moderate harmful effects of TXA in patients with traumatic brain injury could be excluded; further clinical trials are needed for this type of patient.

3. References to the research

3.1 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*, 376(9734): 23–32, doi:10.1016/S0140-6736(10)60835-5. Citation count: 262

3.2 Ker, K, Kiriya, J, Perel, P, Edwards, P, Shakur, H and Roberts, I (2012) Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial, *BMC Emergency Medicine*, 12(3), doi:10.1186/1471-227X-12-3. Citation count: 12

3.3 CRASH-2 collaborators (2011) The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial, *Lancet*, 377(9771): 1096–1101, doi:10.1016/S0140-6736(11)60278-X. Citation count: 97

3.4 Roberts, I, Perel, P, Prieto-Merino, D, Shakur, H, Coats, T, Hunt, BJ, Lecky, F, Brohi K and Willett, K, on behalf of the CRASH-2 Collaborators (2012) Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial, *BMJ*, 345(e5839), doi:10.1136/bmj.e5839. Citation count: 6

3.5 Guerriero, C, Cairns, J, Perel, P, Shakur, H and Roberts I, on behalf of the CRASH-2 trial collaborators (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. Citation count: 20

3.6 CRASH-2 Collaborators (Intracranial Bleeding Study) (2011) Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study), *BMJ*, 343(d3795), doi:10.1136/bmj.d3795. Citation count: 0

Key funding

Roberts, Shakur, Coats, Hunt, The CRASH-2 Trial, NIHR, 2007–2010, £2.5m. Additional funding from Pfizer, Novo Nordisk, The BUPA Foundation, The Moulton Charitable Trust.

4. Details of the impact

A sustained advocacy campaign following the 2010 publication of the CRASH-2 trial results has ensured TXA is being used to treat trauma patients in hospitals all over the world.

In 2010 the CRASH-2 team applied for the inclusion of TXA on WHO's List of Essential Medicines, which guides purchasing decisions by Ministries of Health in developing countries. It was accepted in March 2011[5.1] 'on the basis of the results of a very large trial of the use of tranexamic acid specifically for trauma patients'.

The CRASH-2 findings received blanket coverage across the global media in several languages, helped by a coordinated media campaign by all 40 centres involved in the clinical trial. A *BBC News* report[5.2] quoted WHO's Dr Etienne Krug as saying that doctors needed to be aware of the trial results to 'strengthen trauma response'. He said: 'The problem affects hundreds of millions every year worldwide.' The UK Health Minister Earl Howe said: 'This is a great example of how important research can help the NHS save more lives and spread best practice around the world.'

The CRASH-2 trial has changed the practices of the UK Ministry of Defence (MOD) and the US Department of Defense**.** Roberts began communications with the MOD in 2006 after discovering that British soldiers in Afghanistan and Iraq were being treated with an experimental blood-clotting drug – NovoSeven – that had not been fully tested. After the story broke in the UK, Roberts alerted MOD officials to the potential of TXA. In March 2010, the British Army incorporated TXA into combat care treatment protocols on the basis of the results of the CRASH-2 trial. A subsequent news report on *British Forces News*[5.3] quoted the Surgeon-General as saying that within weeks of the CRASH-2 trial results, they were using TXA to treat wounded troops – the first time the drug

had been used routinely in trauma patients.

The US Army carried out its own analysis of the efficacy of TXA,[5.4] reaching the same conclusions. US Army officials invited Roberts to Washington in June 2011 to discuss the CRASH-2 trial and in the same month announced TXA's inclusion in its treatment protocols.

In May 2011, the CRASH-2 trial won the Research Paper of the Year[5.5] at the 2011 *BMJ* awards, raising the profile of TXA among doctors. Two months later the Directors of Clinical Care for the UK ambulance service agreed that TXA would be given to all adults and teenagers who suffer major injury in the UK. At the same time, the Joint Royal Colleges Ambulance Liaison Committee approved a pre-hospital guideline on the administration of TXA and the Royal College of Paediatrics and Child Health agreed to convene a meeting of its Medicines Committee to consider TXA dosing requirements in paediatric trauma, with advice released in November 2012.[5.6]

In January 2012, *The Independent* reported that TXA was to be fast-tracked for use in the NHS, making it the first drug to be approved under the UK government's new 'medicines innovation scheme', designed to speed up the adoption of promising medication. Ambulance crews in south-west England had already been given access to TXA but the decision by the Department of Health (DH) led to it being rolled out across the UK. Health Secretary Andrew Lansley commented: 'The successful use of this drug to help some of our most seriously wounded troops in Afghanistan really shows the wide potential it has for our civilian emergency services.'[5.7]

As TXA is a low-profit drug it misses out on large advertising budgets but Roberts has led innovative campaigns to ensure more clinicians use TXA. In 2011 he oversaw the production of an animated video featuring cartoon character 'Tranman'. Recorded in several languages, the cartoon is designed to reach doctors in China, India, Brazil, Russia and Africa. The video was published on YouTube and *The Lancet* websites, and the *New York Times*[5.8] covered the making of the cartoon as an example of creative science communication.

The findings from the CRASH-2 trial resulted in follow-on funding (announced in 2010; reported by *BBC News*)[5.9] from the DH and the Wellcome Trust to investigate whether TXA can help to save some of the 100,000 lives lost every year when women bleed to death after giving birth. The ongoing WOMAN trial, coordinated by LSHTM and involving 13 partners, attracted £3.7m in funding. CRASH-3, to investigate TXA for treatment of significant traumatic brain injury, has received £400,000 for the pilot phase.

5. Sources to corroborate the impact

5.1 Inclusion of tranexamic acid on WHO List of Essential Medicines, http://www.who.int/selection_medicines/committees/expert/18/en/index.html (accessed 20 September 2013).

5.2 *BBC News* report and UK Health Minister endorsement http://www.bbc.co.uk/news/10311371 (accessed 20 September 2013).

5.3 British Army starts using tranexamic acid (quotes Surgeon-General) http://www.youtube.com/watch?v=oj6P2cwwRYw (accessed 20 September 2013).

5.4 US Army starts using tranexamic acid: Morrison, JJ, Dubose, JJ, Rasmussen, TE and Midwinter, MJ (2012) Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study, *JAMA Surgery*, 147(2): 113–119, doi:10.1001/archsurg.2011.287.

5.5 The *BMJ Awards:* Research paper of the year winner 2011, http://thebmjawards.bmj.com/previous-winners/2011/research-paper-of-the-year (accessed 21 November 2013).

5.6 Royal College of Paediatrics and Child Health guidelines (2012) *Evidence Statement: Major Trauma and the Use of Tranexamic Acid in Children,* November. London: Royal College of

Paediatrics and Child Health, http://www.rcpch.ac.uk/system/files/protected/page/121112_TXA%20evidence%20statement_final%20v2.pdf (accessed 11 September 2013).

5.7 *Independent* newspaper article, http://www.independent.co.uk/life-style/health-and-families/health-news/from-afghanistan-to-the-ambulance-the-warzone-drug-that-will-save-hundreds-of-lives-6285560.html (accessed 20 September 2013).

5.8 *New York Times* article on Tranman plus Youtube clip, http://www.nytimes.com/2011/11/22/health/trauma-to-highlight-benefits-of-a-clotting-drug-a-cartoon-figure-dies-a-messy-death.html (accessed 20 September 2013).

5.9 WOMAN trial http://www.bbc.co.uk/news/health-11177856 (accessed 20 September 2013).