Institution: University of Leicester		
Unit of Assessment: UOA1		
Title of case study: Tranexamic acid treatment for patients with major trauma		
Period when the underpinning research was undertaken: 2007-2020		
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:**
Prof Timothy J Coats	Professor of Emergency Medicine	2003 - present
Period when the claimed impact occurred: 2013 - 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Our research has shaped the global implementation of tranexamic acid (TXA) for major trauma. In 2011 we proved the efficacy of TXA in treating traumatic bleeding. Our continuing research has driven global change in trauma management protocols, saving an estimated 140,000 lives per year worldwide. In the UK we have led guideline development and our publications have shown an increase in the proportion of trauma patients treated with TXA from 1% in 2010 to 85% in 2016. Based on our more recent studies, NHS guidance was refined in 2020 to deliver TXA within one hour of injury.

2. Underpinning research

The Acute Coagulopathy of Trauma (ACOT), also known as Trauma Induced Coagulopathy (TIC), was first described in 2003 by Coats. He then found a treatment for the condition using the antifibrinolytic agent, TXA. The CRASH2 randomised controlled trial, published in the Lancet 2010 **[R1]**, was performed in 20,000 major trauma patients who had or were suspected of having significant bleeding recruiting from 274 hospitals in 40 countries. Coats was the clinical lead for the study, a co-applicant on the grant and a co-author on both major papers emerging from the trial. CRASH2 was conducted in collaboration with the London School of Hygiene and Tropical Medicine (Chief investigator Prof Ian Roberts). The trial showed that treatment with TXA reduced patient mortality from 16% (control group) to 14.5% (TXA group), thus preventing 9% of all trauma deaths – in other words one life was saved for every 67 patients treated. The key papers of the discovery of ACOT in 2003 (1600 citations) and discovery of an effective treatment in 2010 (1670 citations) are among the most widely cited in the trauma literature.

In 2015 a Cochrane review was published (Coats was last author) which synthesised the evidence in this area and recommended that TXA treatment should be given to all major trauma patients who are bleeding or at risk of bleeding **[R2].** This publication has formed the basis for global treatment guidelines.

A pre-specified subgroup analyses published in 2011 **[R3]** showed that the effect of TXA critically depends on the time interval between injury and the start of treatment. Treatment given within 3 hours of injury substantially reduces death due to bleeding, whereas treatment initiated

after 3 hours is ineffective. In 2019 analysis of national data **[R4]** from the Trauma Audit and Research Network (TARN), which Coats chairs, showed that treatment was being given late. This directly led NHS England to amend the Best Practice Tariff criteria for Major Trauma Centres in England and Wales, (reducing the time window for TXA treatment to achieve the BPT payment to NHS hospitals from 3 hours to 1 hour), which was implemented in 2020/21 financial year. The 2019 publication also showed that the proportion of eligible trauma patients in England treated with TXA increased from 1% in 2010 to 85% in 2016, with a total of 38,511 severely injured patients treated between 2014-2019. This rapid implementation of research results into practice, was achieved by using the TARN National Clinical Audit system and the NHS 'Best Practice Tariff' system to drive improvements in care.

In an individual patient-level data meta-analysis of randomised trials of TXA in acute bleeding **[R5]** no interaction was seen between effectiveness and baseline risk of death due to bleeding, and half of deaths occurred in patients with a low or intermediate risk. This emphasised that the treatment should be given to all patients, even if at low risk.

An analysis of molecular data **[R6]** published in 2020 examined the underlying basis for the mechanism of action of TXA treatment in major trauma. The finding of an "antifibrinolytic gap" of unopposed fibrinolysis has stimulated academic debate and further molecular studies are under way.

3. References to the research

[R1] 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. CRASH-2 trial collaborators, Shakur H, Roberts R, Bautista R, Caballero J, **Coats T**, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S. **Lancet**. 2010 Jul 3;376(9734):23-32.

[R2] Antifibrinolytic drugs for acute traumatic injury. Ker K, Roberts I, Shakur H, **Coats TJ**. **Cochrane Database of Systematic Reviews** 2015, Issue 5. Art. No.: CD004896. DOI: 10.1002/14651858.CD004896.pub4.

[R3] The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial.CRASH-2 collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, **Coats T**, Dewan Y, Gando S, Guyatt G, Hunt BJ, Morales C, Perel P, Prieto-Merino D, Woolley T. **Lancet** 2011. 377:1096-101.

[R4] Implementation of tranexamic acid for bleeding trauma patients: a longitudinal and cross-sectional study. **Coats TJ**, Fragoso-Iñiguez M, Roberts I. **Emerg Med J**. 2019 Feb;36(2):78-81. doi: 10.1136/emermed-2018-207693. Epub 2018 Dec 8.

[R5] The effect of tranexamic acid on death due to bleeding by baseline risk: a meta-analysis of individual patient-level data from 28,333 patients. Ageron FX, Gayet-Ageron A, Ker K, **Coats TJ**, Shakur H, Roberts I, for the Antifibrinolytics Trials Collaboration.
Brit J Anaes Accepted January 2020.

[R6] Individual variation in fibrinolysis after major trauma: Biological Mechanisms and Implications for treatment with tranexamic acid. **Coats TJ**, Morsy M. Emerg Med J. Accepted January 2020. Epub ahead of print. doi:10.1136/ emermed-2019-209181

[G1] CI Prof I Roberts LSHTM, from HTA : "CRASH2 trial". £2.8m. April 2007 for 5 years. (Coats was co-applicant). UoL funding was £211,934.
[G2] CI Prof I Roberts LSHTM, from HTA: "HALT-IT trial". £3.9m for 5 years (Coats was co-applicant).
[G3] The Trauma Audit and Research Network activity is funded by NHS England (through the University of Manchester). Prof Coats Chairs. Approx £1m per annum.

4. Details of the impact

Context

Bleeding after trauma is a global healthcare problem responsible for millions of deaths every year (WHO 2018). The CRASH2 trial showed that 9% of hospital trauma deaths could be prevented, estimated as potentially saving more than 100,000 lives per year worldwide [Source 5]. In the UK there are about 7000 in-hospital deaths from injury per year, and therefore 630 lives could be saved every year. A key advantage of TXA is that it is cheap, with a treatment dose costing around £3, meaning that it is applicable to the 'trauma epidemic' that is fast growing in the developing world. Economic analysis showed a cost of $64 per life year gained in the UK.

Reach and Significance of Impact

Initial implementation in the UK, was led by the Peninsular CLAHRC **[E1]** in collaboration with the CRASH2 researchers. The sustaining pathway to impact has been the inclusion of TXA in the NHS England Best Practice Tariff (BPT) for major trauma, a system administered for England and Wales by the Trauma Audit and Research Network (TARN www.tarn.ac.uk) which is Chaired by Coats. The BPT is an additional per patient funding of £2500 payed to NHS Major Trauma Centres if specific quality criteria are met.

Treatment with TXA has been included in BPT criteria from 2012 to 2020. The national use of TXA **[R4]** in patients who received blood transfusion had changed from near zero in 2010 to 85% in 2016. This was associated with a 19% (95% CI 3%–36%) increase in the national case mix adjusted odds of survival from severe injury between 2008-17 **[E2]** with a step change in 2012 (coinciding with both a major NHS reorganisation of trauma services and the widespread implementation of TXA treatment). NHS England estimated that these changes created an additional 1600 survivors **[E3]** by 2018.

In Europe the pathway to impact has been through the European trauma bleeding guidelines, which form the basis of civilian trauma treatment protocols. Originally, in 2007 and 2010, TXA was suggested as a Grade 2C recommendation, meaning that clinicians "should consider giving TXA". In 2016 the international group responsible for producing the European guidelines evaluated the evidence, including the 2015 Cochrane review [**E3**], and upgraded TXA treatment to a (Grade 1A) "give TXA" recommendation. Coats was a guidelines group member and a co-author of this publication **[E4]**. In the UK this publication was quoted the NICE 2016 guideline NG39 "Major Trauma: assessment and initial management", which recommend intravenous tranexamic acid as soon as possible in people with major trauma and active or suspected active bleeding.

Continuing research has adjusted the implementation. Our 2018 analysis **[E4]** showed that relatively few patients received the treatment in the time window (within an hour of injury) when it is most effective. This directly led to a revision of the NHS BPT criteria **[E6]** for 2019/20 - with

the BPT payment now only being made if the patient receives TXA within 1 hour of injury (previously within 3 hours of injury).

The same process has happened in the developing world, for example in South Africa the University of Cape Town, which is a leader in Emergency Care and publishes guidelines, included TXA in their 'essential medicines' list in 2018 **[E7]**.

The standard global trauma training course (Advanced Trauma Life Support – ATLS) was updated in 2018 to include a recommendation for TXA use. This is reflected in global civilian trauma management Guidelines. Global military protocols have been rewritten to include TXA in major trauma, for example the US military Joint Trauma System Clinical Practice Guideline (JTS CPG) - Damage Control Resuscitation **[E9]**.

The success of the CRASH2 trial has had an impact wider academic fields, stimulating a number of additional large international clinical trials of TXA **[E10]**; The WoMAN trial (Death due to post-partum haemorrhage significantly reduced in women given TXA with a risk ratio of 0·81, 95% CI 0·65–1·00; p=0·045); CRASH3 (Death due to head injury reduced in key subgroups); TITCH2 trial (reduction in early death following haemorrhagic stroke); TITCH3 (under application – Coats is a co-applicant); HALT-IT (currently recruiting in gastrointestinal haemorrhage - Coats is a co-applicant and Trial Management Group member).

The Acute Coagulopathy of Trauma was unknown before 2003. There is now an effective treatment, which has become the global standard of care in both civilian and military systems.

5. Sources to corroborate the impact

[E1] CLARHC Implementation Program: NIHR CLARHC Peninsular Briefing Document
[E2] Changing the System - Major Trauma Patients and Their Outcomes in the NHS (England) 2008–17. Moran CG, Lecky F, Bouamra O, Lawrence T, Edwards A, Woodford M, Willett K, Coats TJ. Lancet EClinical Medicine. 2018, Vol 2. P13-21
[E3] NHS England press release "More than 1,600 extra trauma victims alive today says major new study"
[E4] European Trauma Bleeding Guideline: Spahn, D.R., Bouillon, B., Cerny, V. *et al.* The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care* **23,** 98 (2019).
[E5] Ker K, Kiriya J, Perel P, et al. 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.
[E6] 2019/20 National Tariff Payment System – A consultation notice. NHS Improvement 2019.
[E7] Essential medicines for emergency care in Africa. M.C. Broccoli, J.L. Pigoga, M. Nyirenda, L.A. Wallis, E.J. Calvello Hynes,
[E8] Roberts I, Shakur H, **Coats T**, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients.
[E9] Global civilian and military guidelines
Civilian
(a) Major Trauma: assessment and initial management, NICE guideline [NG39] 2016
(b) US Advanced Trauma Life Support Guideline 2018
(c) University of North Carolina (UNC) Healthcare Guideline 2018

(d) American College of Surgeons 2015: Guidance Document Regarding the Pre-Hospital Use of Tranexamic Acid for Injured Patients
(e) UK West Midlands Ambulance Service Trauma Management Guidelines 2017
(f) British Society for Heamatology Guidance 2015
(g) Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee Section 7.3 Transfusion management of Major Haemorrhage 2013
(h) European Trauma Guideline S3
(i) Irish Association of Emergency Medicine Clinical Guideline 5
(j) State of Maine Protocol
Military
(k) US Military Joint Trauma System Clinical Practice Guidelines – Damage Control Resuscitation
(l) NATO: Use of Tranexamic Acid in Bleeding Combat Casualties
(m) UK Military 2015: Improved survival in UK combat casualties from Iraq and Afghanistan 2003 – 2012
(n) Israeli Military 2015: Tranexamic acid at the point of injury: The Israeli combined civilian and military experience.
(o) US Presidential 'White House Treatment Protocols'
[E10] Cone DC, Spaite DW, **Coats TJ**. Out-of-Hospital Tranexamic Acid for Traumatic Brain Injury. JAMA. 2020;324(10):946-947.