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Abstract

Traumatic coagulopathy and massive transfusion: improving outcomes and saving blood

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Introduction: Dysfunction of the coagulation system, termed trauma-induced coagulopathy (TIC), is a major problem in patients who bleed after injury. Trauma haemorrhage is considered one of the leading preventable causes of death worldwide. Deaths occur early and, despite the presence of trauma teams and large transfusions of blood products, outcomes remain poor.

Methods: We conducted a multimodal programme of work to develop our understanding of coagulopathy and its optimal management. We studied the epidemiology, management and health economics of trauma haemorrhage, including the provision of care during mass casualty events. We combined systematic reviews of the literature with a national study of trauma haemorrhage, its transfusion management and associated health-care costs. We further examined several point-of-care coagulation tools for their ability to diagnose coagulopathy and assess the response to blood component therapy. We progressively implemented our findings into practice and assessed the outcomes of trauma patients presenting to our major trauma centre. To examine different approaches to the provision of blood to casualties in a mass casualty event, we constructed a discrete event model based on data from the 2005 London bombings.

Key results: Our systematic reviews found little strong evidence for the existing diagnostic tools or the practice of delivery of blood components in trauma haemorrhage. Our national study recruited 442 patients in 22 hospitals and found that the 1-year mortality rate for massive haemorrhage approached 50%. Half of these deaths occurred in the first 24 hours after injury and half of these occurred in the first 4 hours. We identified this early time window as a period when the provision of blood component therapy was often below the recommended thresholds and blood component therapy was delivered inconsistently. Studying early TIC we determined that loss of fibrinogen and excessive fibrinolysis were key derangements. We were able to determine that rotational thromboelastometry could identify early coagulopathy within 5 minutes, a large improvement on laboratory tests. We were further able to show how existing damage control resuscitation regimens with high-dose plasma do not maintain haemostatic competency during haemorrhage. In total, the estimated cost of treating a major haemorrhage patient was £20,600 and the estimated cost of treating a massive haemorrhage patient was £24,000. Nationally, the estimated cost of trauma haemorrhage is £85M annually. In mass casualty situations, early results show that the only mutable factor that affects the provision of care to a large degree, in the initial phase of the response, is the level of blood stocks held in the receiving hospital.

Conclusions: This multimodal programme of work has led to new understandings of the epidemiology of trauma haemorrhage and its underlying mechanisms and clinical course. We have defined diagnostic tools and trigger thresholds for identification and management and increased our understanding of how blood component and other therapeutics affect coagulopathy and when they are likely to be most effective. This diagnostic work has been taken forward at an international level to produce new personalised guidelines for the management of trauma haemorrhage. The findings have had important therapeutic implications,

which have led to important changes in practice that have been incorporated into new national and international guidelines.

Funding: The National Institute for Health Research Programme Grants for Applied Research programme.

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List of abbreviations

ACIT	Activation of Coagulation & Inflammation in Trauma
ATC	acute traumatic coagulopathy
CA5	clot amplitude at 5 minutes
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
DCR	damage control resuscitation
FFP	fresh-frozen plasma
INTRN	International Trauma Research Network
MCF	maximum clot firmness
PRBC	packed red blood cell
PT	prothrombin time
ROTEM	rotational thromboelastometry
TARN	Trauma Audit and Research Network
TEG	thromboelastography
TIC	trauma-induced coagulopathy

Plain English summary

Severe bleeding as a result of traumatic injury and damage to blood vessels is life-threatening. We found that some patients do not clot properly because clotting is disrupted by blood loss itself, a condition termed acute traumatic coagulopathy. Blood transfusions are important to treatment but have risks and side effects. Currently, after patients have received red blood cell transfusions, plasma and platelet transfusions are given to replace lost clotting factors. Routine measures of functional blood clotting are not available quickly enough to guide treatment. Thus, some patients potentially receive too few clotting factors and have worse outcomes, whereas others may receive too many and are exposed to extra risks while wasting precious blood stocks.

Few data describe current UK practice in terms of the incidence of transfusion for trauma, patient outcomes, demand for blood components and treatment costs. We conducted a national multicentre study which demonstrated that nearly 7800 adult trauma patients require a life-saving transfusion per year, at a cost of approximately £85M. Of those with massive bleeding we found that, on average, nearly 50% will die and many of these deaths occur within the first few hours after injury. We have identified key aspects of the underlying clotting problem that may be targets for improved treatments in the future, as well as methods to diagnose them quickly so that such therapies could be directed appropriately for each specific treatment. Additionally, we have developed a model for mass casualty events such as terrorist bombings that we are using to test ways in which trauma centres can best manage blood stocks during such events.

This programme of work has led to new understandings of coagulopathy and diagnostic tools for its rapid identification and management. Over the lifetime of the research programme we doubled survival in patients with severe bleeding by applying the results of our research to clinical practice. This work is now incorporated into national guidelines and we continue to study how we can further reduce the ongoing high mortality from this critical condition.

Scientific summary

Introduction

Trauma-induced coagulopathy (TIC) often complicates severe haemorrhage and is associated with significantly worse outcomes for trauma patients. TIC was previously thought to occur late and primarily to be caused by the consumption and dilution of clotting factors. However, the recognition that TIC developed rapidly and was more complex in its aetiology also suggested new management strategies and therapeutic options. There was sparse evidence on the epidemiology of trauma haemorrhage, existing practice patterns, outcomes and costs, as well as little information on the patterns of coagulopathy present on arrival and during haemorrhage and how these responded to transfusion therapy.

Methods

Between 2008 and 2013 we conducted a multimodal programme of work to develop our understanding of coagulopathy and its optimal management. We identified existing evidence, practice patterns and outcomes through systematic reviews of the literature and a national study of trauma haemorrhage, its transfusion management and associated health-care costs. We further examined several point-of-care coagulation tools for their ability to diagnose TIC and to assess the response to blood component therapy. We progressively implemented our findings into practice and assessed the outcomes of trauma patients presenting to our major trauma centre. To examine different approaches to the provision of blood to casualties in a mass casualty event, we constructed a discrete event model based on data from the 2005 London bombings.

Key results

Our national study recruited 442 patients in 22 hospitals and found that the 1-year mortality rate for patients with major haemorrhage [requiring 4+ units of packed red blood cells (PRBCs) in the first 24 hours] was and approached 50% for those with massive haemorrhage (10+ PRBCs). Half of these deaths occurred in the first 24 hours after injury and nearly one-quarter in the first 4 hours. In this critical window the delivery of blood component therapy was often below the recommended thresholds. Studying the pattern of TIC at this time point we determined that loss of fibrinogen and excessive fibrinolysis were key derangements. We were able to determine that rotational thromboelastometry could rapidly identify patients with TIC and high transfusion requirements, based on the clot amplitude at 5 minutes. We were further able to show how existing damage control resuscitation regimens do not maintain haemostatic competence during bleeding. Furthermore, fibrinogen levels started below the recommended range and became dangerously low after 8 units of transfusion without supportive transfusion therapy. Severe fibrinolysis was extremely common (seen in > 60% of patients) and in its most extreme phenotype only detectable by thromboelastometry. In total, the estimated cost of treating a major haemorrhage patient was £20,600 and the estimated cost of treating a massive haemorrhage patient was £24,000. Nationally, the estimated cost of trauma haemorrhage is £85M annually. In mass casualty situations early results show that the only mutable factor that has a large effect on the provision of care in the initial phase of the response is the level of blood stocks held in the receiving hospital.

Conclusions

Outcomes from trauma haemorrhage remain poor at a national level and there are important areas for improvement with regard to the delivery of transfusion therapy within the critical early post-injury phase of care. Implementation of consistent high-dose plasma-based damage control resuscitation improves outcomes but does not correct TIC during haemorrhage. Key features of TIC that may respond to therapy are loss of fibrinogen and excessive fibrinolysis. Thromboelastometry may be able to personalise coagulation therapy using new diagnostic criteria to correct TIC and further improve outcomes for critically injured bleeding trauma patients.

Funding

Funding for this study was provided by the Programme Grants for Applied Research programme of the National Institute for Health Research.

SYNOPSIS

Introduction

Trauma haemorrhage: background

Worldwide, 6 million people die from injuries every year and about 40% of these deaths are due to bleeding.[1] Theoretically, all haemorrhage can be stopped and therefore upwards of 2 million deaths are potentially preventable each year. People still bleed to death, however, because of a number of factors. They may not have their bleeding stopped in time because they do not reach surgery quickly enough; they reach surgery but their bleeding cannot be controlled; or their bleeding is controlled but the severe prolonged shock was too much for the body to recover from. Combined, these factors make trauma haemorrhage exceedingly difficult to manage and around the world mortality from severe bleeding (requiring a massive transfusion) is around 50%.[2]

Trauma haemorrhage resuscitation in 2008

Trauma resuscitation in 2008 was very different from today. The focus at this time was fully on restoring the volume of circulating blood to maintain a normal blood pressure and try to maintain oxygen delivery to cells. This was initially performed with high doses of crystalloids, or colloids in some parts of the world. After two or more litres of saline had been administered, blood transfusion was started using packed red blood cells (PRBCs).[3] The goal was to normalise blood pressure and, therefore, perfusion.

It was known that after transfusion of large volumes of red cells (a massive transfusion), complications could occur because of the lack of clotting factors. After the replacement of an entire circulating blood volume (10 units of PRBCs) it was recommended that laboratory parameters of clotting were checked and, if abnormal, this coagulopathy should be managed with the administration of some volume of fresh-frozen plasma (FFP) (usually 4 units initially). Thus, massive transfusion protocols were principally focused on managing a late dilutional coagulopathy caused by large-volume fluid and PRBC transfusion.[4]

We now know, from our work and the work of others, that our understanding of the disease processes was wrong, that our resuscitation goals were wrong and that our treatment was too little, too late.

What we knew about trauma-induced coagulopathy in 2008

In 2003, the discovery of a clotting disorder present immediately on arrival in the emergency department prompted a change in our understanding of the disease and the way it was treated. This acute traumatic coagulopathy (ATC) was first described in our study with London's Air Ambulance. We looked at > 1000 helicopter patients and found that one in four patients arrived with ATC and that, if present, one in four patients would die.[5] By the start of this study several other groups around the world had confirmed the existence of ATC and we had begun to characterise it and explore its pathophysiology.[6,7]

Trauma-induced coagulopathy (TIC; all different possible clotting disorders that a trauma patient could develop) could therefore take multiple forms at different times in their clinical course and several different coagulopathies might exist at the same time (*Figure 1*). It was becoming clear that TIC was not a single disease entity and therefore probably could not be managed in the same way at all times.[8]

The identification of ATC provided a potential therapeutic focus for new management strategies and therapeutics. This was first approached in retrospective studies, with patients who had received higher doses of plasma during their haemorrhage resuscitation appearing to have significantly better outcomes than those given standard resuscitation regimens.[9] Patients given less crystalloid also seemed to do better.[10] In 2007 a new paradigm of resuscitation was postulated, damage control resuscitation (DCR), a strategy specifically targeting ATC.[11] The evidence for this position paper was weak, but the collective

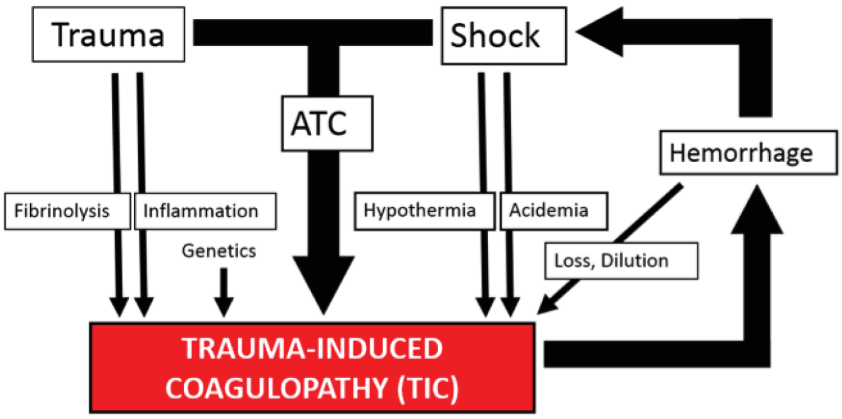

FIGURE 1 Proposed model for the mechanisms and drivers of TIC in 2008. Adapted from Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, *et al.* The coagulopathy of trauma: a review of mechanisms. *J Trauma*, vol. 65, iss. 4, pp. 748–54. 2008.[8] URL: http://journals.lww.com/jtrauma/pages/default.aspx. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact healthpermissions@wolterskluwer.com for further information.

approach had four central tenets: stop bleeding, permissive hypotension until control, avoid fluids and target coagulopathy. The DCR approach was almost the complete opposite of the then current approach to haemorrhage resuscitation. Much more work needed to be carried out to show that this strategy was effective and did not expose patients to unnecessary risks and waste precious blood resources.

What we did not know

At the beginning of 2008, therefore, we understood that the underlying coagulopathies of trauma were more prevalent, more complex and occurred earlier than previously thought. We understood that the existing resuscitation strategies probably did not address these clotting disorders and in many cases may have exacerbated them. However, much of the underlying data were based on relatively weak evidence and there were areas where there were significant gaps in our knowledge. Our programme of work was designed to address the most pressing and central of these to patients, and to the NHS.

- How common is major trauma haemorrhage nationally and what are its immediate and long-term outcomes?
- How are bleeding trauma patients managed, especially in terms of the delivery of blood transfusion therapy?
- What is the cost to the NHS of treating major haemorrhage? What are the most significant areas of cost burden?
- What is the existing evidence for the use of blood products for the treatment of TIC?
- Can we predict who is bleeding or has coagulopathy on arrival to enable activation of the appropriate treatment pathways?
- What is the fastest and most accurate way to diagnose ATC? How can we diagnose various forms of TIC?
- What is the best treatment for the different forms of TIC?
- What are the implications of any changes in the context of a disaster or mass casualty event?

We proposed a multimodal collaborative programme of work to try to address these knowledge gaps, develop a more personalised approach to the management of the bleeding trauma patient and assure the timely, appropriate use of blood products.

What has changed in the management of bleeding trauma patients?

The Royal London Hospital is one of the busiest major trauma centres in the world, with nearly 3000 trauma team activations each year, and treats some of the most severely injured patients in the country. In 2008, patients activating our traditional massive transfusion protocol had a 50% mortality rate.[12]

In partnership with the Barts Centre for Trauma Sciences at Queen Mary University of London we have iteratively implemented our research findings into practice with a multispecialty team of clinicians and transfusion specialists. By the end of our programme grant in 2014 we had more than halved the mortality of this group of patients to 26% (*Figure 2*). We had also halved the number of blood products that they required and almost halved their critical care and hospital stays.

We have a much deeper understanding of TIC in all its forms and a better understanding of the role of clotting therapy in the management of these conditions. We have new therapeutic agents and others in clinical trial pipelines. These changes have been incorporated in new major haemorrhage 'Code Red' protocols, which have been disseminated nationally and internationally and incorporated into clinical guidelines around the world.

In the following sections we describe the programme of work and the central findings that have led to these changes in practice.

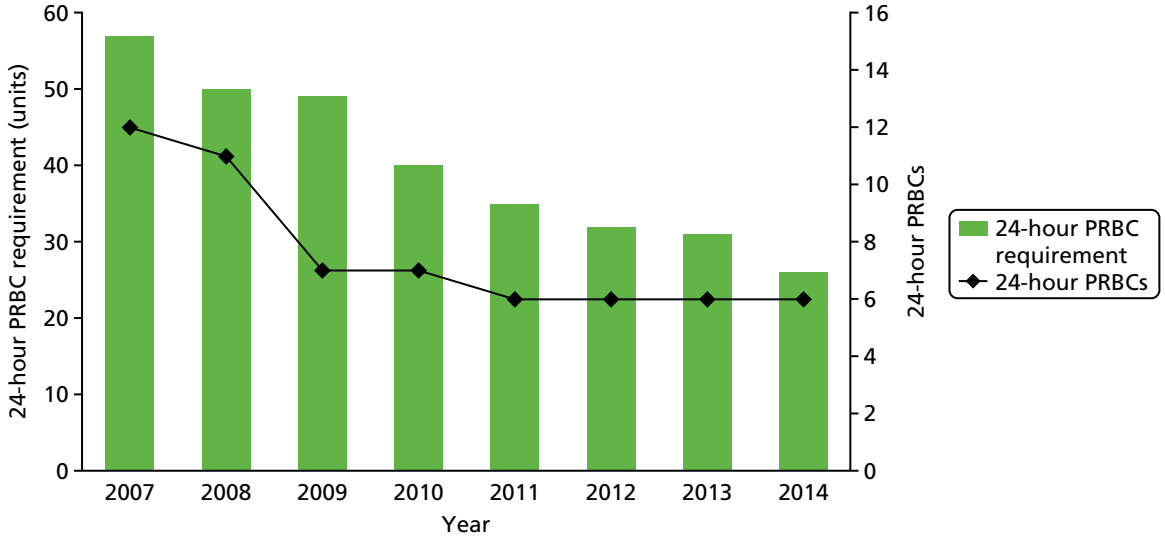

FIGURE 2 Outcomes of 'Code Red' patients at the Royal London Hospital 2007–14. Mortality fell from 57% to 26% and 24-hour PRBC requirements halved from 12 to 6 units.

The programme of work

The original stated objective of our programme of work was to improve outcomes for severely injured bleeding trauma patients. It was designed around the principle that early identification of patients who present with a TIC and effective, directed therapy will lead to improved outcomes, reduced complications, rationalised transfusions and reduced costs to the NHS.

We had six stated aims to achieve this objective.

1. *Aim 1: evidence*. To systematically review the current evidence and develop systematic reviews on the identification of coagulopathy and blood component use in trauma.
2. *Aim 2: epidemiology*. To investigate the national incidence of massive transfusion for trauma, national practice patterns and outcomes.
3. *Aim 3: identification*. To investigate the utility of clinical, point-of-care laboratory analyses for the identification of the need for massive transfusion.
4. *Aim 4: treatment*. To identify the optimum methods to guide therapy and rationalise blood product administration during haemorrhage.
5. *Aim 5: disaster*. To model the hospital use of transfusion services in mass casualty events and develop best practice guidelines.
6. *Aim 6: economics*. To describe the health economic implications of massive transfusion and the impact of changes in practice on the NHS.

What we did

We performed multimodal parallel studies to achieve the overall objectives (*Figure 3*). Although these studies were discrete, the conduct and results of each informed aspects of the others.

The core studies are described in the following sections.

Aim 1: evidence

We conducted several systematic reviews of the existing literature, specifically focusing on the known utility of prediction tools and diagnostic devices to identify patients with TIC and the efficacy of existing blood product transfusions for the treatment of TIC and major haemorrhage.[13–15] All studies were carried out with full adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16] and systematic review best practice.[17]

Aim 2: epidemiology

We conducted a prospective cohort study of patients admitted to 22 hospitals across the country (see *Appendix 1*), with 2 years of data collection (2009–11) and 1 year of follow up (see *Appendix 2*). The study involved a close collaboration between clinicians and transfusion services at each hospital and was co-ordinated nationally through the Trauma Audit and Research Network (TARN) and NHS Blood and Transplant.[18] Hospitals were selected to give a range of large and medium-sized trauma-receiving units, both academic and non-academic. We specifically collected data on the incidence and outcomes of major haemorrhage and on transfusion practice at a national level. In particular, we looked at the hourly delivery and utilisation of blood products by haemorrhaging trauma patients in the first 24 hours. In parallel, we conducted a health economic assessment of the epidemiology study data to determine the baseline resource utilisation and costs associated with major trauma haemorrhage (Aim 6: economics).[19] In total, 442 trauma patients with major haemorrhage (requiring at least 4 units of PRBCs) were enrolled over a 2-year period at the 22 representative hospitals across England and Wales.

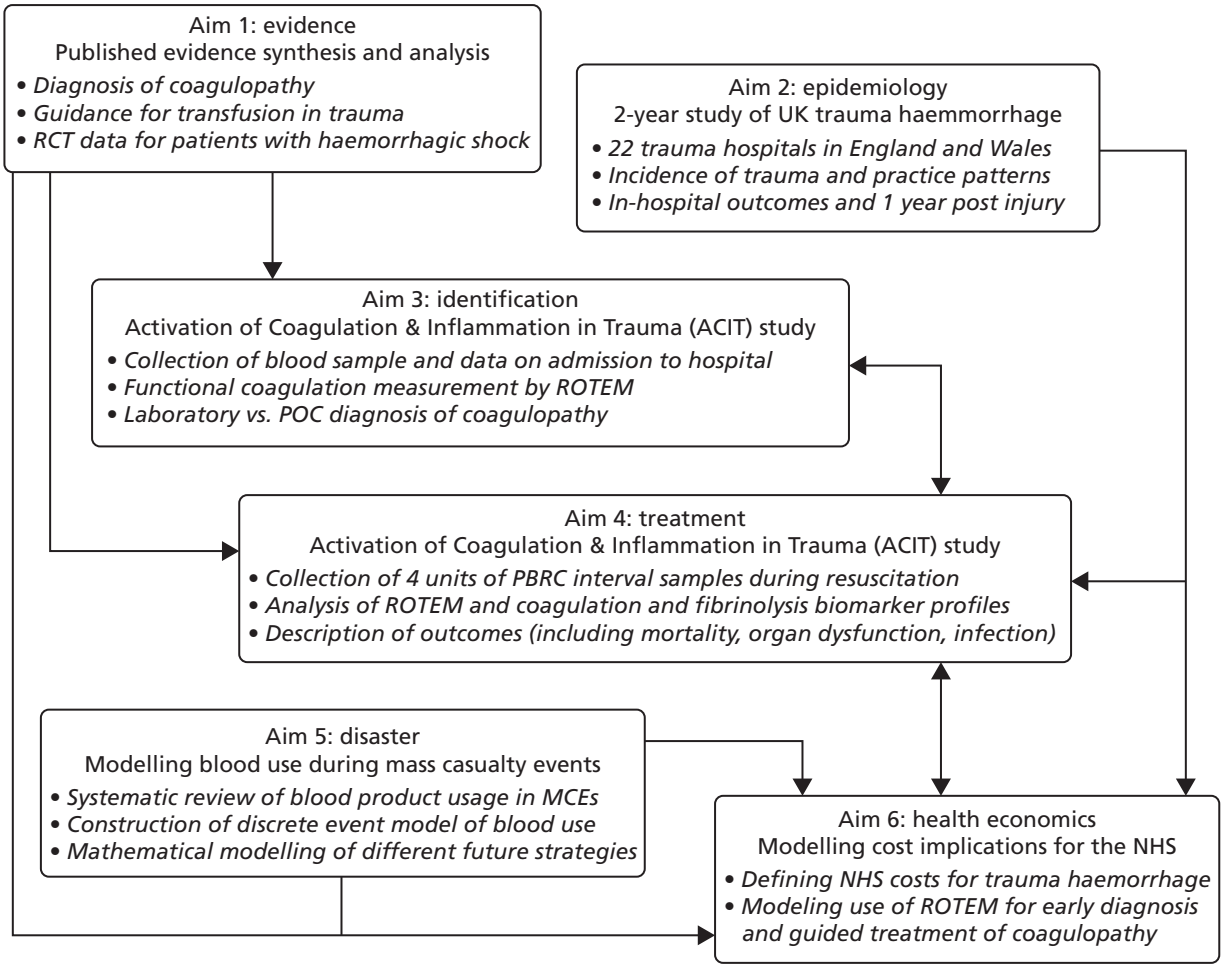

FIGURE 3 Inter-relationships of the different aims of the research programme. MCE, mass casualty event; POC, point of care; RCT, randomised controlled trial; ROTEM, rotational thromboelastometry.

Aim 3: identification and aim 4: treatment

We conducted a prospective observational cohort study of trauma patients at two major trauma centres in England (Royal London Hospital and the John Radcliffe Hospital, Oxford). In this study, the Activation of Coagulation & Inflammation in Trauma (ACIT) study, blood samples were collected from trauma patients immediately on arrival in the emergency department and while they were bleeding and requiring blood product transfusions (see *Appendices 3–5*).[20] The blood was analysed for functional and molecular markers of coagulation. As we had detailed data on what blood, fluid and other therapy patients had received between sampling intervals, we could closely examine the response of the body to our therapeutic attempts to normalise the clotting system. In particular, we were interested in whether point-of-care diagnostics such as thromboelastometry could be used in the emergency setting to identify TIC and guide transfusion management. Patients were closely followed for outcomes including mortality, organ dysfunction, infection, thromboembolism and quality of life. We also collected data on this cohort to evaluate the baseline costs and potential savings associated with new diagnostic and therapeutic approaches (Aim 6: economics).

Over the duration of the programme grant 1095 patients were enrolled into the ACIT study at the two UK sites. Additionally, we opened new ACIT sites in the largest trauma centres in Oslo, Copenhagen, Amsterdam and Cologne, under the umbrella of a new research collaborative, the International Trauma Research Network (INTRN). Over the duration of the programme grant 2201 patients were recruited into the ACIT study across the INTRN partners. Recruitment continues on this important platform and to date we have recruited > 3500 patients into the ACIT study. As the study progressed we also retrospectively reviewed the effect of changes made to practice on outcomes and blood product usage to track the

performance of our work against our stated overall objective.[12] From 2008 to 2014, 800 trauma patients activating the major haemorrhage protocol were treated at the Royal London Hospital major trauma centre and we tracked the progress and outcomes of these patients.

Aim 5: disaster

We performed a systematic review of blood product utilisation in mass casualty events over the past century, in part to evaluate the potential to predict the PRBC and component requirements during potential events.[21] We then constructed a mathematical discrete-event model of PRBC utilisation and flow during mass casualty events, based on data from the London bombings of 7 July 2005. We used this model to test different strategies to preserve blood stocks during such events.

Key findings and outputs

The epidemiology of trauma haemorrhage in England and Wales

Incidence

Our national epidemiology study (see *Appendix 2*) identified 442 patients with major haemorrhage (requiring at least 4 units of PRBCs for resuscitation) and 146 cases of massive haemorrhage (requiring at least 10 units of PRBCs) at 22 hospitals (see *Appendix 1*).[18]

Nationally (for England and Wales), this gives an estimated incidence of 4700 trauma patients a year with major haemorrhage, 1300 of whom will have massive haemorrhage. We unexpectedly found that the incidence was much higher in elderly patients (*Figure 4*), with more than double the incidence of trauma haemorrhage than in the general population (196 per million vs. 83 per million).

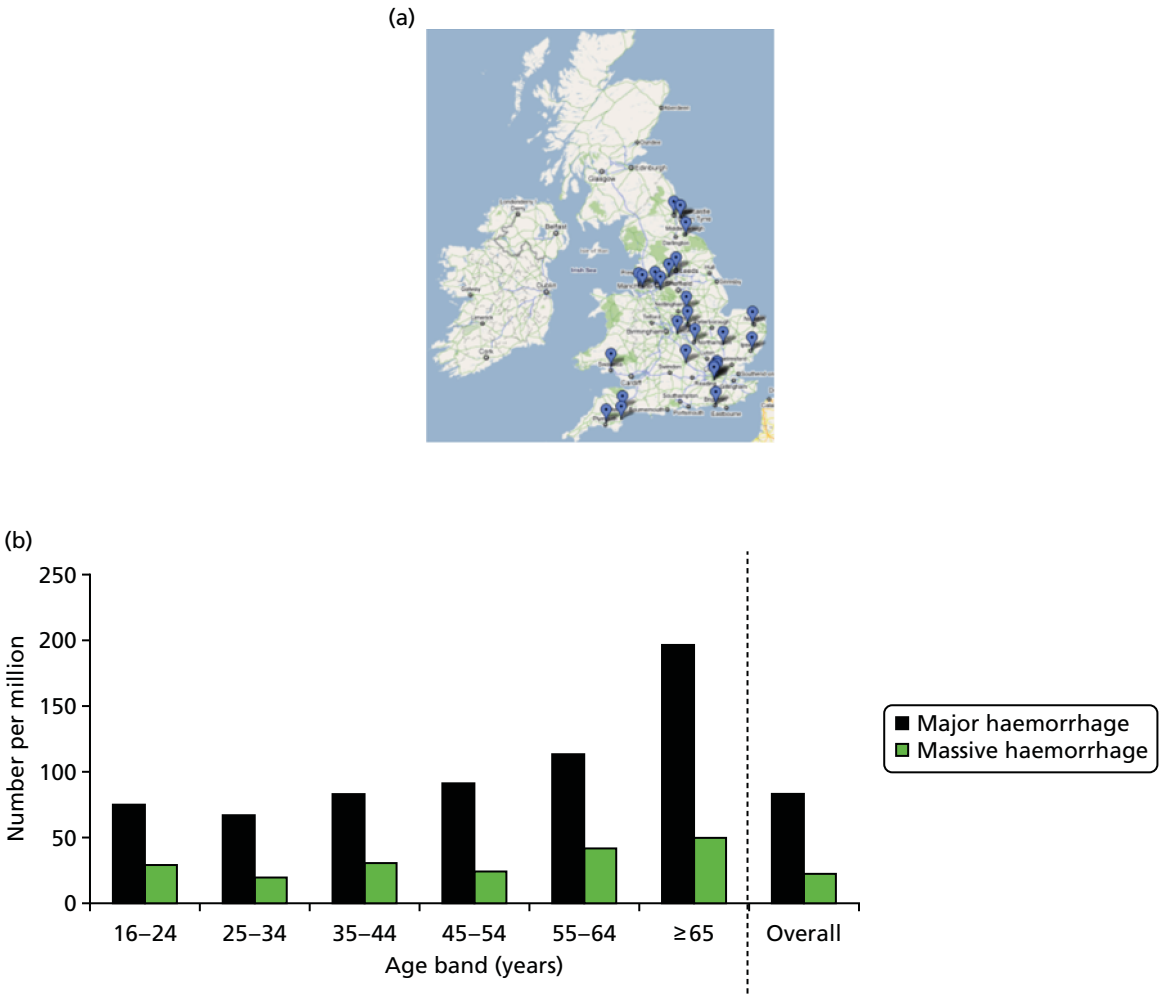

FIGURE 4 National incidence of major and massive haemorrhage due to trauma: (a) distribution of the 22 participating UK hospitals; and (b) population-based incidence by age group. Source: data from Stanworth *et al.*[18] Reproduced with permission from Stanworth SJ, Davenport R, Curry N, Seeney F, Eaglestone S, Edwards A, *et al.* Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. *Br J Surg* 2016;**103**:357–65[18] © 2016 BJS Society Ltd Published by John Wiley & Sons Ltd.

Mortality

Mortality in our study was high. Nearly half of trauma patients with massive haemorrhage died (and one-third of major haemorrhage patients). This extrapolates to > 1550 people dying of major haemorrhage each year in England and Wales (585 dying of massive haemorrhage).[18]

Deaths occurred early, with over half occurring within the first 24 hours of injury and half of these occurring within the first 4 hours of injury (*Figure 5*). It is clear that improvements in practice have to occur in this critical post-injury window if outcomes from trauma haemorrhage are to improve.

Resource utilisation and health-care costs

On average, major haemorrhage patients received 11 units of blood products (PRBCS, plasma, platelets or cryoprecipitate) and massive haemorrhage patients received 26 blood product transfusions in the first 24 hours. Patients spent just under 3 hours in the emergency department and over half required urgent surgery.[19]

Over 80% of trauma patients with major haemorrhage required critical care admission and they spent on average 7 days in critical care and 3 days on a ventilator. They spent on average an additional 20 days in hospital.

Intensive care unit (ICU) costs accounted for the largest proportion of health-care costs, at £4600–9500 per patient. The next largest cost utilisation areas were operating theatres and other ward areas. Blood product transfusions cost approximately £2300 per major haemorrhage patient (£4200 for massive haemorrhage).[19]

In total, the estimated cost of treating a major haemorrhage patient was £20,600 (£24,000 for massive haemorrhage). Extrapolating nationally this gives an estimated cost of major haemorrhage after trauma of approximately £85M annually. One-third of all costs are accounted for by elderly trauma patients.[19]

Evolution of Code Red major haemorrhage protocols

Before 2008, the Royal London Hospital major trauma centre had a massive transfusion protocol in place, based on traditional guidelines such as the British Commitee for Standards in Haematology[4] and College of American Pathologists[22] recommendations. These massive transfusion protocols were activated for patients

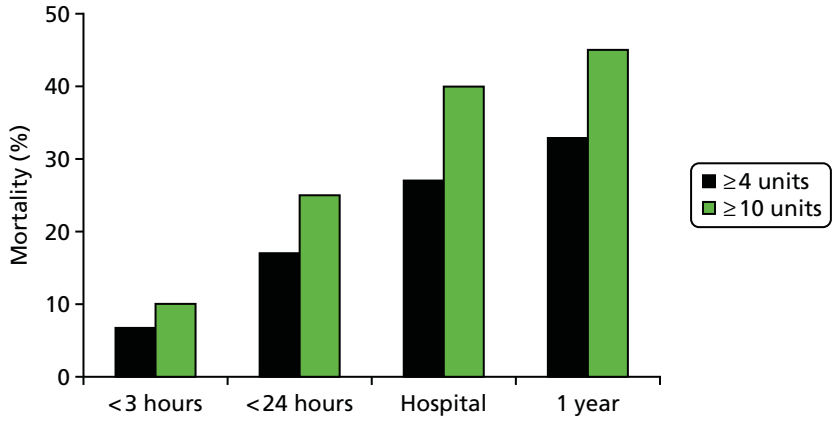

FIGURE 5 National mortality associated with trauma haemorrhage. One-year mortality approached 50% for patients with massive haemorrhage. Half of all deaths occurred within the first 24 hours and half of these deaths occurred within the first 4 hours of arrival. Source: data from Stanworth *et al.*[18] Reproduced with permission from Stanworth SJ, Davenport R, Curry N, Seeney F, Eaglestone S, Edwards A, *et al.* Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. *Br J Surg* 2016;**103**:357–65[18] © 2016 BJS Society Ltd Published by John Wiley & Sons Ltd.

likely to require large volumes of red cells, although without clear criteria for activation. Furthermore, they were primarily targeted at the treatment of late complications of large-volume blood and fluid administration, most specifically dilutional coagulopathy. The protocol was associated with a wide variation in the amount of blood products (e.g. plasma) given to patients. There was also a significant amount of waste, especially of platelets. The mortality rate in patients who activated the protocol was 57%.[12]

Activation was tightly controlled so that wastage would be reduced. We reviewed the performance of massive transfusion prediction tools and used data from nearly 5700 trauma patients to develop our own prediction algorithm.[23] We determined that there was no specific prediction tool that performs better than another and no algorithm suitable for early (even pre-hospital) activation of a protocol. Additionally, we recognised that activating haemorrhage protocols only on the basis of a specific number of PRBCs transfused precludes improvements in care that reduce PRBC requirements in the future.[23]

In late 2008, coinciding with the start of the programme grant, the trauma centre instituted a new major haemorrhage protocol for trauma patients. This Code Red protocol aimed to identify early patients who were bleeding and prevent (rather than treat) dilutional coagulopathy. Treatment followed the principles of DCR based on the limited evidence available at the time. As our research (and that of others) progressed we iteratively updated the protocol to include new research findings and practices.

Immediately after institution we found that we reduced the wastage of products but there was no immediate impact on survival.[12] We progressed, limiting crystalloids, improving the delivery of products and introducing new therapeutics and evidence-based point-of-care coagulation assessments, and we saw a stepwise reduction in mortality. By the end of the programme grant mortality had reduced to 26%, with an associated reduction in all blood product administration and waste, as well as reductions in critical care and hospital stays.

The Royal London Hospital's Code Red protocol (*Figure 6*) has been adopted by almost all major trauma centres in the UK (modified for local practice) and has been disseminated internationally. Further refinements continue to occur as more research results become available from this programme of work and the work of others.

We have subsequently revised our Code Red protocol again based on our subsequent work using point-of-care functional coagulation assessment. In the following sections we detail our work on using these point-of-care devices to diagnose coagulopathy, predict major haemorrhage and individualise therapy to optimise blood product utilisation and patient outcomes. The protocol is currently being implemented and will be evaluated in a randomised controlled trial as part of a subsequent European Union FP7 programme of work.[24]

Rapid diagnosis and characterisation of acute traumatic coagulopathy

Aim 3 of the programme grant was specifically focused on the early identification of coagulopathy and, specifically, ATC. By 2008 ATC had been identified and defined as a prolongation of the laboratory prothrombin time (PT) and was thought to be caused by the systemic activation of anticoagulant factors.[25] Data from our ACIT study (see *Appendices 3–5*) showed that the laboratory PT was not available in a clinically useful time frame, on average becoming available to the treating trauma team only after 90 minutes.[20] We also investigated a hand-held PT device, used for home warfarin monitoring. These devices are not, however, calibrated for low haematocrit levels found in bleeding patients and we found they significantly under-read compared with the laboratory value.[20]

We wished to evaluate the potential for a point-of-care functional coagulation analyser – rotational thromboelastometry [ROTEM® (Tem International GmbH, Munich, Germany)] – to identify patients with

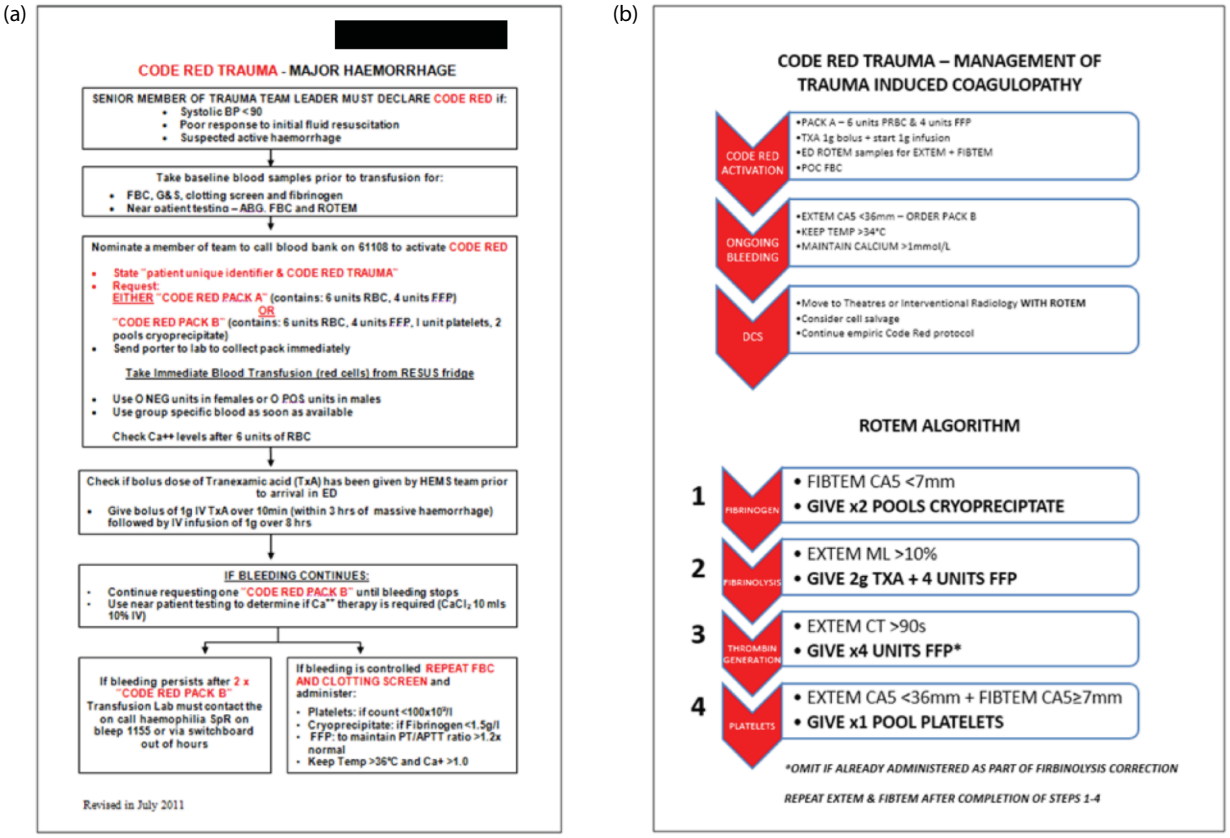

FIGURE 6 Evolution of the Royal London Hospital major trauma centre Code Red protocols: (a) 2008; and (b) 2011. ABG, arterial blood gas; APTT, activated partial thromboplastin time; BP, blood pressure; Ca^{++}, calcium; CA5, clot amplitude at 5 minutes; CT, clotting time; DCS, damage control surgery; ED, emergency department; FBC, full blood count; G&S, Group & Save; HEMS, Helicopter Emergency Medical Services; IV, intravenous; ML, Maximum Lysis; O NEG, O negative; O POS, O positive; POC, point of care; PT, prothrombin time; RBC, red blood cell; ROTEM, rotational thromboelastometry; SpR, specialist registrar.

ATC. ROTEM measures the strength of a blood clot as it forms over time in a small well of the device. Different activators and inhibitors can be added to assess different parts of the coagulation system.

In our first study we analysed the ROTEM traces of 300 trauma patients.[20] For the first time we were able to fully characterise the functional characteristics of ATC. We found that the primary functional disorder of ATC is a loss of clot strength [reduction in maximum clot firmness (MCF)]. In contrast, prolongation of clot activation (the PT) is a mild and rather late component of the coagulopathy.

Although measurement of the MCF takes half an hour or more, we were able to identify a ROTEM parameter available within 5 minutes that correlated closely with the MCF (*Figure 7*). The clot amplitude at 5 minutes (CA5) was able to accurately identify ATC and to predict the need for massive transfusion. It also showed an excellent negative predictive value, suggesting that it could also be used to curtail a major haemorrhage protocol to reduce waste or overtransfusion. We have since validated our finding in a later cohort and across the six INTRN partner sites in a study of 808 ACIT patients.[26] The CA5 remains the fastest and most effective point-of-care diagnostic marker of ATC.

Resuscitation of trauma haemorrhage: effectiveness of high-dose plasma therapy

Early approaches to the treatment of TIC focused on treatment with high-dose FFP. This was based on early assumptions about the mechanism of TIC: at this time it was thought to be caused by a loss or consumption

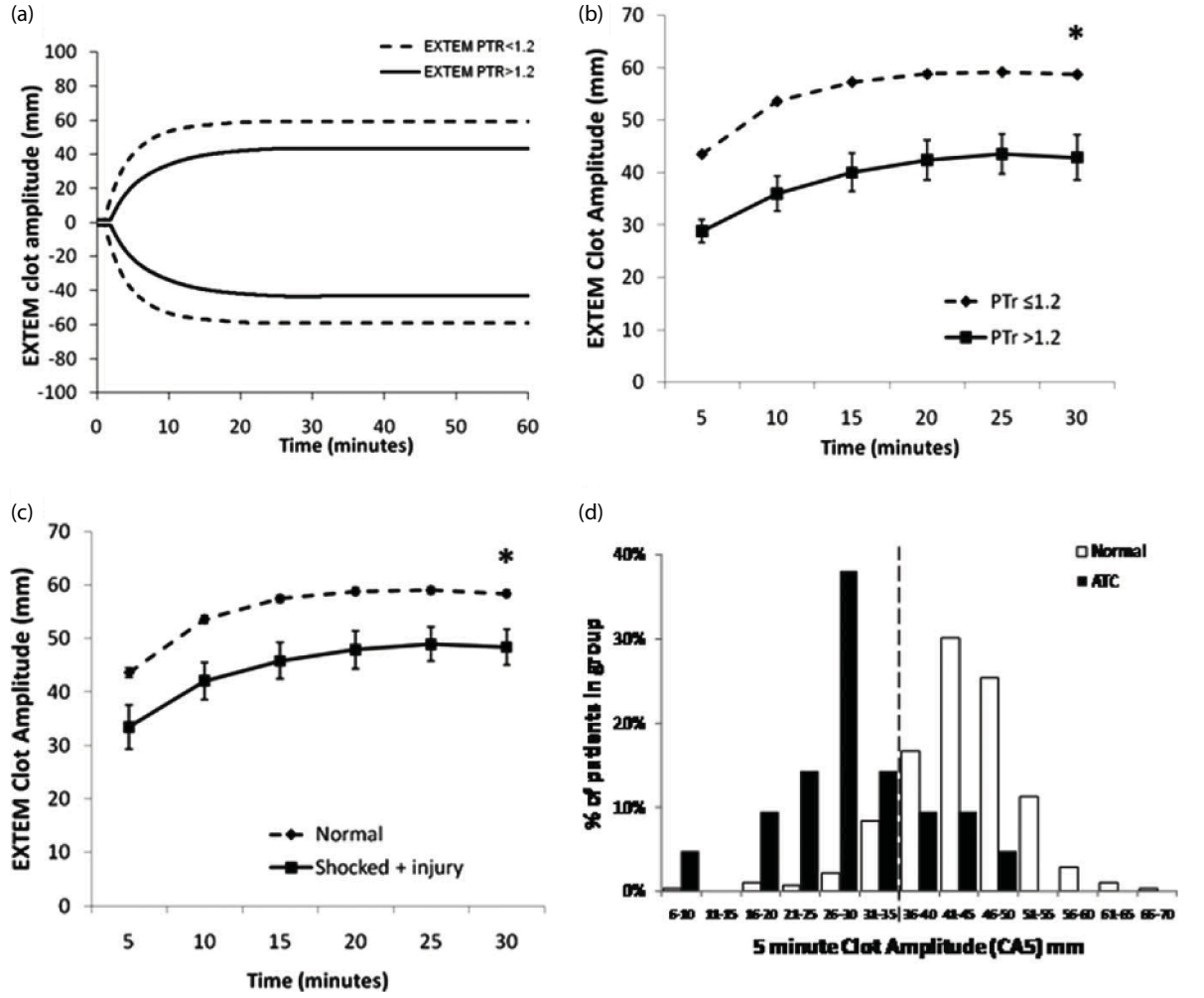

FIGURE 7 Functional characterisation of ATC: (a) averaged ROTEM curves for normal and ATC patients; (b) identification of CA5 of ≤ 35 mm to identify patients with ATC; (c) combined effects of trauma (injury severity score > 15) and shock (base deficit > 6) on the ROTEM trace; and (d) histogram demonstrating the distribution of CA5 among normal and ATC patients. The dotted line represents the new threshold for ATC (CA5 ≤ 35 mm). Source: reproduced with permission from Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, Stanworth S, Brohi K. Functional definition and characterisation of acute traumatic coagulopathy. *Critical Care Medicine*, vol. 39, issue 12, pp. 2652–8, URL: http://journals.lww.com/ccmjournal/pages/default.aspx.[20] Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact healthpermissions@wolterskluwer.com for further information.

of procoagulant factors. It also appeared to be supported by retrospective military and civilian studies[27] that showed improved outcomes when patients were given higher doses of FFP than in standard therapy.[9] The best outcomes appeared to be obtained when 1 unit of FFP was transfused for each 1 or 2 units of PRBCs.

There were significant concerns about this approach, however, which involved transfusion of four to five times the amount of emergency FFP than patients usually received. This would have a major resource impact on blood services worldwide and expose patients to a lot more blood products, with the associated potential risks of immunosuppression and infection. No group had ever been able to study the effect of FFP transfusions on coagulation during the resuscitation of a bleeding trauma patient.

We examined the coagulation system response to high-dose FFP transfusion (*Figure 8*).[28] We were able to show that giving FFP in high doses certainly appeared to reduce the dilutional coagulopathy that occurred as patients continued to bleed and receive PRBC resuscitation. With low-dose FFP, plasma levels of procoagulant factors such as factors II and X fell to low levels after transfusion of 12 PRBC units, whereas, with high-dose FFP, levels were somewhat protected.

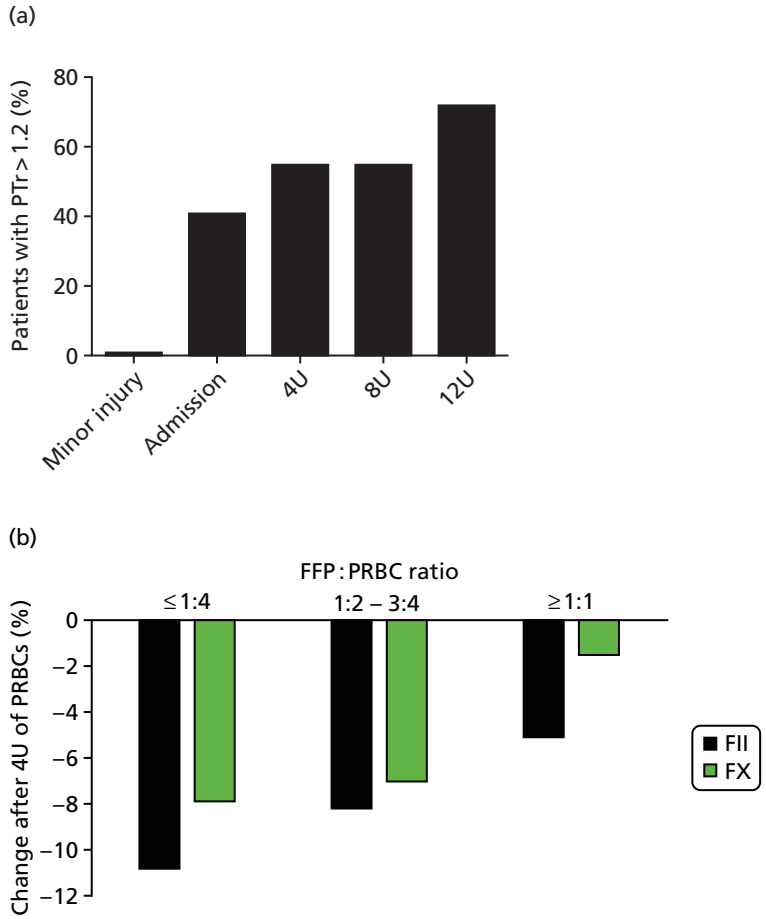

FIGURE 8 Progression of coagulopathy during bleeding and resuscitation: (a) overall incidence of coagulopathy during haemorrhage and resuscitation; and (b) reduced loss of activity of some procoagulant factors with high-dose plasma administration. FII, factor II; FX, factor X; PTr, prothrombin ratio; U, units. Source: reproduced with permission from *Intensive Care Medicine*, Damage control resuscitation using blood component therapy in standard doses has a limited effect on coagulopathy during trauma haemorrhage, vol. 41, 2015, pp. 239–47, Khan S, Davenport R, Raza I, Glasgow S, De'Ath HD, Johansson PI, Curry N, Stanworth S, Gaarder C, Brohi K, © Springer-Verlag Berlin Heidelberg and ESICM 2014 with permission of Springer.[26]

However, these plasma regimens did not treat an existing coagulopathy. They were protective against further deterioration, but trauma patients presenting with ATC never corrected their coagulation parameters to normal until bleeding had stopped and compensatory mechanisms had taken over. Although high-dose plasma was effective in avoiding dilutional coagulopathy, there was still an opportunity to improve outcomes with focused, targeted anti-ATC therapy early in the clinical course.

We also reviewed transfusion practice nationally (Aim 2) as part of our prospective cohort study.[18] We found that there were a number of opportunities for improvement in practice that could directly translate to improved outcomes. We particularly looked at delays in the delivery of FFP and other blood products (*Figure 9*) and times when the unavailability of products would leave patients exposed to a risk of dilution with PRBCs or intravenous fluid replacement (e.g. crystalloids).

Bleeding trauma patients tended to receive PRBCs first and there was a delay of 1–3 hours before receiving the first doses of FFP. During resuscitation, there was variation in the delivery of FFP leading to variation in the ratio delivered. There were times when no blood products were available. A large proportion of deaths occurred in the early phase of care when plasma and other blood product delivery was absent or inefficient. There are therefore important opportunities for practice improvement on a national level based on our current understanding of the optimal management of trauma haemorrhage.

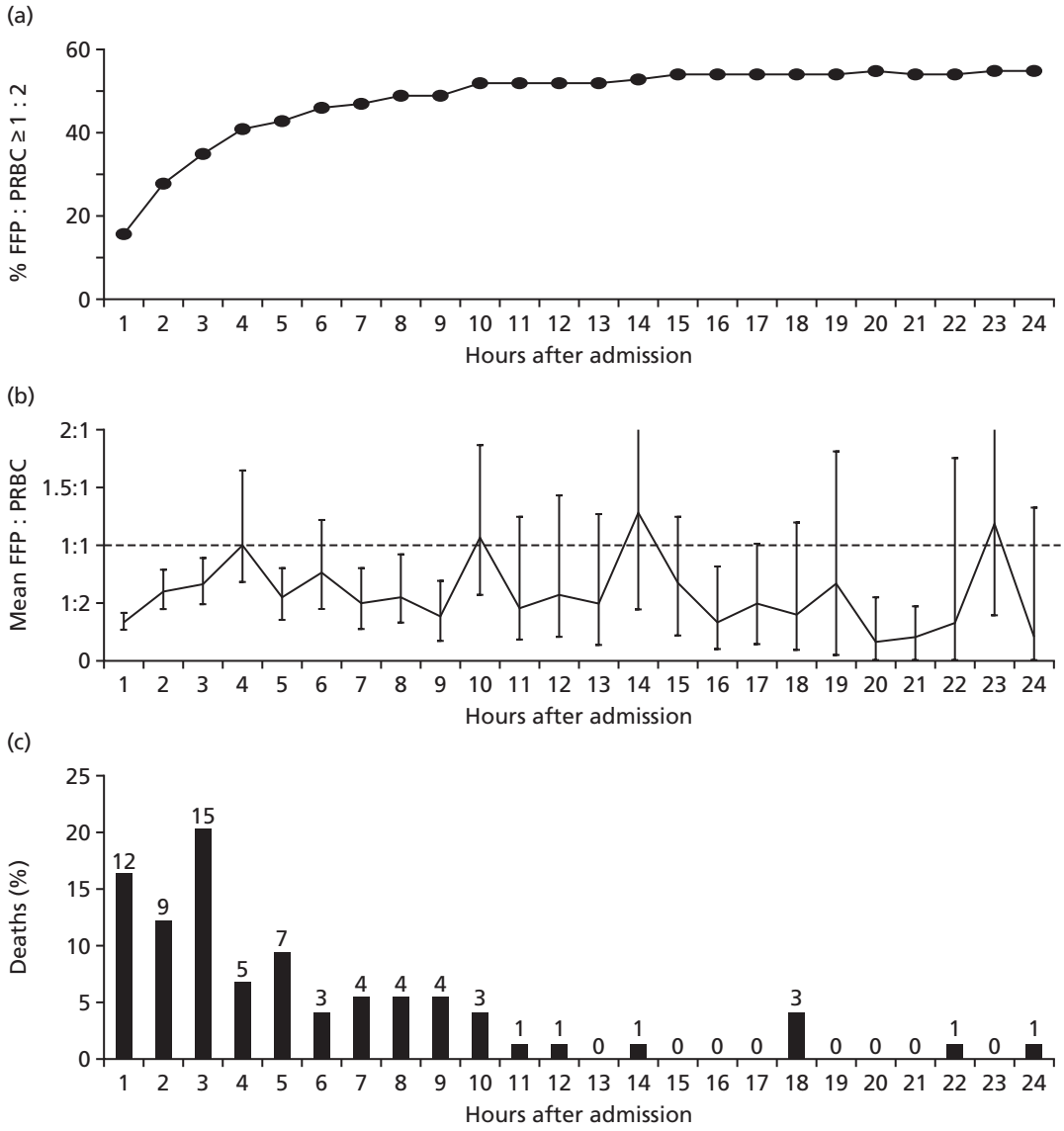

FIGURE 9 National patterns of transfusion therapy in trauma haemorrhage: (a) late FFP availability results in < 50% of patients achieving a FFP : PRBC ratio of ≥ 1 : 2 by 4 hours after admission; (b) the FFP : PRBC ratio varies and balanced resuscitation is not delivered consistently during resuscitation; and (c) mortality by hour showing the concentration of deaths when FFP is not available or administered. Source: data from Stanworth *et al.*[18] Reproduced with permission from Stanworth SJ, Davenport R, Curry N, Seeney F, Eaglestone S, Edwards A, *et al.* Mortality from trauma haemorrhage and opportunities for improvement in transfusion practice. *Br J Surg* 2016;**103**:357–65[18] © 2016 BJS Society Ltd Published by John Wiley & Sons Ltd.

Acute trauma coagulopathy: fibrinogen loss and replacement

We identified reduced clot strength as a central functional component of ATC early in the course of this programme.[20] We investigated the cause of this and rapidly turned our attention to fibrinogen, the substrate for all blood clot formation.[29] We found that trauma patients with ATC arrive with a dramatically reduced level of fibrinogen (*Figure 10*) – around half of the normal level – and that this level decreases rapidly as bleeding continues. When no fibrinogen-containing blood products were administered, fibrinogen levels were near zero after transfusion of 8 units of PRBCs. Even with high-dose FFP (which contains some fibrinogen), fibrinogen levels continued to decline during bleeding. Only when fibrinogen was replaced with cryoprecipitate were fibrinogen levels maintained. Much closer attention is paid now to fibrinogen levels during haemorrhage and cryoprecipitate usage has increased worldwide over the last few years.

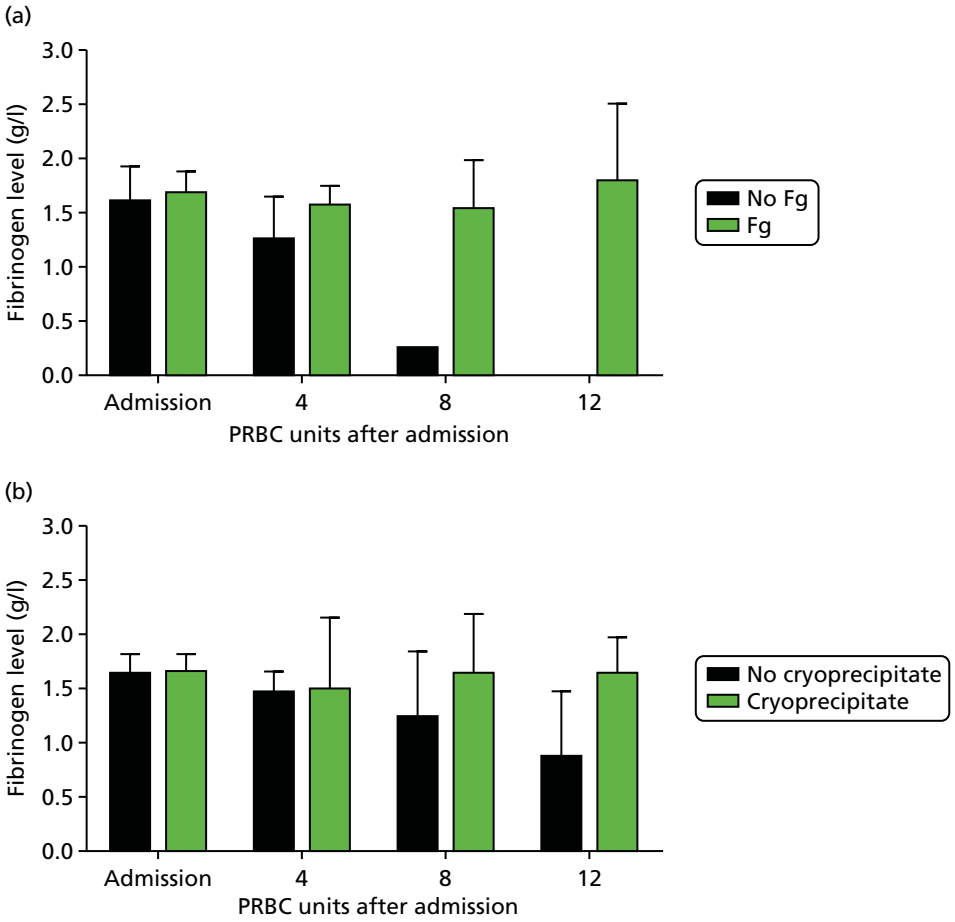

FIGURE 10 Fibrinogen levels during trauma haemorrhage: (a) fibrinogen levels are low on admission and decrease dramatically in the absence of any fibrinogen replacement (FFP or platelets or cryoprecipitate); and (b) cryoprecipitate as administered in the Code Red protocol maintains but does not correct fibrinogen levels. Fg, fibrinogen.
Source: data from Khan *et al.*[26]

Although cryoprecipitate administered in standard doses can maintain fibrinogen levels during bleeding, it does not correct fibrinogen to normal levels.[29] Trauma patients who arrive with ATC with insufficient fibrinogen substrate to form clots never achieve normal levels of fibrinogen. We therefore conducted ex vivo spiking experiments to determine how much fibrinogen would be necessary to normalise levels. In parallel with the programme grant we then conducted a pilot randomised controlled trial (CRYOSTAT) of early, high-dose cryoprecipitate in bleeding trauma patients.[30] We wanted to see whether or not we could deliver high-dose cryoprecipitate quickly to trauma patients and, in doing so, normalise fibrinogen levels and hence potentially improve outcomes.

The trial was conducted between the Royal London Hospital and the John Radcliffe Hospital, Oxford.[30] We also recruited patients at the Camp Bastion Military Hospital in Afghanistan. We recruited 40 patients and showed that we could deliver high-dose cryoprecipitate (equivalent to 4 g of fibrinogen supplementation) within 90 minutes to bleeding trauma patients who activated the major haemorrhage protocol. Patients in the early high-dose cryoprecipitate arm maintained their fibrinogen levels throughout the bleeding phase (*Figure 11*). Furthermore, these patients had a much lower mortality rate than patients in the control arm (less than half of our current Code Red mortality rate), although this was not statistically significant in this small pilot trial.

We are currently recruiting to the Phase III CRYOSTAT2 trial to determine whether or not early high-dose fibrinogen replacement significantly improves outcomes in trauma haemorrhage.

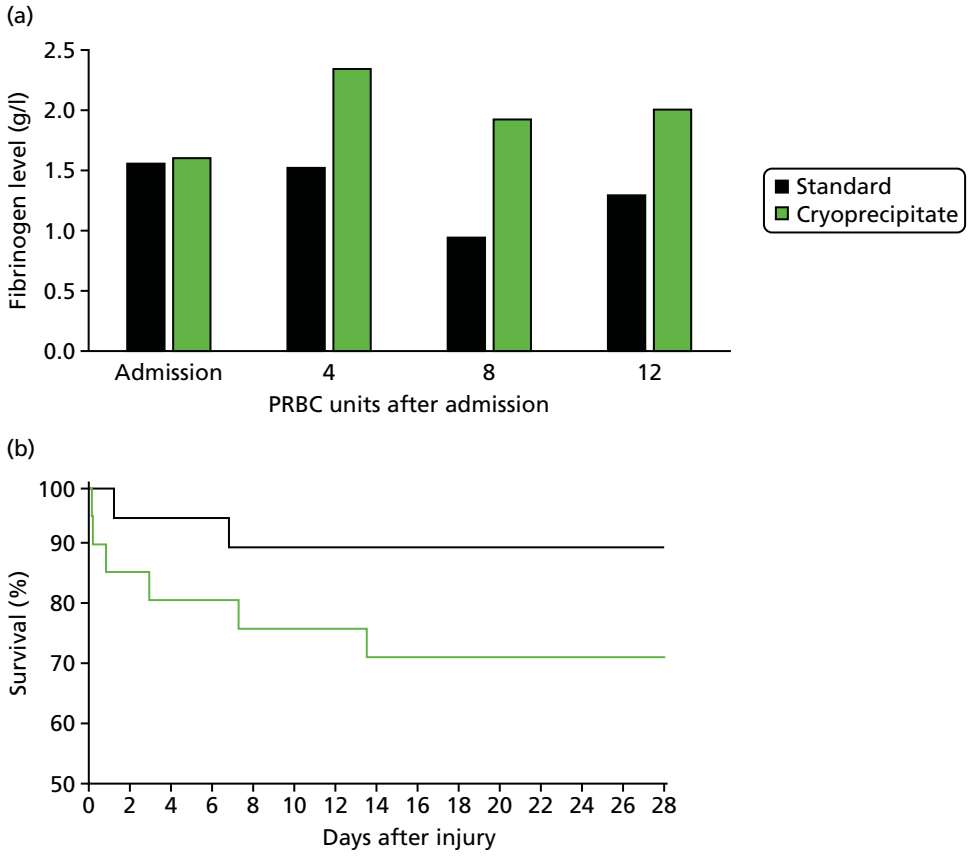

FIGURE 11 CRYOSTAT study results: (a) early high-dose cryoprecipitate is able to correct fibrinogen levels during trauma haemorrhage; and (b) survival curves for the high-dose cryoprecipitate (green) and standard therapy (black) groups (not significant). Source: data from Curry *et al.*[29]

Acute trauma coagulopathy: fibrinolysis and tranexamic acid

In earlier work we had identified excessive clot breakdown (hyperfibrinolysis) as a key characteristic of ATC.[25] However, there was conflicting evidence on hyperfibrinolysis. In studies using functional coagulation tests such as ROTEM, hyperfibrinolysis was very rare and almost uniformly fatal. In a large randomised controlled trial [Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2)] by our close collaborators at the London School of Hygiene & Tropical Medicine, a relatively low dose of an antifibrinolytic agent, tranexamic acid, led to significant improvements in survival.[30] This seeming paradox, together with a potential risk of thromboembolism, had restricted the implementation and uptake of tranexamic acid by the NHS and internationally. Some bodies mandated the use of functional clotting assays to guide therapy, whereas others refused to adopt this treatment.

We explored fibrinolysis in trauma patients by examining the fibrinolytic pathway in our ACIT cohort.[31] We found that > 60% of trauma patients have extreme fibrinolysis even in the first minutes after injury (*Figure 12*). More importantly, this lytic activity is not detectable in viscoelastic assays until endogenous antifibrinolytic proteins are exhausted. This fibrinolysis in trauma patients is common and occult and, therefore, viscoelastic assays should not be used as criteria for antifibrinolytic therapy.

We incorporated tranexamic acid into our Code Red protocol in 2011. In the first civilian study of tranexamic acid in a developed civilian trauma system setting, we showed improved outcomes including survival (*Figure 13*).[32] Patients presenting in shock had the greatest benefit, with a fourfold reduction in the relative risk of death. We also showed that early tranexamic acid administration not only treats hyperfibrinolysis but also protects clot strength throughout trauma haemorrhage.

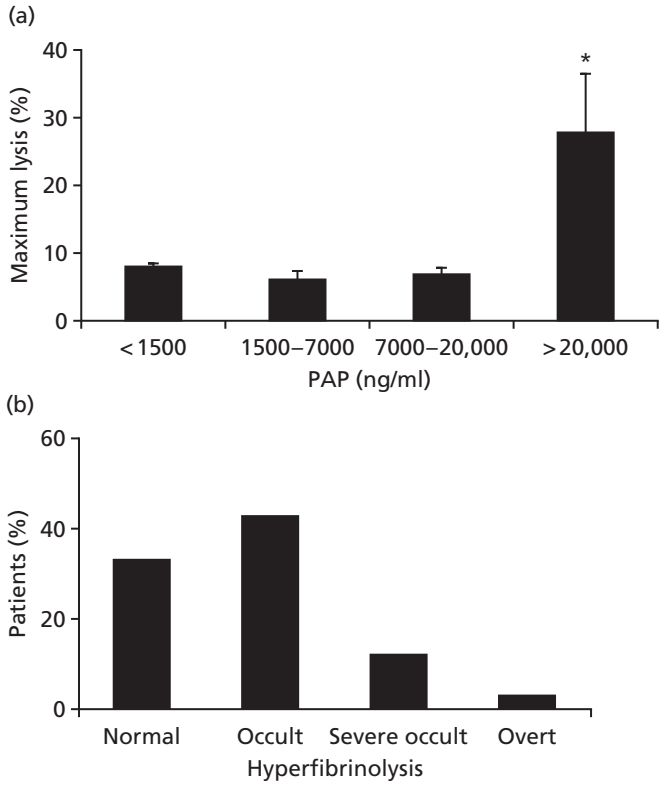

FIGURE 12 Thromboelastometry is insensitive to fibrinolysis in TIC: (a) maximum lysis occurs only at extremely high levels of plasmin production; and (b) 60% of patients have occult lysis evidenced by PAP levels of > 10× normal and which is not visible on thromboelastometry. PAP, plasmin–antiplasmin. Source: data from Raza *et al.*[31]

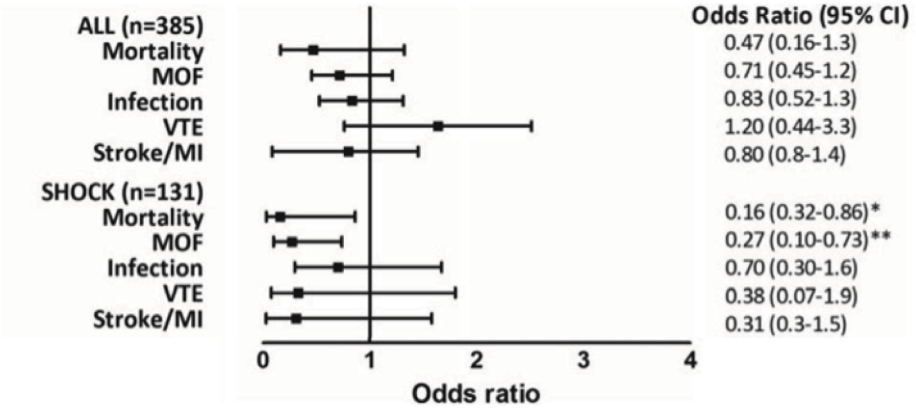

FIGURE 13 Tranexamic acid reduces mortality and multiple organ failure (MOF) in trauma patients presenting with shock (which is defined by base deficit of > 6 mmol/l). MI, myocardial infarction; VTE, venous thromboembolism. Source: reproduced with permission from Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. *Ann Surg* vol. 261, iss. 2, pp. 390–4.[32] 2015. URL: http://journals.lww.com/annalsofsurgery/pages/default.aspx. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact healthpermissions@wolterskluwer.com for further information.

This work has supported the uptake of tranexamic acid into clinical guidelines and major haemorrhage protocols. It is now widely used across the country and is given by pre-hospital teams to patients suspected to have haemorrhage before arrival at trauma centres.

The evolved concepts of damage control resuscitation and trauma-induced coagulopathy

In overview, we have used the principles of DCR as a starting point and refined its principles, practice and treatment, iteratively generating evidence and implementing it into practice (*Figure 14*).

Our new concept of TIC is simpler, with a more mechanistic basis. Essentially, there are two main coagulopathies: the endogenous ATC and a subsequent dilution/consumption phenotype that progresses during haemorrhage and resuscitation.

We now believe that the central features of ATC are fibrinogen loss and hyperfibrinolysis. Tranexamic acid has been introduced into practice for hyperfibrinolysis and early fibrinogen replacement is awaiting a next-phase clinical trial.

Dilutional/consumption coagulopathy is now managed by avoiding crystalloids, even in the pre-hospital phase of care; streamlining the delivery of transfusion products; and delivering plasma in a 1 : 1 ratio with PRBCs.

We believe that we have demonstrated that robust implementation of these principles and practices can have a dramatic impact on outcomes for trauma patients. Nationally, trauma haemorrhage mortality remains very high, but we now have a roadmap to begin to reduce these deaths.

Mass casualty and event response plannings

Blood is one of the most constrained resources in the response to mass casualty events such as the London bombings of 2005.[21,33] Restocking of the hospitals involved in a response is difficult or impossible during the early phases of the event. At least initially, hospitals must rely on the stocks already present before the event occurs (*Figure 15*). New DCR paradigms requiring transfusion of more blood products per casualty will also increase the strain on these limited resources.[34] There are important implications, therefore, for major incident preparedness, as well as for planning for expected events such as the London Olympics.

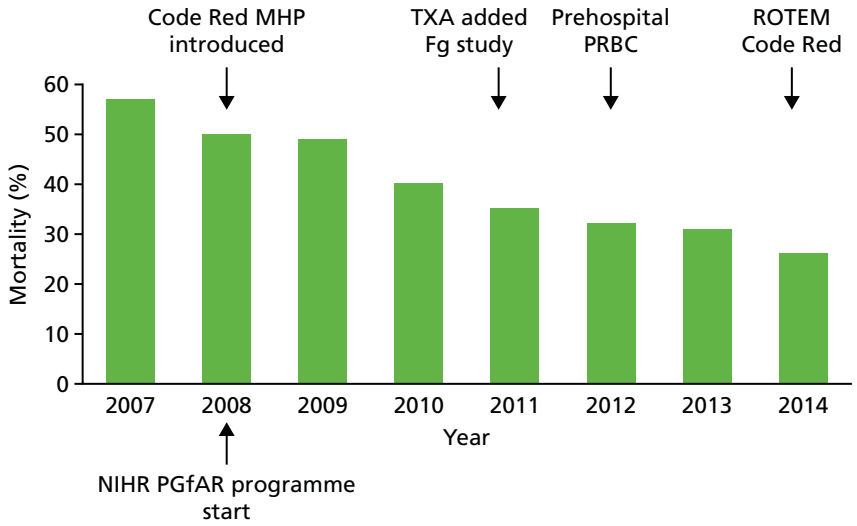

FIGURE 14 Interventions associated with Code Red protocol evolution at the Royal London Hospital major trauma centre. Fg, fibrinogen; MHP, major haemorrhage protocol; NIHR, National Institute for Health Research; PGfAR, Programme Grant for Applied Research; TXA, tranexamic acid.

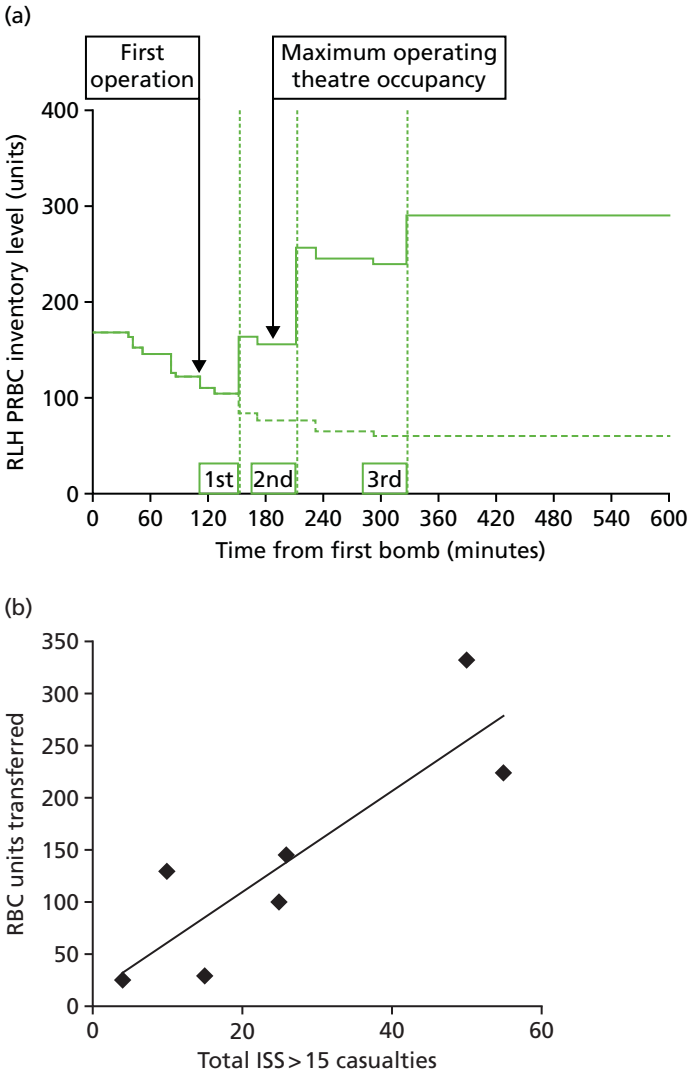

FIGURE 15 Provision of red cell transfusions during mass casualty events: (a) red cell stocks at the Royal London Hospital during the bombings of 7 July 2005; and (b) the best correlation of red cell requirements is with the number of critically injured casualties in a mass casualty event. ISS, Injury Severity Score; RBC, red blood cell; RLH, Royal London Hospital. Source: reproduced with permission from Glasgow S, Davenport R, Perkins Z, Tai N, Brohi K. A comprehensive review of blood product use in civilian mass casualty events. *J Trauma Acute Care Surg* vol. 75, iss. 3, pp. 468–74. 2013.[21] URL: http://journals.lww.com/jtrauma/pages/default.aspx. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer. Please contact healthpermissions@wolterskluwer.com for further information.

We studied the utilisation of blood stocks during mass casualty events through a systematic review of the literature and a detailed examination of blood utilisation during the London bombings and Norway attacks.[21]

We were able to correlate PRBC transfusions with the number of critically injured casualties (as opposed to other measures of casualty load). As these numbers are relatively constant for specific types of events, this can be used to plan the numbers of PRBC and blood product stocks that need to be held for specific events. We were able to feed this information into the planning process for the 2012 London Olympics.[34]

We then created a model of casualty flow and blood utilisation by hospitals during a mass casualty event.[35] We populated this with the data collected from the literature, our specific investigations and the results of interviews with hospital staff and specialists. Once the model was constructed (*Figure 16*), we could modify parameters to investigate the benefits of alternative methods of utilising and preserving blood resources during such events.

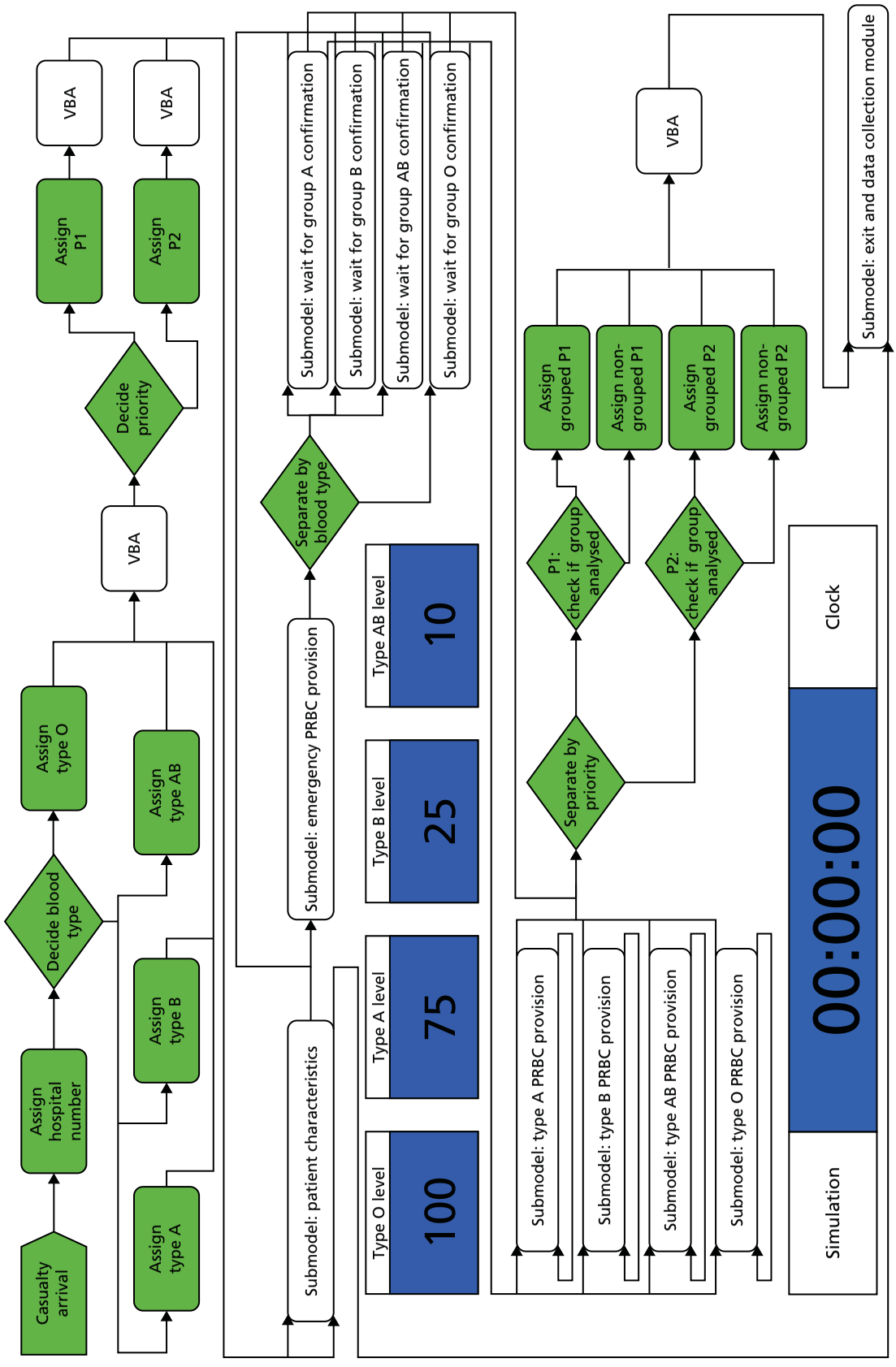

FIGURE 16 Overview of the queuing model for examining red cell management during mass casualty events. VBA, Visual Basic for Applications.

Exploring the model we can see how increased casualty loads and stock levels have the most profound effect on how quickly casualties receive the blood products they need and how blood stocks are preserved (*Figure 17*). These cannot easily be mitigated by increasing the number of technicians, reducing processing time or otherwise trying to increase efficiencies within the system.

Mass casualty response planning therefore has to focus on methods for restocking supplies. In addition, blood utilisation may need to be restricted during these events. We examined several strategies and found that both overall limitation of total PRBC transfusions and the restriction of emergency type O blood transfusions were effective in providing the best care for the most casualties. However, the clinical acceptability of these strategies still needs to be explored.

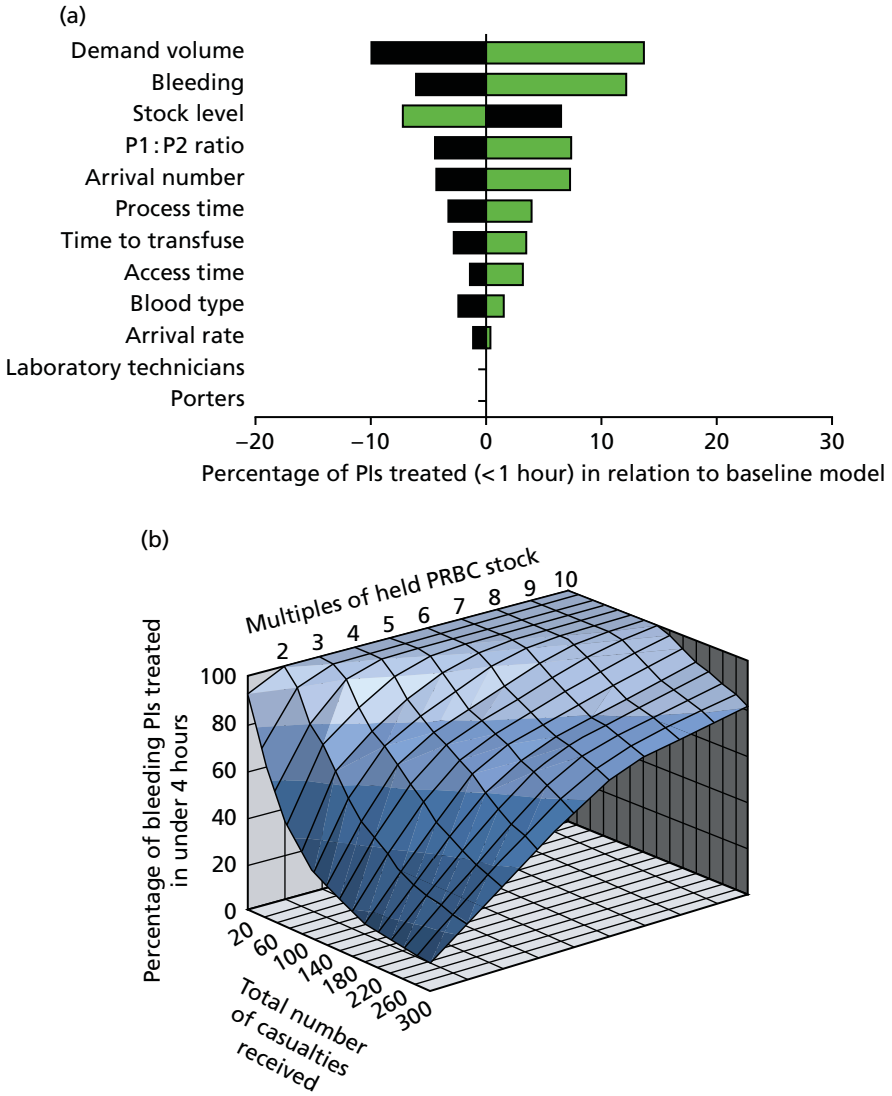

FIGURE 17 Example modelling outputs for red cell provision during mass casualty events: (a) tornado plot showing sensitivity analysis for how changing event variables affects the number of P1s receiving timely red cell transfusions; and (b) waterfall plot showing the effect of casualty numbers and the size of red cell stocks on the timely transfusion of P1 casualties.

Limitations

There are several limitations to our studies and the findings. These are discussed in detail in our papers and are summarised in the following sections.

Epidemiology

In our national study we used a representative sample of large and small hospitals with an element of selection as we relied on the submission of TARN data to assist with data collection. As this work mostly predated the introduction of regional trauma systems, it is possible that we have underestimated the incidence of trauma haemorrhage because of incomplete data reporting. It is also possible that our national estimate is inaccurate because of the hospitals not being representative of the country as a whole. However, the picture of national mortality and other outcomes and of overall transfusion practice and blood product delivery is unlikely to be affected by these potential variations.

Our health economic analysis was as detailed and accurate as possible based on the cost and resource utilisation information available to us. However, these are cost estimates and there was wide variation across the country and between patients. Nevertheless, the total figures represent the most accurate assessment to date of the costs of treating patients with trauma haemorrhage and help to understand where the main cost burden – and potential savings – may lie.

Diagnosis and treatments

The studies on diagnosis and treatment were based principally on the examination of a large cohort from two major trauma centres. As such, although trends and associations can be investigated and hypotheses generated, it is not possible to determine causality from these studies. However, we have looked deeply into mechanisms to support the clinical research findings and, when possible, we have taken these findings into a randomised controlled trial (CRYOSTAT) or collaborated with other trial groups (e.g. CRASH-2). Our findings on diagnostic test accuracy and thresholds for treatment need external validation and utilisation and these projects are ongoing through the INTRN.[36] Our cohorts were not large enough to look at responses to other blood products such as platelet transfusions and further work is required in this area.

Mass casualty management

As with all models the quality of the output is dependent on the base information available for model development. We gathered as much evidence as possible from the literature and specific event information available to us. However, this may not be representative of all possible events or even the average event. However, the model does allow us to vary the input parameters and assess the effects of such variations within the model response. We also have not been able to develop a model that includes plasma and other blood components and this is an area for future work.

What we know now the programme grant is complete

This integrated programme of work has generated a lot of new knowledge and, combined with parallel research by other groups, has led to a major shift in our understanding of trauma haemorrhage and coagulopathy. The work has of course also led to new questions and, therefore, new directions for research and innovation.

We have a much stronger understanding of the epidemiology of trauma haemorrhage nationally. We know not only that nearly 5000 adults will suffer major haemorrhage after trauma each year but also that older patients seem to have a much higher rate of bleeding after trauma, with the reasons for this not being clear. Our study did not include children and paediatric trauma haemorrhage remains an area for further study.

Massive haemorrhage carries an unacceptably high mortality rate nationally, approaching nearly 50%. We found that one-quarter of these deaths occurred in the first hours after injury. These deaths are probably due to exsanguination and reducing this mortality will require innovations in the control of internal haemorrhage and faster, more effective ways to augment blood clotting ability in this critical time window.

One-quarter of deaths in people who survived the initial exsanguination phase occurred in the first 24 hours. These deaths are likely to result from a fulminant physiological failure and the inability of resuscitation to rapidly and effectively restore homeostasis. Improved management during haemorrhage including precision haemorrhage control is required to have an impact on these deaths – and we believe that this is the cohort on whom we have probably made the most impact with work done in this programme. Better diagnostics, therapeutics and focus on consistent delivery of clotting products has allowed us to provide a much more effective, balanced resuscitation.

We demonstrated that, currently, patients tend to receive coagulation therapy late in their clinical course and are often subject to gaps in the provision of blood-derived clotting products while they are bleeding. Our investigations into the underlying pathophysiology of coagulopathy have shown that the central disorders are loss of fibrinogen and increased clot breakdown. Previously, loss of procoagulant factors was thought to be the central problem and efforts were focused on this area. Our evidence has supported the uptake of the antifibrinolytic tranexamic acid into national guidance and it is now given by ambulance crews in the field. We continue to explore the potential benefit of early high-dose fibrinogen replacement therapy, which may also allow early augmentation of clot strength in the immediate post-injury phase. There are undoubtedly further gains to be made in this area in the future with novel haemostatic agents and blood products.

We have also shown that point-of-care devices can identify changes in coagulopathy during haemorrhage and that thresholds can be derived to initiate (or stop) clotting therapy. Use of these devices in trauma care might allow us to move away from our current blind ‘blunderbuss’ approach to a more individualised, precise approach that specifically treats the coagulopathy identified at that time, in that patient. Timely, effective treatment of coagulopathy may reduce bleeding, support resuscitation and improve survival. These devices may also reduce the total number of blood products required and thus reduce wastage of these precious resources. Logistic hurdles still exist for the uptake of these devices but our work is informing the design and implementation of the next generation of point-of-care coagulation analysers for emergency environments.

Half of all deaths occurred after the first 24 hours. Many of these deaths will be the result of multiple organ dysfunction syndrome or its consequences. Better resuscitation should reduce the incidence and severity of later multiple organ dysfunction and it is likely that improvements have also been seen here based on our observed reductions in organ support requirements and critical care stays. Organ dysfunction is responsible for a large proportion of the morbidity experienced by patients and nearly half of all resource

use costs were incurred in critical care. Understanding post-traumatic organ dysfunction and developing new therapeutic and management strategies should also be a focus of future research efforts.

Our parallel work on modelling blood use in mass casualty events has shown that initial blood stocks and planned restocking must be central to plans for these events. We have shown that aspects traditionally thought to make a difference, such as the number of available technicians or cross-matching time, have a minimal impact on the provision of blood to critically injured casualties. This work informed London Olympics 2012 planning and is now being used nationally to plan stocks and restocking in the response to larger-scale terrorist attacks such as that seen in Paris in 2015.

Future work and directions

There are multiple avenues for further research and development based on our current findings. Key areas include methods to manage bleeding and coagulopathy within the first hours after injury; understanding how coagulopathy and bleeding lead to organ dysfunction and late deaths; and understanding TIC in specific populations including children, the elderly and patients with traumatic brain injury. The immediate imperatives centre on clinical studies of fibrinogen concentrates; personalised ROTEM-/thromboelastography (TEG)-guided TIC therapy; and the role of platelet dysfunction and transfusion.

Further validation of our findings is required in relation to diagnostic test accuracy and the role of ROTEM/TEG in guiding individualised coagulation therapy. We have formed a collaboration with other trauma research centres around the world (INTRN) to continue to recruit patients to the ACIT study in order to validate our findings in new patient cohorts.

As there was such large variation between patients we were not able to look in detail at the response of coagulation to other coagulation therapies, such as platelet transfusion. This is an expensive and difficult resource to manage and more work is required to understand the role of platelet transfusions in the management of trauma haemorrhage.

Work needs to be continued on how functional coagulation analysers can be incorporated into major haemorrhage guidelines and how they can be efficiently and effectively implemented in major trauma centres. We have been working with the device manufacturers on refinement of the devices for the emergency environment, as well as on improvements to the user interface to aid diagnosis and subsequent management. Implementation research in this area will be important in parallel with standard clinical trials of effectiveness.

Our work also highlights the opportunities for very early intervention to correct ATC, something only partially addressed by current management paradigms. Tranexamic acid has been introduced into practice. Early high-dose fibrinogen supplementation is the clear next opportunity, either with cryoprecipitate or fibrinogen concentrates. There is also a potential role for devices for immediate haemorrhage control and cardiac support in the pre-hospital and hyperacute phase, or when blood products are not available.

In parallel with this, further work is required to specify the different phenotypes of and mechanisms responsible for ATC and other forms of TIC. This work requires further analysis of samples already collected and further studies of the cellular components of blood as well as the response of the endothelium and other components of the inflammatory system.

Further mechanistic work will be particularly important in targeting the 50% of deaths that occur after the first 24 hours. These deaths are not purely due to exsanguination and coagulopathy, but have an intrinsic component of inflammation, multiple organ failure and immunosuppression. These processes are likely to be initiated in the immediate post-injury phase and the quality and nature of immediate resuscitation will set patients on a specific clinical trajectory. A reduction in these late deaths will require further investigation into these aspects of the coagulation and inflammatory response.

Outcomes other than mortality also need to be investigated in these patients. The burden of organ dysfunction, infection and thromboembolism and the effect on reconstruction and rehabilitation all need further investigation. In particular, long-term quality of life and capacity are important in the assessment of both the clinical effectiveness and the cost-effectiveness of new therapeutics and management strategies in the NHS.

Conclusion

In conclusion, this multimodal programme of work has led to new understandings of the epidemiology of trauma haemorrhage and its underlying mechanisms and clinical course. We have identified diagnostic tools and trigger thresholds for identification and management and increased our understanding of how blood components and other therapeutics affect TIC and when they are likely to be most effective. Through a parallel programme of research implementation and engagement we have disseminated findings into clinical practice throughout the NHS and internationally. We have shown major improvements in clinical outcomes over the course of the programme and beyond. The programme has also allowed us to grow in capacity and capability as a trauma sciences research centre, to widen national and international collaborations and to train the next generation of trauma clinician scientists.

Acknowledgements

Contributions of authors

Karim Brohi (Consultant, Trauma) was the chief investigator for the programme.

Simon Eaglestone (Research Manager, Trauma) co-ordinated the programme, conducted the analysis of the national incidence and current practice of transfusion in trauma haemorrhage and prepared the results for publication and final reporting.

Contributions of others

Shubha Allard (Consultant, Haematology) co-managed the collaborative observational study to describe the national incidence and current practice of transfusion in trauma haemorrhage.

Helen Campbell (Senior Researcher, Health Economics) conducted the review of health-care costs in trauma and led the analyses employing economic models.

Nicola Curry (Clinical Research Fellow, Haematology) conducted the reviews of coagulopathy, transfusion and randomised controlled trials, led the prospective recruitment to the observational studies at John Radcliffe Hospital and co-led the study of fibrinogen depletion in clinical studies.

Ross Davenport (Clinical Research Fellow, Trauma) led the prospective recruitment to the observational studies at the Royal London Hospital, conducted the identification of ATC by ROTEM and led the analyses of transfusion treatment and outcomes.

Antoinette Edwards (Project Co-ordinator, TARN) conducted the analysis of the national incidence and current practice of transfusion in trauma haemorrhage.

Simon Glasgow (Clinical Research Fellow, Trauma) conducted the review of and model development for blood resource usage in mass casualty events.

Harriet Hunt (Research Fellow, Public Health) conducted the systematic review of diagnostic test accuracy.

Chris Hyde (Professor, Public Health and Clinical Epidemiology) was the study lead for the review of diagnostic test accuracy.

Sirat Khan (Clinical Research Fellow, Trauma) conducted the analysis of major haemorrage protocol practice and transfusion ratio effectiveness in the treatment of trauma haemorrhage.

Charlotte Llewelyn (Manager, NHS Blood and Transplant Clinical Studies Unit) co-managed the collaborative observational study to describe the national incidence and current practice of transfusion in trauma haemorrhage.

Imran Raza (Clinical Research Fellow, Trauma) conducted the biomarker analysis and characterisation of elevated fibrinolysis in trauma patients.

Claire Rourke (Research Assistant, Trauma) co-led the study of fibrinogen depletion in clinical studies and conducted the ex vivo analysis of coagulopathic patient blood ROTEM.

Frances Seeney (Principal Statistician, Transfusion Medicine) led the analysis of data from the observational study of the national incidence and current practice of transfusion in trauma haemorrhage.

Simon Stanworth (Consultant, Haematology) was co-investigator for the programme.

Elizabeth Stokes (Researcher, Health Economics) conducted the analysis of health-care costs in trauma and the development of the economic models.

Maralyn Woodford (Executive Director, TARN) co-managed the collaborative observational study to describe the national incidence and current practice of transfusion in trauma haemorrhage.

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Aim 1: evidence

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Aim 3: identification

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Data sharing statement

All available data can be obtained by contacting the corresponding author.

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Appendix 1 Aim 2 (epidemiology): participating trauma-receiving hospitals

Major trauma centres	Medium-sized hospitals with trauma units
• Addenbrooke's Hospital • Coventry & Warwickshire Hospital • Derriford Hospital • James Cook University Hospital • Hope Hospital • John Radcliffe Hospital • King's College Hospital • Leeds General Infirmary • Royal London Hospital • University Hospital Aintree • Queen's Medical Centre • St George's Hospital	• Ipswich Hospital • Leicester Royal Infirmary • Morriston Hospital • Newcastle General Hospital • Northamptonshire General Hospital • Royal Devon and Exeter Hospital • Sunderland Royal Hospital • Stepping Hill Hospital • Torbay District General Hospital • Whiston Hospital

Consecutive enrolment of eligible patients across all centres commenced on 1 April 2009 and continued until 30 March 2011.

Appendix 2 Aim 2 (epidemiology): Trauma Audit and Research Network standard operating procedure

[redacted]

Traumatic Coagulopathy and Massive Transfusion:
Improving Outcomes and Saving Blood.

STANDARD OPERATING PROCEDURE

Data Collection – TARN Local Data Coordinators

[redacted]

Signed off by:

_____ Date:

Dr Simon Stanworth (Chief Investigator)

[redacted]

Author:

_____ Date:

[redacted]

INTRODUCTION

The objective of this Standard Operating Procedure (SOP) is to ensure the local Trauma Audit Research Network (TARN) data coordinators collate and enter the relevant data in the additional data fields as part of the Traumatic Coagulopathy and Massive Transfusion survey in compliance with the study protocol.

DATA ENTRY – TARN Data Coordinators

1. Identify patient for TARN data entry as per existing TARN inclusion criteria and allocate TARN submission ID number

2. Inclusion criteria for trauma study – Has patient received 4 units of blood/blood components in first 24 hours post admission? If uncertain contact your hospital Transfusion Laboratory Manager to confirm

3. Collate and photocopy all patient drug charts, fluid charts and blood/blood product transfusion charts from admission up to 24 hours post admission to include:

   - Blood/Blood products transfused: Red blood cells, Fresh Frozen Plasma, Platelets, Cryoprecipitate and Beriplex/Octoplex
   - Fluids: Dextrose, Colloid, Crystalloid, Polygelatine (Haemaccel), Starch, Hypotonic Saline, Albumin and Hartmans

   Where possible using a 24 hour clock please record the time blood/blood products or other intravenous fluids were commenced and completed – if times not available please state

   - Drugs/Anticoagulants given: From drop down box please insert Aspirin, Heparin, Warfarin, Fragmin and Enoxaparine
   - Drugs/Procoagulants given: From drop down box please insert Factor VIIa, Tranexamic Acid, Aprotinin, e-aminocaproic Acid
   - Anticoagulants patient taking pre injury: From drop down box please insert either Warfarin, Aspirin, Clopridogrel or Dipyridamole

   Where possible using a 24 hour clock please record the time anticoagulants or procoagulants were given – if times not available please state

   - Pre existing bleeding conditions: From drop down box please insert e.g. Haemophilia or Von Willebrands Disease

4. Anonymise all data photocopied using TARN submission ID number and send to TARN recorded delivery. All data entry will be completed by TARN centrally not by the TARN coordinator

5. Complete existing and additional TARN data fields

6. Contact the Transfusion Laboratory Manager in blood bank and provide them with the TARN submission ID number, this will be used to anonymise the 30 transfusion report which the TLM will send directly to TARN

TARN Data Coordinators **will not** enter data related to transfusion related complications, this information will be collated by the Central Research Nurse/Study Coordinator.

ADDITIONAL GUIDANCE/REFERENCE NOTES:

Blood Results:

	minimum values	maximum values
Haemoglobin level	1.0	23.0g/L
Platelet Count	0	3000 10^9/L
Fibrinogen levels	0.1	10 g/L
PT (Prothrombin Time)	10	160 sec
INR (International Normalised Ratio)	0.5	15
aPTT (Activated Partial Thromboplastin Time)	20	200 sec
aPPTR (Activated Partial Thromboplastin Time Ratio)	0	1.5

Red Blood Cells – In non urgent cases generally given as a dose of 1 unit at a time over a period of 2 - 4 hours **but** in urgent massive haemorrhage situation more units will be transfused rapidly.

Fresh Frozen Plasma (FFP) – Adult dose generally given as 4 units at a time

Platelets – Generally given as 1 unit at a time

Cryoprecipitate – Issued by Blood Bank as a pooled product – typical adult dose is 2 pools (containing 5 units each)

[redacted] will liaise by telephone and undertake site visits to meet the TARN data coordinators and Transfusion Laboratory Manager/blood bank staff regarding any data collection issues or missing data.

Contact details: [redacted]

[redacted]

[redacted]

Appendix 3 Aim 3 (identification) and aim 4 (treatment): study protocol

Activation of Coagulation & Inflammation in Trauma

ACIT II - Version 1.5; 20th Sept 2008

Royal London Hospital

Site:

The Royal London Hospital

Whitechapel Road

London E1 1BB

020 7377 7695

077 0319 0545

Principal Investigator:

Karim Brohi BSc FRCS FRCA

Consultant in Trauma, Vascular & Critical Care Surgery

Co-investigators:

[redacted]

[redacted]

[redacted]

Researcher:

[redacted]

Synopsis

The Activation of Coagulation & Inflammation in Trauma (ACIT) study is designed to identify the clinically significant mechanisms and pathways by which the inflammatory and coagulation pathways are activated immediately following major trauma, how they lead to clinical coagulopathy and transfusion requirements, produce organ injury, and how they affect outcome in terms of organ failure and death.

Severe trauma patients will be enrolled into the study in the emergency department. Blood samples will be collected immediately and over the following three day period to characterise the nature, extent and duration of the response of the inflammation and coagulation systems to trauma. Samples will also be processed for DNA banking to assess the impact of population genetic factors to the response to trauma.

A subset of patients who are intubated, ventilated and sedated will have bronchial washing specimens analysed for markers of acute lung injury.

Clinical data on blood product transfusions, organ system failure, morbidity, ICU & hospital stay and mortality will also be collected up to day 28.

Study Aims & Hypotheses:

Aim 1: Coagulopathy and Massive Transfusion
To identify the key derangements in coagulation, fibrinolytic and endothelial cell function following trauma, determine the response to blood component therapy and identify and characterise the subsequent hypercoagulable state.

> Hypothesis ACIT: 1A
> Acute traumatic coagulopathy is caused by tissue hypoperfusion through the systemic activation of anticoagulant and fibrinolytic pathways.
>
> Hypothesis ACIT:1B
> Subsequent transfusion of red cells and blood component therapy has specific effects on the acute coagulopathy, which may be beneficial or harmful dependent on the current clinical state.
>
> Hypothesis ACIT: 1C
> Early coagulopathy leads to exhaustion of the anticoagulant system and up-regulation of antifibrinolytic systems, resulting in a hypercoagulable state.

Aim 2: Development of Organ Injury
To elucidate the effect of derangements in coagulation, fibrinolytic and endothelial cell function on the inflammatory response and the development of acute lung injury, multiple organ failure (MOF), and death.

> Hypothesis ACIT: 2A
> There is a dose-dependent effect of the severity of trauma on coagulation, fibrinolytic and endothelial cell function. These correlate with activation of a pathological systemic inflammatory response which leads to acute lung injury.

Hypothesis ACIT: 2B
There is a dose-dependent effect of the degree and duration of tissue hypoperfusion on coagulation, fibrinolytic and endothelial cell function. These correlate with activation of a pathological systemic inflammatory response which leads to acute lung injury.

Hypothesis ACIT: 2C
While tissue trauma (ACIT:2A) and cellular hypoperfusion (ACIT:2B) are different initiators, the resulting activation of the coagulation and inflammatory systems is identical and is the final common pathway in acute lung injury. Tissue trauma and cellular hypoperfusion have an additive effect on the development of ALI. The acute lung injury caused by tissue trauma and tissue hypoperfusion can be temporally separated.

Aim 3: Prediction model
To develop a prediction model for massive transfusion requirements and the development of organ injury following trauma.

Hypothesis ACIT:3A
Massive transfusion requirements can be predicted by initial physiological variables and immediate analysis of coagulation parameters. Conversely, the requirement for blood component therapy might be reduced by targeted measurement of coagulation function and biomarkers during transfusion.

Hypothesis ACIT:3B
Acute lung injury / ARDS and Acute Renal Injury can be predicted in the first hours after trauma based on trauma severity scores, tissue damage, severity and duration of tissue ischemia, with biochemical markers of coagulation or inflammation. Identify specific markers which may be clinically relevant.

Aim 4: Proteomic, analysis
To process and store samples for subsequent proteomic and genomic techniques to identify new loci for investigation, targeting drug discovery and identification of genetic susceptibility to poor outcome following trauma.

Aim 5: Trauma DNA Bank

To process and store samples for subsequent DNA typing and analysis. There appears to be a background race and genetic susceptibility to the effects of trauma. These alterations may well lie within the coagulation and inflammatory systems. Early identification of patients at risk may, in the future, allow therapy to be targeted depending on patients' racial background or even specific genetic make-up.

Hypothesis ACIT:5A

There are genetic mutations of coagulation and inflammatory genes (Factor V Leiden, Prothrombin 20210, Mannose Binding Lectin) that may protect against or increase susceptibility to the effects of tissue trauma and hypoperfusion.

Hypothesis ACIT:5B

There are Haplotype-specific (and thus race-related) variations in susceptibility and response to tissue trauma and hypoperfusion.

Background:

Over the past 100 years, advances in emergency medical systems, trauma surgery and trauma resuscitation have allowed patients who would otherwise have died on the streets to reach hospital and receive emergent treatment of their life-threatening injuries.

Patients who are bleeding may develop a disorder of the blood clotting system which leads to further bleeding, shock and potentially irreversible physiological derangements that lead to death. The nature of the clotting disorder is currently unclear, and there are no tests that have sufficiently characterised it. As such it is currently impossible to immediately assess the nature or degree of derangement of the clotting systems (coagulopathy) and no tools to guide therapy. Many patients who are bleeding get inadequate numbers of blood products. Conversely patients may be given blood products unnecessarily leading to all the complications associated with blood transfusion, including depression of the immune system, which is critical in major trauma patients.

Although they may survive this critical phase of their care, many of these patients will still die. Death, which usually occurs one to six weeks later, is due to a progressive failure of body systems – a syndrome called multiple organ failure. There is currently no specific treatment for multiple organ failure. Patients are supported on ventilators, dialysis machines and other organ support devices while the process runs its course. Patients who survive multiple organ failure may spend months in hospital, years in rehabilitation, and are usually left with some permanent disability.

Recent studies suggest that this late mortality due to multiple organ failure may be due to the body's responses to tissue damage and to blood loss that occur immediately following injury. There is a significant body of both basic science and clinical evidence that implicates the activation and dysregulation of the coagulation and inflammatory systems in the development of multiple organ failure. However, most of this data comes from research into sepsis. The mechanisms for the activation of the relevant pathways in trauma, and their relationship to clinical disease and outcomes have yet to be delineated. Identification of these key pathways will provide new directions for drug development and perhaps a specific treatment for post-traumatic multiple organ failure.

We postulate two mechanisms for the activation of these systems in trauma: tissue damage itself, and cellular hypoperfusion.

Tissue damage

Recently, two studies, the first from our group at the Royal London Hospital, have shown that trauma patients may arrive in the emergency department with severely deranged blood coagulation[1,2]. Patients with coagulopathy were three to four times more likely to die than those without. The incidence of coagulopathy was closely related to the severity of injury, and not to the volumes of fluid administered, suggesting that the injury load itself was

responsible for the activation of the coagulation systems. The mechanisms by which tissue injury activates the coagulation and inflammatory systems have not been previously studied.

Tissue hypoperfusion / hypoxia

Ischemia following hemorrhagic shock is known to lead to multiple organ failure and increased mortality. Several studies have shown that the severity of shock on admission correlates with eventual outcome. One of us (Karim Brohi) has recently finished a study examining the duration of tissue ischemia, as measured by base deficit and lactate, and found that even when sub-clinical tissue ischemia persists for over 12 hours, mortality is 38%, over twice that of patients who do not suffer a prolonged ischemic episode. Tissue hypoxia leads to endothelial injury and priming of cellular and humoral components of the inflammatory pathways.

Goals and Expected Outcomes

The entire pattern of activation of the inflammatory and coagulation systems has not been fully elucidated in trauma patients, and it remains unknown if and how this results in multiple organ failure and death. We hope that this study will allow us to fully characterise the coagulopathy of trauma and allow us to better target blood and component therapy by identifying clinically useful markers of early coagulopathy and the response to transfusion. Conversely, we expect that identifying those patients without coagulopathy might suggest that specific measures of coagulation during a massive transfusion would lead to a reduction in the total number of blood products transfused and a reduction in the number of complications.

We further hope that we will identify key junctures in the pathways that could be targeted for drug discovery and development programs. This will allow us to better understand which patients may benefit from the newer procoagulant agents such as recombinant factor VIIa. Further, it may allow us to intervene early to avoid the late complications of multiple organ failure. There has already been some headway in this area in the field of sepsis research. The anticoagulant activated Protein C (dotrecogin alpha) has recently been introduced and is the only pharmacological therapy that has shown to be effective in reducing mortality in severe sepsis. The final common pathways of sepsis induced multiple organ failure may be similar to those of tissue hypoperfusion.

Study Design

Prospective cohort multicentre observational study
The study will follow the clinical course of trauma patients on admission to the emergency department and for the next five days. Blood samples and, in some patients, bronchial washing samples will be analysed for markers of activation of the coagulation and inflammatory systems. These will be correlated with their injuries, their resulting physiological disturbances and their subsequent clinical course and outcome.

Blood sampling
Trauma patients will have blood samples drawn to measure markers of coagulation, fibrinolysis, endothelial activation and inflammation. Samples will be collected in the

emergency department at 0, 24 and between 60 to 72 hours post admission. Patients who are actively bleeding in the emergency department will have additional samples taken after administration of the 4th, 8th and 12th units of blood products, if used.

Bronchoscopy and lavage
Patients who are sedated, intubated and mechanically ventilated will have bronchoscopy and bronchial washing specimens sent for markers of acute lung injury. Samples will be collected within the first 24 hours, and subsequently at 48 and 72 hours, unless the patient is extubated before this time.

Data will also be collected on:
Patient demographics, mechanism of injury, injury type and severity, degree and duration of shock and tissue hypoperfusion, incidence and severity of organ dysfunction. These data are routinely collected in the management of injured trauma patients. No additional monitoring or interventions will be required.

Patient questionnaires
Quality of life assessment will be measured by the EuroQol EQ-5D questionnaire at hospital discharge or Day 28 and again at one year following injury. Health economic implications of massive transfusion and resource use will be collected with an additional questionnaire at the one year follow up. The in hospital questionnaire will be given to the patient and can be completed in under five minutes.

The 12-month questionnaire will be posted out to surviving patients along with a return stamped addressed envelope. The EuroQol EQ-5D questionnaire has been previously administered over the telephone, but responses can differ from those given when the patient is allowed to complete the questionnaire themselves. In addition patients will be required to answer questions on visits to outpatient clinics and GPs which is not practical in a telephone interview. Completion of the whole questionnaire will take approximately five minutes. Patients not responding within two weeks of the initial request will be telephoned as a reminder to complete the questionnaire. Confirmation with the GP and scrutiny of the hospital care record system will ensure only those patients alive at 12 months receive a questionnaire.

Outcome measures

Primary
Aim 1: Blood products transfused in the first 24 hours
Aim 2: Incidence & severity of acute lung injury & multiple organ failure

Secondary

28-day mortality, ventilator free days, ICU stay, hospital stay, blood transfusions in first 24 hours, number of infections

Procedures

Blood samples

Trauma patients will have blood samples drawn to measure activation of coagulation, fibrinolysis, endothelial injury and inflammation. Samples will be drawn at 0, 12 and between 60 to 72 hours post admission. Patients who are actively bleeding in the emergency department will have additional samples taken after administration of the 4th, 8th and 12th units of blood products, if used. Each sample is 20mls.

Severe trauma patients not enrolled in the study would normally have blood samples drawn at minimum at 0, 12 and 24 hours and daily thereafter. Most trauma patients have blood tests drawn more frequently, especially those who have signs of hypoperfusion, coagulopathy, on-going blood loss or those that are mechanically ventilated. As most major trauma patients have an arterial or central line placed, most blood draws are not painful to the patient. Whenever possible we will coordinate our blood draws with those of clinical need, to reduce the number of needle-sticks. We will not be able to use blood that has already been collected and placed into specimen tubes as our samples will require specific handling and processing.

Coagulation markers to be tested will include: Prothrombin fragments 1+2, Protein C, Endothelial Protein C Receptor (EPCR), Thrombomodulin, Tissue factor, Plasminogen Activation Inhibitor-1 (PAI-1), tissue Plasminogen Activator, Tissue factor Activatable Fibrinolysis Inhibitor (TAFI), D-Dimers. Markers for endothelial injury will include von Willibrand Factor (vWF) and E-selectin.

Inflammation markers will include TNF-α, IL-1,IL-6,IL-8,IL-10, Complement components, heat shock proteins. Samples will also be processed and stored for DNA and proteomics analyses.

Rationale for sequential blood sampling

1. The activation pattern of coagulation following trauma is a dynamic process and the full picture will not be apparent on a single blood draw immediately following injury. Some coagulation factors are used up and the levels of others increased with increased genetic expression. Many trauma patients exhibit a hypercoagulable state in the later stages of injury [6]. How this change occurs is currently unknown, but would be identified by this protocol. This would have major implications for the treatment of coagulopathy – especially new therapies such as activated Factor VIIa.

2. A prolonged shock state has a known poor outcome[7]. This may be due to continued activation of the coagulation and inflammation systems. Further a procoagulant state has been identified late in severely injured trauma patients. Serial measurements will allow us to detect these changes and correlate them with injury and physiological factors.

3. Medical therapy in terms of fluid and blood transfusions may affect these processes – but to what degree and in which direction is currently unclear. Trauma patients receiving more than two blood transfusions are known to have a worse outcome[8]. Serial sampling will allow

us to assess the impact of fluid and blood resuscitation on the coagulation and immune systems.

Bronchoscopy & Lavage

Patients who are intubated and sedated will have bronchial washing specimens sent for markers of acute lung injury within the first 24 hours, and subsequently at 48 and 72 hours following emergency department arrival (provided they remain intubated for this time). This involves passing a fine tube through the breathing tube of a patient, injecting a small volume of saline and re-aspirating the fluid. A 50mls (three tablespoons) sample is adequate for the lavage sampling and a maximum of 150mls of saline (in 50ml aliquots) will be instilled to produce this return.

Bronchoalveolar lavage is a standard procedure on many intensive care units for the diagnosis of ventilator associated pneumonia and is similar to tracheal suctioning that is performed on all intubated patients multiple times a day. It carries minimal morbidity. The main risk of the bronchial catheter is a transient episode of mild hypoxia. We will minimise risks of the procedure by excluding patients who require high oxygen concentrations (receiving 80% oxygen or greater). Patients will be suctioned and then placed on 100% oxygen for five minutes prior to and during the procedure the procedure. If there is any significant decrease in oxygen saturation, the procedure will be discontinued (after suctioning of any remaining saline).

Experience from the Royal London intensive care unit and elsewhere[9] demonstrates that bronchoscopy and lavage can be safely performed on these trauma patients with no significant episodes of hypoxia. The alternative procedure of bronchial aspiration through a catheter has been demonstrated to be inadequate for the investigation of acute lung injury[10]. Bronchial washing will be performed by senior intensive care staff or trained members of the research team proficient in the technique.

As these patients are sedated for the purposes of mechanical ventilation, patient discomfort will be minimal. Consent for bronchial washing specimens will be in addition to the standard consent for the blood sampling, and patients' families may opt out of this segment of the study if they so wish, while still consenting to the rest of the study protocol.

Markers of Acute Lung Injury (Bronchial washing specimens) will test for the following: Cell count, differential, total protein, PC, EPCR, TF, TFPI, PAI-1, IL-6, Endothelial: vWF, Epithelial: HT156, PCP-III, SP-D, KL-6, PBEF, and samples stored for genomics/proteomics study.

Risks & Benefits

Risks

All parts of the study will be carried out to avoid patient risk and minimise discomfort at all times. At no time will patient care be compromised or delayed for the purposes of the study. The risks of blood sampling are limited to some potential bruising at the site of venepuncture, and discomforts are limited to needle puncture (where no arterial line is already in place).

Bronchoscopy is a safe procedure with a complication rate of less than 1 in 1000. The complication rate is lower in patients who have a protected airway, as in our study. Most complications are a transient episode of hypoxemia (low blood oxygen level). Rarer complications include infection and airway abrasions. Complications of bronchial lavage will be minimised in the study population as we are limiting it to sedated patients who are intubated and on controlled mechanical intervention, with full cardiorespiratory monitoring. Patients with high oxygen requirements will be excluded from the procedure, and additional oxygen will be given to all patients before and during the procedure. If there is an episode of hypoxemia the procedure will be terminated and normal ventilation continued with higher oxygen concentrations as required.

We will record all adverse events associated with the study and review them as they occur, and collectively at monthly intervals.

Participation in research may involve some degree of loss of privacy. However this risk will be minimised by our data protection methods and we are not performing any tests that might subsequently result in significant personal, financial or social risk to the research subjects. We will make every effort to ensure that our data is secured and patients' privacy is protected.

Benefits to subjects

None

Potential benefits to society

Trauma remains the leading cause of death in patients between 1 and 45 years of age, and is the fifth most frequent cause of death overall. The World Health Organization predicts that by 2020 road traffic accidents alone will be the third leading cause of death worldwide. In general, injured patients die either from major hemorrhage, traumatic brain injury or multiple organ failure. Patients who die from hemorrhage or brain injury do so within the first few days following injury. For those patients who die after the first 24 hours, 60% will die of multiple organ failure. Those patients with multiple organ failure who do not die have extensive intensive care and hospital stays and are very expensive in terms of cost, resources and personnel.

It is clear from several studies that the outcome of trauma patients is determined in the first few hours following injury[4,5]. However we currently have very little understanding of the processes at work during this early injury period. We currently have an almost total lack of understanding of the initiation and progression of activation of the coagulation and inflammation systems, and how they lead to multiple organ failure – questions this study is designed to investigate.

Trauma patients tend to be young, active members of society, often with good jobs and young families to support, who are essentially 'cut down in their prime'. We hope that this study will allow us to identify specific points in the genesis of multiple organ failure that may be

used to target interventions in the future, and hence reduce this huge burden of death and disability.

Risk/benefit analysis

Although the study carries no benefit to the subjects, the bulk of the study is observational, and interventions that are carried out are routine, carry small or minimal risk, and the study has been designed to reduce discomfort and risks to the study subjects.

Subjects

Estimated number of subjects to be enrolled: 500

The study population will include adult trauma patients admitted to the Royal London Hospital via the emergency department. Only patients who have a trauma team activation will be considered for enrolment into the study. Only sedated, intubated and mechanically ventilated patients will be considered for the collection of bronchoscopic lavage specimens.

As the study is investigating the immediate post-injury phase, patients will be recruited into the study before their full list of injuries is known (before they have X-rays, CT scans, angiograms, operations etc). From our trauma database at the Royal Hospital we know that using all major trauma activations, with the exclusion criteria listed below, will provide us with a study population with an injury severity distribution of approximately 35% severe injuries, 55% moderate injuries and 7% minor injuries.

The study will, of necessity, include trauma patients who are unable to give consent for themselves. The study may also include patients whose first language is not English. There is some evidence that patients from different racial groups have altered responses to injury, and excluding them would bias the study in favour of native English-speaking populations.

Inclusion criteria

Adult trauma patients admitted via a trauma team activation to the emergency department at the Royal London Hospital.

Exclusion criteria

- Age < 16
- Patients transferred from other hospitals
- Patients presenting more than 120 minutes after time of injury.
- Patients who have received more than 2000mls of intravenous fluids prior to emergency department arrival.
- Patients with burns > 5% of their body surface area.
- Patients taking anticoagulant medication other than aspirin (<650mg/day).
- Patients with a known bleeding diathesis.
- Patients with moderate to severe liver disease (Child's classification B or C3).

Consent

Informed Consent will be obtained by the chief investigator or co-investigators. If patients are deemed unable to consent for themselves a legally authorised representative will be

asked to give permission to enroll the patient into the study. For the first blood draw, as part of the trauma team resuscitation, this will be the Trauma Team Leader who is independent from the research protocol.

This research study focuses on the very early post-injury phase (time of injury and first few hours), and is investigating the long-term effects of injury and physiological derangements seen at this time. The majority of severely injured trauma patients are either unconscious from a traumatic brain injury or hypovolaemic shock, intubated in the prehospital phase of their care or intubated acutely in the emergency department. These patients are the core of the research study as it is patients with severe injury who will go on to develop multiple organ failure. Patients who are not unconscious have recently been through a major psychologically disturbing event, may have been a victim of violence, and are often in pain. As such they may be unable to comprehend, or it may be inappropriate to discuss, the details of a complex research trial at this time.

All trauma patients routinely have bloods drawn in the resuscitation room as part of their standard evaluation, and this study will induce no extra stress or morbidity except for the extra volume of blood drawn at this time. The patient population is unlikely to have complications related to the extra volume of blood drawn. The 20ml blood draw (equivalent to four teaspoons), is minimal compared to the total blood volume (~5 litres). Additionally, intravenous fluid and blood transfusion is commenced as soon as patients arrive in the emergency department. Blood sampling will not delay this, or any other therapy.

Where patients are awake and have relatively minor injuries, such that they would be able to comprehend the research protocol and its implications, we would consent them as soon as possible in the emergency department. However, as we are able to use blood from the initial draw for trauma management, we are still requesting a professional legally appointed representative consent to take this sample. Consenting a patient in the initial phases of trauma evaluation would be difficult and would seriously compromise patient care.

If a patient remains unidentified, the police and hospital social workers will continue to assist the investigator in identification of the patient. Daily attempts to locate family to discuss the patient's condition and study involvement will be made. Documentation of these attempts will be made in the patient's medical record.

When a personal legally authorised patient representative is found, all study procedures already performed and yet to be completed will be explained, and their consent for continued participation requested. They will also be informed that they have the right to deny continued participation. For patients who are sedated and ventilated, the legally authorised representative will also be asked to give written consent for bronchoscopy and bronchial lavage samples.

The patient will be examined regularly to determine if and when he/she is able to consent for himself/herself even if surrogate consent has already been obtained. While the duration of unconsciousness for trauma patients is very variable, the majority will regain consciousness in 2-10 days. At this time, the trial and all study procedures - performed and yet to be completed - will be explained to the patient. Again, patients will be given the option to give consent to continue participation or to withdraw from the study.

A quarterly report will be sent to the LREC regarding the Consent Process. It will include the number of subjects entered in the study, the number of subjects for who consent was obtained prior to entry, the number of subjects for whom consent was waived, the number of subjects or surrogates who later refused or agreed to continue in the study, and ongoing study results available.

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Appendix 4 Aim 3 (identification) and aim 4 (treatment): exemplar information sheet

[redacted]

Patient information sheet

DIRECTORATE OF SURGERY AND ANAESTHESIA

ROYAL LONDON HOSPITAL, WHITECHAPEL, LONDON E1 1BB

Information Sheet A – Subject

Version 1.3, 20.09.2007

East London and the City Research Ethics Committee 1

REC number: 07/Q0603/29

Title: Activation of Coagulation & Inflammation in Trauma II

Principal Investigator: Mr. Karim Brohi, FRCS FRCA

Date: ___/___/_____

Subject Name: _____. NHS Ref: _____ Study Ref: _____

Introduction

You are being invited to take part in a research study. This research will help us to improve the care of patients who suffer severe injuries in the future. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Why is this research being carried out?

Trauma (serious injury) is the leading cause of death and disability in children and young adults worldwide. Over half of all trauma deaths are due to bleeding or the complications resulting from it. Injury, shock and blood loss all contribute to a failure of the body's normal blood clotting mechanisms (coagulation), which then leads to more bleeding. The mechanisms of these disorders in blood clotting and how they affect the body are not well understood, and we hope that this research will help us to determine why, when and how the blood clotting mechanisms fail, and what the consequences of this are.

Why have I been chosen?

On ___ - ___ - _____ (date), you were injured and admitted to the Royal London Hospital. At the time, you were unable to give informed consent. When you arrived in the emergency department, a full trauma team of doctors and nurses attended to you. The trauma team leader, who is not part of this research study, gave consent as your representative for you to be enrolled in this study. As part of the immediate management blood is taken and sent to the laboratory for analysis. A small amount of extra blood (approximately four teaspoonfuls) was drawn and saved for research purposes. We are now asking for your consent to allow us to use the samples we have collected and to continue to participate in the study, since all the procedures have not yet been completed. Should you not wish to continue your involvement in the trial we may ask for your consent to place the samples already collected in a registered research tissue bank for use in future research.

Do I have to take part?

No, participation is completely voluntary. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to continue with the study the following will happen:

1. We will store and process the samples we have already collected.

2. We will continue to collect blood samples until the third day in hospital. We will draw ___ blood samples in total. ___ (number) of these have already been obtained. Each blood sample is equivalent to four teaspoonfuls, and the total amount of blood drawn over three days is less than four fluid ounces. Wherever possible we will draw the blood out of a line already in a blood vessel, or coincide the blood draw with tests required for your care, in order to minimise any discomfort from the procedure.

3. While you were unconscious, we used a small catheter to collect bronchial washing samples from your lungs. Bronchial washing and aspiration is a safe procedure that is performed on the intensive care unit by trained personnel. During the procedure a small, flexible tube is passed down the breathing tube into the windpipe and air passages. A small volume of fluid is then passed down the tube into the lung, and then sucked back and collected in a specimen jar. Now that you are awake, no further bronchoscopies will be performed.

What do I have to do?

If you agree to continue with the study the following will happen:

We will collect ___ (number) of further blood samples from you, on _____

(date/times)

What are the possible disadvantages and risks of taking part in the study?

There are no long-term risks to you from participating in this study. The specific risks associated with each sample are as follows:

1. Blood samples
   The risks of drawing blood include temporary discomfort from the needle stick and bruising.

2. Bronchial lavage & aspiration
   The risks of obtaining bronchial washings in patients with a breathing tube in place are rare, and are limited to episodes of low oxygen in the blood (hypoxemia). To minimise this risk we will administer extra oxygen during the procedure and continuously monitor the level of oxygen in the blood. Again, now that you are awake, no further aspirates will be performed.

What are the possible benefits of taking part in the study?

There will be no direct benefit to you from participating in this study, but we hope that the information we get will help to improve the care of trauma patients in the future.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

This Completes Part I.

If the information in Part 1 has satisfied you and you are considering continuing in the study, please read the additional information in Part 2 before making any decision.

PART 2

What will happen if I don't want to carry on with the study?

If you decide, at any time, to withdraw from the study all study procedures will be stopped immediately. Any information and samples that have already been collected will be processed as part of the study unless you wish to have your samples withdrawn from the study, in which case we will destroy them. Your decision will in no way result in a change in the type or quality of care you subsequently receive. Should you not wish to remain in the trial we may ask for your consent to place the samples already collected in a registered research tissue bank for use in future research.

What if I am not happy about the study?

We will only make very minor changes to the way we look after you. It is extremely unlikely that this small change to normal practice would cause any problems. However, if you are harmed by taking part in this study, there is no special compensation arrangement. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. Please contact Patient Advisory Liaison Service (PALS) if you have any concerns regarding the care you have received, or as an initial point of contact if you have a complaint. Please telephone 020 7377 6335, minicom 020 7943 1350, or email pals@bartsandthelondon.nhs.uk, you can also visit PALS at any hospital.

Will my taking part in the study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential and will be stored securely in coded form. Data collected may be sent outside of the Trust for statistical analysis but uncoded identifiable personal patient information will not leave the local research group. If you consent to take part in the research the people conducting the study will abide by the Data Protection Act 1998, and the rights you have under this Act. Only authorised personnel such as researchers and research auditors will have access to the data. We will store your information for 15 years and your samples until the end

of this research project. Any subsequent use of the samples will have to be performed with approval from a research ethics committee, otherwise the samples will be destroyed.

What will happen to the samples that I give?

These samples will be used for more than one study, but one of these is a study aimed at identifying genetic differences in patients that makes them more or less susceptible to the effects of traumatic injury. We hope that this will allow us to identify new areas of investigation and potentially allow future trauma care to be specifically tailored to the characteristics of each individual patient. Your samples will be stored in a secure facility that can only be accessed by authorised researchers. Some samples may be sent outside of the Trust (and the UK) for processing by other research laboratories. Your samples will be identifiable only in a coded format separate from your personal information. Any further use of your samples outside of this research study will have to be approved by a research ethics committee.

Will any genetic tests be done?

We will store a sample of your DNA, obtained from the blood sample for future testing. This is performed to see if there are genetic differences between patients that make them more or less susceptible to the effects of injury. We will not be testing for genetic diseases or named inheritable conditions and therefore this test will be of no individual significance to yourself in terms of inherited risk, insurance issues or to your children. The DNA will be stored in a coded form in a special DNA bank, with the same data protection safeguards that apply to your other blood samples. Any future studies outside the scope of this study that would use your DNA will have to be independently authorised by a research ethics committee.

What will happen to the results of the research study?

We hope to publish the results in a scientific journal. It will not be possible to identify any individual who has taken part from this scientific report. Copies of the report will be available on request.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by East London Research Ethics Committee 3.

Who can I contact for further information?

1. If you require further information about the study, please contact the ACIT Study offices via the Trauma Surgery secretary at [redacted] or email: [redacted]
2. If you require impartial, local advice, please contact the Patient Advice and Liaison Service, telephone: [redacted] or e-mail: [redacted]

Thank you for taking the time to read this sheet.

Date: ___/___/_____ Researcher Signature: _____ _____

Appendix 5 Aim 3 (identification) and aim 4 (treatment): exemplar consent form

[redacted]

EXEMPLAR CONSENT FORM

Consent form

DIRECTORATE OF SURGERY AND ANAESTHESIA

ROYAL LONDON HOSPITAL, WHITECHAPEL, LONDON E1 1BB

Consent Form A – Subject

Version 1.3, 20.09.2007

East London and the City Research Ethics Committee 1

REC number: 07/Q0603/29

Title: Activation of Coagulation & Inflammation in Trauma

Principal Investigator: Mr. Karim Brohi, FRCS FRCA

Please initial box to indicate agreement

1. I confirm that I have read and understood the information sheet dated 20.09.2007 (version 1.3) for the above study and have had the opportunity to ask questions. I have been given a copy of the patient's information sheet to keep. [ ]

2. I understand that my participation in this study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

3. I understand that sections of any of my medical notes may be looked at by professional individuals involved in this study or by regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that my personal data will be processed and stored securely in compliance with the 1998 Data Protection Act. [ ]

4. I agree to take part in the above study. [ ]

Name of patient	Date	Signature

I have explained this in terms which, in my judgement, are suited to the understanding of the patient.

Name of person taking consent (if different from Investigator)	Date	Signature

Investigator	Date	Signature

Appendix 6 Patient and public involvement

Patients and the public were not involved in the initial development of the programme as this was early in the development of the trauma centre as well as our research programme and PPI in general. Over the course of the programme, however, we formed a group consisting of ex-patients who were active in reviewing all aspects of the studies, including ethics and consent issues, study recruitment, preliminary results and final outcomes. This group has continued and grown and also includes relatives and members of the public. Out of this has grown a patient experience and support website, AfterTrauma.org [see www.aftertrauma.org (accessed 14 August 2017)], which we continue to develop and have expanded to national scope. From a research perspective, members of the group, and others, have been important in reflecting on the outputs of our study and highlighting priorities for future studies.

A number of outputs and engagement events have been directed at patients and the public during the course of the programme grant and are ongoing.

Media

Cohen D. *Code Red – Repairing Blood in the Emergency Room*. *New Scientist*, 19 October 2011. URL: www.newscientist.com/article/mg21228352–900-code-red-repairing-blood-in-the-emergency-room/ (accessed 9 September 2015).

BBC World Service and BBC Radio 4. *Frontline Medicine: Survival*. 2012. URL: www.bbc.co.uk/programmes/b017Ld83 (accessed 28 August 2017).

BBC Television. *Trauma Medicine: the Fight for Life*. 2014. URL: www.bbc.co.uk/programmes/b04svfs5 (accessed 28 August 2017).

Science and medicine education

Royal Society Summer Science Exhibition, London, 2011.

Moscow Science Fair, Moscow, 2011.

Big Bang Fair, Birmingham, 2012 (Wellcome Trust People Award WT098159A1A).

Centre of the Cell: Trauma Surgery: Science of the Bleeding Obvious, 2011–2014. Shortlisted for a *Times Higher Education* Widening Participation Award, 2012.

Appendix 7 Research training

PhDs completed

Ross Davenport. *Acute Traumatic Coagulopathy: Functional Characterisation of the Protein C Pathway and Haemostatic Response to Transfusion*. PhD Thesis. Glasgow: University of Glasgow; 2011.

Nicola Curry. *The Coagulopathy of Trauma Related Major Haemorrhage*. PhD Thesis. London: Queen Mary University of London; 2014.

Sirat Khan. *Blood Component Therapy in Trauma Haemorrhage*. PhD Thesis. Glasgow: University of Glasgow; 2015.

Simon Glasgow. *Modelling Red Blood Cell Provision in Mass Casualty Events*. PhD Thesis. Glasgow: University of Glasgow; 2015.

Appendix 8 Affiliated and follow-on grant income

Academic Department of Military Surgery and Trauma (2010) – Bayesian modelling of ATC (£63,209).

Royal College of Surgeons of England (2010) – RCS Fellowship for PhD student (£51,183).

Unrestricted Grant, Octapharma Ltd (2010) – Optimising procoagulant therapy and response (£72,280).

Central and East London Comprehensive Local Research Network (2011) – Research capacity (£95,017).

Barts and The London Charity (2012) – Saving lives in bleeding trauma patients (£104,075).

Central and East London Comprehensive Local Research Network (2012) – Research capacity (£41,809).

Engineering and Physical Sciences Research Council (2012) – Doctoral Training Award (£71,000).

Fulbright Commission (2012) – UK–US Scholarship for early career clinical scientist (£50,000).

Royal College of Surgeons of England Fellowship (2012) – RCS Fellowship for PhD student (£49,984).

European Union FP7 Award (2013) – TACTIC – Targeted Action for Trauma-Induced Coagulopathy (€5,880,192).

Haemonetics, Inc. (2013) – TEG in trauma haemorrhage ($1,000,000).

NHS Blood and Transplant (2013) – CRYOSTAT (£34,846).

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HTA
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