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**I****mproving trauma care   
for critically bleeding patients:**

**A history, evidence summary and   
proposed quality improvement approach**

September 2020

# Contents

[List of abbreviations 3](#_Toc51149332)

[Background 4](#_Toc51149333)

[Introduction 4](#_Toc51149334)

[The current state of critical haemorrhage in New Zealand 6](#_Toc51149335)

[Reducing preventable deaths 7](#_Toc51149336)

[The current response to trauma-related critical haemorrhage in New Zealand 9](#_Toc51149337)

[A national audit of massive transfusion protocol usage by the New Zealand Blood Service 11](#_Toc51149338)

[Coagulopathy in major trauma and its treatment 12](#_Toc51149339)

[Ensuring appropriate use of tranexamic acid 14](#_Toc51149340)

[Promoting increased use of goal-directed therapy 15](#_Toc51149341)

[Limiting the use of crystalloid to elevate blood pressure in trauma patients 16](#_Toc51149342)

[Why a new trauma-focused critical bleeding bundle of care for New Zealand? 17](#_Toc51149343)

[Process improvement to reduce time from injury to haemorrhage control 20](#_Toc51149344)

[What will a national critical bleeding bundle of care for New Zealand look like? 21](#_Toc51149345)

[Education and monitoring to accompany and support process change 22](#_Toc51149346)

[Quality improvement informed by data analysis/intelligence 22](#_Toc51149347)

[The critical haemorrhage project 23](#_Toc51149348)

[How to get involved 24](#_Toc51149349)

[Appendix A: Core expert reference group 25](#_Toc51149350)

[Appendix B: Wider expert reference group 26](#_Toc51149351)

[Appendix C: Theory of change diagram 27](#_Toc51149352)

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# List of abbreviations

|  |  |
| --- | --- |
| ACC | Accident Compensation Corporation |
| ADHB | Auckland District Health Board |
| ANZ-MTR | Australian and New Zealand Massive Transfusion Registry |
| BP | blood pressure |
| CAT | Critical Administration Threshold |
| CC | Code Crimson |
| CI | confidence interval |
| CRASH-2 | Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 |
| DHB | district health board |
| ED | emergency department |
| ERG | expert reference group |
| FFP | fresh frozen plasma |
| ICU | intensive care unit |
| INR | international normalised ratio |
| MATTERs | Military Application of Tranexamic Acid in Trauma Emergency Resuscitation |
| MOF | multiple organ failure |
| MTP | massive transfusion protocol |
| NNT | number needed to treat |
| NZBS | New Zealand Blood Service |
| NZTR | New Zealand Trauma Registry |
| PROMMTT | Prospective, Observational, Multicenter, Major Trauma Transfusion |
| PROPPR | Pragmatic, Randomized Optimal Platelet and Plasma Ratios |
| RBCs | red blood cells |
| ROTEM® | rotational thromboelastometry |
| RR | relative risk |
| TEG® | thromboelastography |
| THOR | Trauma Hemostasis and Oxygenation Research |
| TXA | tranexamic acid |
| VEM | viscoelastic monitoring |

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# Background

The national improving trauma care for critically bleeding patients project(also known as the critical haemorrhage project) is a partnership between the National Trauma Network (the Network), the Accident Compensation Corporation (ACC), the Health Quality & Safety Commission (the Commission), the New Zealand Blood Service (NZBS), the Australian and New Zealand Massive Transfusion Registry (ANZ-MTR), ambulance services and district health boards (DHBs; specifically, emergency departments, perioperative teams and intensive care units).

The Network is guided by an overarching governance group, the membership of which includes the Ministry of Health, Waka Kotahi NZ Transport Agency, DHBs, ACC and the Commission.

This document is an early output from the critical haemorrhage project. It provides a narrative describing the history of managing critical haemorrhage in New Zealand, an evidence summary that justifies the proposed next steps, and a description of the intended critical haemorrhage project approach.

Its development has been informed by two expert reference groups (ERGs) (refer Appendices A and B).

# Introduction

The critical haemorrhage project commenced in January 2020. It seeks to reduce mortality and complications in critically haemorrhaging trauma patients by working in partnership with the sector and experts to:

1. support the ambulance sector and hospitals to review and update existing massive transfusion protocols (MTPs) to meet current best practice trauma care
2. develop a national best practice critical bleeding bundle of care for ambulance and hospitals to adjust to their local context and implement
3. develop associated national critical bleeding best practice guidance.

These will support New Zealand health care providers with early recognition and appropriate action for trauma-related critical haemorrhage across ambulance services, emergency departments (EDs), perioperative teams, and intensive care units (ICUs). While other types of critical haemorrhage (eg, obstetric haemorrhage, large blood loss surgery, transplants and gastro-intestinal haemorrhage) are out of scope, general hospital haemorrhage patients will benefit from improved guidance and practice.

The critical haemorrhage project’s aspirational goal is to achieve zero in-hospital deaths from trauma-related critical haemorrhage, and the overall project aim is to eliminate avoidable deaths from trauma-related critical haemorrhage and related multiple organ failure (MOF) by 2025.

Understanding the history, current state and evidence is an important part of quality improvement. This document seeks to describe the history of managing critical haemorrhage in New Zealand and provide the evidence base for the project’s approach. More about the proposed project approach is provided at its conclusion.

Major reduction in mortality and morbidity from critical haemorrhage has been achieved both internationally and nationally in the last decade by:

1. ensuring rapid identification and appropriate treatment of the subset of trauma patients who will die or develop body organ system failure due to haemorrhage
2. developing a targeted approach to managing these patients, primarily by delivering life-saving first-aid interventions such as tourniquets, restricting fluids that do not improve outcome (eg, crystalloids) and providing ‘just in time’ blood products that maintain substrates for oxygenation and coagulation processes
3. proactive treatment with a focus on avoiding any delays to surgery or interventional radiology to address the cause of blood loss and deliver key therapies.

In New Zealand, local and regional critical haemorrhage management improvement work has been ongoing for some time. In this context, areas that offer an immediate opportunity for process, system and patient outcome improvement have been identified. They are:

* ensuring early recognition and control of bleeding (including pre-hospital recognition and control and advance warning to receiving hospital)
* improving the supply of products to treat blood loss, including improving access to and use of these pre-hospital and during early patient arrival in the ED
* ensuring more appropriate (ie, better targeted) use of blood products, which would result in improved outcomes for critical haemorrhage patients AND a reduction in the total use of blood products (which would in turn reduce pressure on blood donations and health system costs)[[1]](#footnote-1)
* increasing the use of goal-directed therapy using viscoelastic monitoring (VEM)
* reviewing the composition of existing MTPs[[2]](#footnote-2) and exploring how these could be modified and/or better applied to the subset of critical haemorrhage patients for whom the supply of blood products may be insufficient to stop haemorrhage morbidity or mortality
* use of a best practice critical bleeding bundle of care that sets parameters for its activation and, once activated, directs treatment towards the most appropriate treatment for trauma-related critical haemorrhage (eg, the use of tranexamic acid (TXA) and restriction of the use of crystalloid)
* ensuring process and system changes are accompanied by education for those impacted to support them to make the necessary changes
* monitoring to ensure the sustainability of the changes.

# The current state of critical haemorrhage in New Zealand

The New Zealand Trauma Registry (NZTR)[[3]](#footnote-3) has been collecting national data from 1 July 2017 (data prior to 2017 exists but it does not cover the whole country). It collects data about trauma patients hospitalised with severe or life-threatening injuries. The NZTR defines major trauma as an injured patient with an Injury Severity Score[[4]](#footnote-4) greater than 12 (as per Abbreviated Injury Scale 2005 with 2008 updates), or hospital death following trauma principally due to the injuries sustained.[[5]](#footnote-5)

New Zealand’s major trauma caseload for the 2018/19 financial year, as recorded in the NZTR, was 2,355 cases, with 198 deaths (8.4%). Of these, 25 deaths were from haemorrhage (1.1% of caseload; 12.6% of deaths). An additional 16 deaths (0.7% of caseload; 8.0% of deaths) were from MOF, some of which may be the consequence of haemorrhage. (The NZTR does not capture those who die from haemorrhage before they have arrived at hospital.)

In addition, a cohort of patients experienced multiple-organ dysfunction or failure without dying. These latter patients usually require prolonged critical care and consume substantial resources.[[6]](#footnote-6) Data from the NZTR shows that more than a third of major trauma patients require an ICU stay (37%), with an average ICU length of stay of 6.3 days. This equates to approximately 860 major trauma patients requiring 5,380 ICU bed-days annually. Ventilation is required for 57% of major trauma patients with an ICU stay. In such patients the average length of ICU stay is 8.6 days, with ventilation on average for 6.5 days.

Patients who die from haemorrhage typically die within the first few hours of arrival at hospital. Of all in-hospital haemorrhage deaths, 37% occurred within the first hour of arrival at hospital, and more than half occurred within 4 hours. However, a small proportion of deaths attributed to haemorrhage (17%) occurred after 24 hours from arrival at hospital (all of whom died at their first receiving hospital).

Patients who died from MOF tended to survive in hospital for longer periods of time. Nevertheless, times were variable: 27% of deaths attributed to MOF occurred within 24 hours of hospitalisation, 38% occurred between 1 and 7 days, and the remaining 34% of MOF deaths occurred in patients with hospital stays longer than a week. Of these patients who died from MOF, 28% had ICU stays shorter than 2 days, 20% had ICU stays between 2 and 7 days, and 21% had ICU stays longer than a week.

Patients in the NZTR retrospectively assessed as being at risk of haemorrhagic death by physiological and anatomical injury markers also tended to have longer length of stay than other patients, even after taking injury severity into account using the Injury Severity Score.

The majority of haemorrhagic deaths in New Zealand result from blunt rather than penetrating trauma. However, a much larger proportion of penetrating trauma deaths are the result of haemorrhage than is the case for blunt trauma (Table 1).

Table 1: Blunt versus penetrating trauma

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Blunt trauma** | | | **Penetrating trauma** | | |
| Deaths | Haemorrhage | MOF | Deaths | Haemorrhage | MOF |
| 735 | 77 (10%) | 58 (8%) | 36 | 16 (44%) | 4 (11%) |

MOF = multiple organ failure.

# Reducing preventable deaths

As trauma is the leading cause of death in persons younger than 40 years in New Zealand,[[7]](#footnote-7) reducing preventable deaths over the next five years is the primary aim of the critical haemorrhage project. Most survivable trauma haemorrhage deaths are now seen as avoidable through the development of sophisticated identification and treatment processes from the point of injury to surgical treatment. Haemorrhage causes 60% of trauma deaths that occur within the first six hours after injury.[[8]](#footnote-8)

Haemorrhage remains the most improvable cause of death. In the early 1970s, Trunkey and Lim demonstrated with autopsy findings that 35.2% of deaths in the first six hours from admission were due to haemorrhage, and they make up the majority of deaths in the first hour (see Figure 1 below).[[9]](#footnote-9) Their review showed 50% of deaths in the first few hours were preventable. Specifically looking at survivable injuries, 91% were related to haemorrhage, split between injuries involving the torso (67%), junctional (8%), and the extremities (14%).

Figure 1: Trimodal distribution of trauma deaths in the first six hours from admission[[10]](#footnote-10)

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From the NZTR, patients at high risk of death were identified using the criteria of either having both a systolic blood pressure of ≤ 90 mmHg and a pulse rate of ≥ 120 beats per minute or having a base deficit of −6 mmol/L or more negative. These criteria identified 583 blunt and penetrating trauma patients (between July 2015 and March 2019), of whom 153 (26%) died in hospital. One third of these deaths were attributed to either haemorrhage or MOF (20% and 13% of deaths respectively).

A 2019 review at Auckland City Hospital showed that death from haemorrhage had reduced from 11% of trauma deaths in 2018 to 6% in 2019.[[11]](#footnote-11) It is that residual group that requires a new and more targeted approach to treatment.

# The current response to trauma-related critical haemorrhage in New Zealand

Over the last 12 years, New Zealand hospitals have been developing focused responses to critical haemorrhage both related to trauma and to other areas (such as obstetric haemorrhage, large blood loss surgery, transplants and gastro-intestinal haemorrhage).

In the subgroup of trauma, this focus has led to limiting crystalloid use to treat hypovolaemia, coupled with best practice methods for delivering blood products, often referred to as massive transfusion protocols or MTPs.

At Auckland City Hospital in 2008 this led to the creation of the Auckland DHB (ADHB) MTP (see Figure 2), which was agreed by the hospital Blood Transfusion Committee and the NZBS. Its purpose, to ensure the delivery of a prescribed volume of red blood cells (RBCs), fresh frozen plasma (FFP) and platelets to keep haemoglobin, fibrinogen and platelet counts above agreed thresholds during massive haemorrhage.

A 2011 audit of effectiveness of the ADHB MTP in 83 bleeding patients (of which 45% had trauma) showed good maintenance of international normalised ratio (INR) (< 1.3), platelet count (> 75,000) and fibrinogen (> 1.5 g/L), despite a raised lactate (> 4 mmol/L) and median use of four MTP boxes (see Figure 2 below).

Figure 2: ADHB Adult Massive Transfusion Protocol (MTP)

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Importantly, the ADHB MTP’s functionality, as measured by blood product box delivery times, was confirmed, with the delivery time longest for the second blood box (mean 27 minutes) and later box delays reduced to 5 minutes. This audit result was considered justification for extending use of the MTP to general hospital haemorrhaging patients.

In 2010, Capital & Coast and Canterbury DHBs adopted the same MTP, and Waikato, MidCentral, Counties Manukau, Waitematā and Southern had followed by 2014. These DHBs use approximately 84% of New Zealand’s blood products. Smaller DHBs adapted the MTP to allow for reduced availability of blood products locally (most often platelets).

# A national audit of massive transfusion protocol usage by the New Zealand Blood Service

A national audit of MTP usage was led by Dr Richard Charlewood from the NZBS in 2015/16.[[12]](#footnote-12) This audit included 353 MTP activations, the majority being initiated in operating theatres (48%) or EDs (33%). Trauma patients accounted for 26% of the activations, making trauma the single largest indication for MTP activation. The majority (82%) of activations were initiated by senior trainees, or consultants.

The audit showed that MTPs successfully achieved an effective fibrinogen 1:1 ratio of FFP and cryoprecipitate to RBCs in most DHBs with some significant variation when returned units were included. The national average ratio of FFP to RBCs was 0.79 (excluding a significant volume of cryoprecipitate given, which would support fibrinogen levels in these patients).

The audit showed use of whole blood in MTPs was limited to Auckland, Canterbury and Capital & Coast DHBs, and totalled 128 units over the audit (2,046 units of RBCs were transfused, so whole blood made up 6% of RBCs given within the MTP).

The duration of MTP activation ranged from 0 to 12.25 hours (median 59 minutes), with 80% terminated within 2 hours.

Box delivery median times were 28 minutes, and blood sample intervals were 28 minutes. These times are in line with the ideal parameters set in the MTP and indicate good system functioning.

Blood results indicated haemoglobin was adequately maintained throughout the haemorrhage (96 g/L), and only 4% of patients achieved a nadir platelet count < 50,000 × 106.

Importantly, fibrinogen was maintained above 1 g/L in 93% of cases, with a median concentration of 1.8 g/L.

While the general functionality of MTPs in New Zealand was confirmed, the audit did note the following areas for improvement relevant to the critically bleeding trauma patient.

* A record of TXA administration could only be found in 46% of cases. Despite being highlighted in the protocol, many critical haemorrhage patients may not be receiving this drug, and this is something that the critical haemorrhage project will attempt to address.
* Despite a relatively fixed delivery of blood products in MTPs here in New Zealand, there was still a large amount of variability in the ratio of blood products delivered (from 0.66 to 1.03 FFP/RBCs). However, most cases fitted the 1:2 or 1:1 ratio range the proponents of fixed ratio blood products recommend in trauma.
* Wastage was variable in different DHBs, mainly related to the ability of DHBs to reuse thawed blood products.
* Despite the availability of VEM, such as thromboelastography (TEG®), in New Zealand hospitals, its use in guiding transfusion could only be documented in 26% of MTP activations. This result may mean that VEM is currently mainly used in operating theatres. Its wider use could have significant positive implications for critical haemorrhage patients’ outcomes, and this is something that the critical haemorrhage project will attempt to address.

# Coagulopathy in major trauma and its treatment

Critically haemorrhaging patients have a 20% mortality, which increases to 40–50% if they also have a coagulopathy, meaning they are eight times more likely to die in the next 24 hours with a coagulopathy than not.[[13]](#footnote-13) Understanding why critically bleeding trauma patients continue to bleed despite intervention has troubled clinicians for decades, with the physiological response to shock (the associated coagulopathy) considered the most likely reason.

Results from the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR)[[14]](#footnote-14) and Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT)[[15]](#footnote-15) studies suggest that rapid resuscitation with fibrinogen-rich blood products may reduce bleeding and improve short-term survival, but not reduce overall in-hospital mortality.

The development of a coagulopathy has been recognised since 1918 when Cannon[[16]](#footnote-16) identified the deleterious effect of resuscitation of patients with clear fluids in battlefield trauma. However, the resulting dilutional coagulopathy does not explain the profound blockade in coagulation in the shock trauma patient.

Evidence currently points to poorly perfused endothelium, stimulated by a hyper-adrenergic sympathetic system exuding thrombomodulin and activated Protein C into the microcirculation.[[17]](#footnote-17),[[18]](#footnote-18) The effect to plasminogen activator inhibitor-1 (PAI-1) promotes fibrinolysis, inhibits ability of factors five (FV) and seven (FVII) to stimulate thrombin, and thus limits clot forming in the microcirculation. While this may preserve the organ if perfusion is re-established, the systemic effects are to induce non-surgical bleeding that increases mortality in the trauma patient. Thus, and in tandem with the above effects, the previously intact glycocalyx is damaged.[[19]](#footnote-19) When large crystalloid resuscitation fluids are used, the protein and heparan matrix within the extra-endothelial layer loses its integrity. Fluid loss through the basement membranes increases, and the effectiveness of the circulation is impaired.

Indicators of increased mortality using coagulation parameters show that they are the result of profound shock. Elevated Protein C levels, Syndactin–C levels (indicating glycocalyx destruction) and elevated adrenaline levels all are associated with abnormalities in coagulation parameters (INR, activated partial thromboplastin time or aPPT), and observed TEG® abnormalities.[[20]](#footnote-20) Similar changes in platelet aggregation also occur. The resulting clinical problems are a patient in shock with bleeding from non-surgical wounds, who continues to bleed after the trauma pathology is fixed. This ongoing bleeding can lead to abdominal compartment syndrome, MOF and death.

Empiric responses to this profound shock and coagulopathy are:

1. rapid recognition of patients at risk with immediate first aid measures (for example, tourniquets and pelvic binders)
2. early call to receiving facility with incoming critical haemorrhage, which would trigger a specific system response
3. rapid transport to a definitive site of bleeding control (operating theatre or interventional radiology), and in doing so keeping the patient warm
4. damage control surgery, which involves rapid surgery limited to stopping bleeding
5. damage control resuscitation, which involves limiting crystalloid
6. empiric use of TXA at a dose of 15 mg/kg bolus plus an infusion over 8 hours
7. blood given in either a 1:1:1 fixed ratio of FFP, RBCs and platelets, or targeted to TEG® or rotational thromboelastometry (ROTEM®)
8. (sometimes) permissive hypotension
9. patients with persistent acidosis and hypothermia are managed in the ICU until stabilised before definitive trauma surgery.

Together these actions and treatments, when considered alongside the findings of the 2015/16 NZBS audit of MTP usage and international and national literature, provide the basis for a bundle of care that has the potential to reduce mortality from massive haemorrhage in trauma substantially.[[21]](#footnote-21)

Developing and introducing a best practice critical bleeding bundle of care for New Zealand health care providers to adjust to their local context is a key output for the critical haemorrhage project. The subsequent sections discuss points for inclusion and their associated evidence. Early thinking about the proposed makeup of the bundle for use in New Zealand is provided below in section 13.

# Ensuring appropriate use of tranexamic acid

Hyperfibrinolysis describes a situation with markedly enhanced fibrinolytic activity, resulting in increased, sometimes catastrophic bleeding. It occurs in 80% of trauma haemorrhage.[[22]](#footnote-22)

Multiple studies have shown TXA to be effective and safe in reducing blood loss in elective surgery, with a low incidence of venous or arterial thrombosis.

The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) study demonstrated the importance of early modulation of the fibrinolytic pathway in trauma. [[23]](#footnote-23) This study of just over 20,000 patients showed that the administration of TXA (1 g bolus, followed by 1 g infusion over 8 hours) reduced overall mortality (14.5% deaths in TXA group vs 16% in placebo group; relative risk (RR) 0.91, 95% confidence interval (CI) 0.85–0.95; *p* = 0.0035) and reduced risk of death from bleeding (4.9% TXA vs 5.7% placebo; RR 0.85, 95% CI 0.76–0.96; *p* = 0.0077).

Importantly, subsequent analysis of the data showed that the earlier TXA is administered the greater the outcome benefit. The most pronounced effect was in a subgroup of patients with a systolic blood pressure (BP) < 75 mmHg.

Immediate therapy with TXA was associated with improved survival (odds ratio 1.72, 95% CI 1.42–2.10; *p* < 0.0001) and the survival benefit then was shown to decrease by 10% for every 15-minute delay in treatment, up to 3 hours. There was no associated reduction in transfusion, but the spectrum of patients enrolled into the study had only 50% of patients receiving any red blood cell transfusion.

Initiation of TXA greater than 3 hours after injury was associated with an increased risk of death (RR = 1.3, CI 1.12–1.84).

The results of the study were corroborated by the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study in wounded soldiers receiving RBCs.[[24]](#footnote-24) The severity of bleeding and shock was more advanced than in the CRASH-2 trial and achieved a significant survival benefit in patients receiving TXA who also received > 10 units of RBCs (17.4% vs 28.1%, *p* = 0.04, number needed to treat (NNT) = 7).

This degree of bleeding more closely approaches what is/would be the case for the trauma-related critical haemorrhage patient.

The pre-hospital Cal-PAT trial prospectively studied TXA administered pre-hospital and reproduced a survival advantage.[[25]](#footnote-25) However, pharmacological studies do not confirm the dosing in the original CRASH-2 trial; instead they suggest that they may in fact be less than ideal.[[26]](#footnote-26)

Many international protocols vary in initial dose and the presence or omission of an infusion. Most limit initiation of TXA post 3 hours of injury. Alternative indicators of the benefit of TXA administration are not well validated in trauma.

VEM, such as TEG®, often seen as a useful tool to determine preoperative hyperfibrinolysis, was relatively insensitive to indication of changes in patients with trauma enrolled into CRASH-2 and MATTERs. Using TEG® as a marker of fibrinolytic changes in trauma, Moore et al have suggested three different phenotypes exist: hyperfibrinolysis, physiological fibrinolysis and fibrinolytic shutdown.[[27]](#footnote-27)

In some series the percentage of patients with fibrinolytic shutdown was as high as 30%, possibly due to reduced or extinguished generation of tissue plasminogen activator. The RR of mortality in receiving TXA is 1.65. Hence there may be risk in indiscriminate use of TXA in all trauma patients. However, TEG® is not widely available to patients in the first three hours of injury in New Zealand, we do not have a system to determine TXA dosing due to TEG monitoring, even if the data suggesting a contraindication to TXA in patients with fibrinolytic shutdown was proven.[[28]](#footnote-28)

Therefore, there is a need for New Zealand to develop a system that ensures TXA is administered to all haemorrhaging trauma patients (with the parameters for this set at a national level, by way of an evidence-based national critical bleeding bundle of care). Based on the current evidence described above, arguably a national critical bleeding bundle of care would specify that TXA should be given immediately (ideally within 3 hours of injury) on activation of the bundle.

# Promoting increased use of goal-directed therapy

As previously stated, the NZBS 2015/16 audit of MTP usage found that despite the availability of VEM, such as TEG®, in New Zealand hospitals, its use in guiding transfusion could only be documented in 26% of MTP activations. This result may mean that VEM is currently mainly used in operating theatres. Its wider use could have significant positive implications for critical haemorrhage patients’ outcomes, and this is something that the critical haemorrhage project will attempt to address.

There are valid concerns in NZ that the widespread adoption of TEG across the whole hospital would not improve patient outcome. While the most robust evidence comes from the operating room (OR), in cardiothoracic surgery and transplant, the data in trauma patients is also OR centric. There are small studies showing the TEG can aid in determining patients that will require a massive transfusion, will die from a haemorrhagic death, and will need specific treatment pathways with anticoagulants or inherited disorders, evidence is lacking that widespread use in EDs is either possible or indicated.[[29]](#footnote-29)

The concept of goal-directed therapy where abnormalities are corrected only in bleeding patients has the advantage of focusing therapy on laboratory abnormalities. The most validated of these is using TEG® or ROTEM®. It further allows treatment with less exposure to allogenic blood products, and less system waste.[[30]](#footnote-30),[[31]](#footnote-31) But it usually needs specialist skills and a dedicated person controlling the resuscitation to individualise treatment options.

Damage control resuscitation focuses on the innate inability of bleeding trauma patients to form a clot. The main aims of damage control resuscitation are to rapidly address life threatening bleeding that may be controlled by first-aid measures, then to pre-emptively deliver substrates of clotting proteins and platelets and then maintain them during ongoing bleeding. This is amplified by the reduction in crystalloid and the addition of drugs (like TXA) that have been shown to have a survival benefit.

Red blood cell transfusion continues in the background, but is no longer used as a major volume expander, and manageable hypovolaemia and hypotension is allowed until damage control surgery acutely reduces surgical bleeding. Different resuscitation goals need to be developed for paediatric patients. Further improvement in outcome has occurred by adding blood transfusion (either resuspended RBCs, whole blood or FFP) pre-hospital, and targeted blood therapy using VEM like TEG® or ROTEM®.

The introduction and adoption of this management of patients has led to a significant reduction in mortality and morbidity in trauma patients. In a longitudinal study in the Royal London Hospital, Cole et al showed a 52% reduction in deaths in the 24 hours after injury, from 33% to 16%.[[32]](#footnote-32)

# Limiting the use of crystalloid to elevate blood pressure in trauma patients

Initiated during the Vietnam and Korean wars, a resuscitative strategy of using high volume crystalloid (3:1 ratio of crystalloid volume/volume of estimated blood loss) became popular as an alternative to monitored exsanguination.

This approach was questioned in the 1994 seminal paper by Bickell et al.[[33]](#footnote-33) Survival to discharge was improved from 62% to 70% (*p* = 0.04) and hospital stay shortened when crystalloid was limited, and hypotension was not treated preoperatively. Of note, however, total crystalloid administration in the operating room was not limited and thus total crystalloid administration was not different in the two groups. As this was before modern balanced blood management, red blood cell and plasma transfusions were minimal. It did, however, question the logic of liberal crystalloid administration to normalise systolic BP, and popularised the concept of permissive hypotension and limiting crystalloid administration. While the independent advantage of permissive hypotension may be limited in human studies,[[34]](#footnote-34) the benefit of limiting crystalloid to maintain a ‘low-normal’ systolic BP has logic, especially when blood alternatives may be available via parameters set in a critical bleeding bundle of care.[[35]](#footnote-35)

Significant concerns remain on allowing a systolic BP < 110 mmHg or mean arterial pressure < 75 mmHg in patients with associated traumatic brain injury.[[36]](#footnote-36)

Based on expert opinion (and as per the NICE guideline[[37]](#footnote-37)), there seems to be agreement that if the dominant threat to life is bleeding as opposed to traumatic brain injury, then a permissive hypotensive strategy should be maintained.

At a point in resuscitation the delivery of volume stops being limited to reduce bleeding and is increased to reduce shock. This has implications to the degree and duration of hypotension. Based on animal studies, the duration where normalisation of BP should be considered is a duration > 60 min.[[38]](#footnote-38) The Trauma Hemostasis and Oxygenation Research (THOR) Network consensus document into management suggests that in this circumstance blood products should be used in preference to crystalloid. This is based primarily on animal model data and recommends a systolic BP aim of 110 mmHg.[[39]](#footnote-39)

It is still unclear if the deleterious effects of crystalloid administration in exsanguination are due to secondary dilution of clotting factors and platelets, injury to the endothelium, or other primary effects. Even volumes as low as 1.5 litres may be deleterious.[[40]](#footnote-40),[[41]](#footnote-41)

Based on the above evidence, crystalloid administration should be limited, and not used when blood products are available until control of bleeding is achieved. The volume of blood product should be limited to achieve a systolic BP > 90 mmHg unless a traumatic brain injury is present.

# Why a new trauma-focused critical bleeding bundle of care for New Zealand?

Currently, there is no single identifier of either massive or critical bleeding in trauma. Historically, massive haemorrhage has been classified as ‘greater than or equal to 10 units of RBCs transfused in 24 hours’.[[42]](#footnote-42) The difficulty with this criterion is that transfusion now includes non-red blood cell components and crystalloid fluids in large volumes, and therefore fixing it on one component does not capture adequately the size of the volume loss.

The other main issue is that of survivor bias, where the massively haemorrhaging patient dies early in the transfusion process, before being delivered this 10-unit red blood cell minimum.[[43]](#footnote-43) Lowering the minimum red blood cell transfusion and varying the duration changes the dynamic of the patient and increases the likelihood of capturing massively haemorrhaging patients. The ANZ-MTR captures all patients in recruiting hospitals with administration of > 5 units of RBCs in six hours.[[44]](#footnote-44) This creates a more appropriate subgroup for critical bleeding but suffers the same issues of survivor bias.

The PROMMTT study[[45]](#footnote-45) used the concept of ‘Resuscitation Intensity’ to overcome these issues. They included crystalloid and different blood components to construct a single unit of resuscitation volume. Mortality increased three-fold when three units of volume were infused over 30 minutes or less. A similar development from Savage et al[[46]](#footnote-46) includes the concept of Critical Administration Threshold (CAT). This criterion is triggered with the delivery of greater than three units of RBCs over one hour. Using CAT was more predictive of mortality than the 10 units/24-hour model. Being a dynamic indicator, it may be present multiple times, or absent in many trauma patients, and the number of CAT episodes also predicts mortality. The ideal critical haemorrhage definition of blood volume transfusions needs to include both features.

Internationally, many single-centre trauma hospitals or national quality improvement programmes have looked at creating haemorrhage protocols and bleeding bundles of care to reduce the incidence of preventable haemorrhagic deaths. Internationally, in similar fashion to New Zealand, the period of 2009–12 resulted in the introduction of a plasma-based MTP, consideration of TXA, and trials with haemostatic agents such as recombinant activated coagulation factor VII (rFVIIa).

Moran et al[[47]](#footnote-47) reported the results of changes in the UK with the introduction of their national trauma system, comparing outcomes over the period 2008 to 2017. Trauma care reorganisation was associated with a 19% increase in the odds of survival in 167 enrolling hospitals. Over the investigated period the administration of TXA within 3 to 6 hours of injury increased from near zero to 90% (*p* = 0.0001), and MTPs became universally available.

A ‘before and after’ introduction of a bleeding control bundle of care study[[48]](#footnote-48) analysed the effect of a bundle that included pelvic binders, haemostatic dressings, extremity tourniquets, resuscitative endovascular balloon occlusion of the aorta, minimising crystalloid infusions, coagulation monitoring by TEG®, use of TXA selectively, and pre-hospital/early in-hospital whole blood or TEG® guided transfusion (see Figure 3 below).

Figure 3: Reduction in trauma haemorrhage deaths with the introduction of a critical bleeding bundle of care (Cause of death in 2005‒06 before and then 2012‒13 after bundle introduction)



\* Significant decrease in haemorrhage-related deaths and unknown (p < 0.01). The cumulative percentage is greater than 100% due to patients with multiple contributing causes of death.   
MOF = multiple-organ failure, PE = pulmonary embolism, UNK = unknown.

A significant reduction in haemorrhage-related mortality (from 35.9% to 24.9%; *p* = 0.01) was found. This confirmed the change from the original trimodal presentation of deaths shown by Trunkey and Lim[[49]](#footnote-49) to a unimodal distribution, with 26% of deaths occurring in the first hour of hospital arrival. Eighty-one percent of the deaths occurred in the first hour of arrival, indicating the benefit of a bleeding bundle of care. This study indicates process improvement bundle introduction can reduce trauma mortality in the early admission period by better applying interventions, while traumatic brain injury remains stubbornly high as a cause of death.

In a 10-year review of the introduction of a ‘Damage Control Resuscitation Bundle’ at the Royal London Hospital,[[50]](#footnote-50) deaths from severe bleeding (Code Red) fell from 47% to 27%. This was associated with a 20% increase in discharge to home, as opposed to another care facility. Bundle components included restriction of crystalloid, use of pre-hospital blood, and revised MTPs with 1:1:1 components or ROTEM® guided transfusion. TXA was given to 98% of patients. Paradoxically, due to faster and more effective bleeding control, massive haemorrhage (defined as > 10 units of RBCs over 24 hours) reduced from 68% to 24% (*p* = 001). The median red blood cell use reduced from 12 units to 4 units. Net blood product costs dropped substantially over the period of improvement.

In some areas, introducing a critical bleeding bundle of care has reduced haemorrhagic mortality more substantially. The introduction of an agreed package of care in the Netherlands[[51]](#footnote-51) was associated with a reduction in mortality from 9% to 3% covering the period of 2007 to 2016 (*p*< 0.001). Lower absolute mortality rates may be determined by limiting analysis to in-hospital deaths but offers the prospect that significant reduction in mortality to near zero is possible by the introduction of a comprehensive critical bleeding bundle of care.

# Process improvement to reduce time from injury to haemorrhage control

The modern trauma pathway includes a process of key identified decision and treatment points that are satisfied to reduce missed diagnoses and risks. In the haemorrhaging patient these key points need to be maintained, with an imperative that movement to a definitive place of haemorrhage control (the operating theatre or interventional radiology suite) should not be delayed. Any delay in these key decision and treatment points can arguably lead to preventable death.

The key pathway points that need to be identified in the critical bleeding bundle of care include:

1. identification of significant injury at scene
2. identification of significant haemorrhage associated with the injury
3. limiting scene time and expediting transfer to a trauma centre
4. inadequate response to volume replacement and local haemorrhage management
5. ongoing shock on ED arrival
6. identified source of bleeding that needs surgery or interventional radiology
7. rapid transfer of patient from scene to operating theatre or interventional radiology within a system that diagnoses key metrics of the trauma but does not delay movement to definitive care.

A key part of 1 and 2 above is accurate ‘tasking and dispatch’, which refers to, where possible/ available, ensuring that the response to the critically bleeding patient involves early dispatch of the most appropriate ambulance service (either land or air), which means one that carries the tools and expertise to deal with a critically haemorrhaging patient.

A specific process for the haemorrhaging patient has been set up in many trauma hospitals, separate to the usual tiered trauma team activation systems. These are commonly called Code Crimson, Code Red, or Red Blanket. These processes include a specific resuscitation plan, including activation of an MTP before the patient arrives in ED, mobilisation of key personnel, notification of impending arrival to the operating theatre or interventional radiology, and agreement of criteria for passage through the system.

Evolving evidence suggests such a system reduces delay and improves outcome in haemorrhaging trauma patients. Tovmassian et al[[52]](#footnote-52) reviewed a Code Crimson (CC) system in New South Wales, Australia. They found that in adults (age > 15 years) over the period 2010 to 2015, 89 of 220 patients had a CC activated, 92% of which fitted the activation criteria of an Assessment of Blood Consumption score > 2, with a median Injury Severity Score of 27 and a mortality of 16%, in comparison to the non-haemorrhagic cohort where the mortality was 11%. Time to operating theatre was reduced from 95 minutes to 25 minutes. There was a very significant difference in blood product use, with CC patients receiving a mean 17.8 units of blood product vs 2.2 in the non-CC group.

The literature[[53]](#footnote-53),[[54]](#footnote-54) suggests that delays in movement to definitive care can increase the risk of preventable death between 25% and 40%. The utility of early MTP activation is to prevent a haemorrhagic arrest before surgery, while limiting crystalloid and resuscitating with plasma and platelets. Ideally, systems such as these reduce procedural errors and improve communication but require a more complex activation system and may cause areas of the hospital to reduce productivity in cases of over-triage. There needs therefore to be a belief that the benefits outweigh the costs. Mortality reduction related to the introduction of these systems has not yet been proven and is unlikely to be in isolation of the other treatment advances included in a haemorrhage bundle.

# What will a national critical bleeding bundle of care for New Zealand look like?

Building on the current systems in New Zealand, an improved process recognising key evidence-based additions to treat the more severe bleeding trauma patient can be developed. These additions would lead to a modified, specific treatment bundle for the critically bleeding trauma patient.

Based on the history and evidence described earlier in the document, it is likely that a national critical bleeding bundle of care for New Zealand will explore and/or cover some or all (but not limited to) the following aspects:

1. Understanding the acute trauma systems that are operating in New Zealand to ensure an agreed bundle is complementary to them and not seen as a separate patient care pathway.
2. Developing a pathway of patient movement from injury to haemorrhage control in an operating room or radiology suite that minimises delay. Along this pathway determinants such as triggering, resuscitation, and activation of personnel and theatres are understood and acted on.
3. Determining a nationally agreed trauma triggering score for New Zealand. A core ingredient of an improved national system is agreement on a scoring system to trigger activation of the critical bleeding bundle of care.
4. Confirming and defining the use of TXA. Administration of TXA in patients with severe trauma is the subject of recent and ongoing research. For example, as mentioned previously, the CRASH-2 study demonstrated the importance of early modulation of the fibrinolytic pathway in trauma.[[55]](#footnote-55)
5. The use of whole blood or equivalents into our delivery systems from pre-hospital to early massive haemorrhage management in hospitals. With the move to 1:1:1 resuscitation in trauma, the logic of returning to whole blood resuscitation has reawakened.
6. The availability of fibrinogen concentrate for targeted support of fibrinogen.
7. Limiting the use of crystalloid to elevate blood pressure in trauma patients.
8. Delivery of platelets in remote sites, and the introduction of frozen platelets into clinical practice.
9. An increase in the use of VEM to dictate transfusion.

By necessity, introduction of a nationally agreed critical bleeding bundle of care needs to understand the pre-existing capabilities of existing centres in New Zealand with already functioning systems and align to them without reducing their current effectiveness.

Due to the large variation in trauma volumes in different centres in New Zealand, a bundle will require modification to the resources in those centres and the ability to introduce all the facets of the bundle. Resourcing challenges exist in terms of staff, blood products, and equipment. However, the tenets of 1) identification of the exsanguinating patient, 2) movement to definitive bleeding control with minimal delay, and 3) appropriate resuscitation, will support achievement of a triple aim of reduced harm and improved outcome with minimal additional resources. Overall, a strong focus on these three tenets in the form of a critical bleeding bundle of care can help reduce the preventative mortality associated with haemorrhage in the trauma patient in New Zealand.

# Education and monitoring to accompany and support process change

Developing and agreeing national guidance and an agreed critical bleeding bundle of care is one thing. Seeing it translate into practice change and process improvement is another. A human factor approach to understanding and supporting change enables trauma teams to look at the specific challenges faced within their organisation and locality. This approach has proven to be of real benefit in a series of in-situ simulation-based trauma scenarios, first piloted here in New Zealand in 2018 by Trauma NetworkZ, and now established as part of the NetworkZ programme.[[56]](#footnote-56) This type of educational support will be a key component of success for the implementation of any agreed guidance and bundle.

Introduction of any change to practice requires a level of monitoring that enables an organisation to know that the change is happening and to what extent the change is an improvement over current practice. To that extent, the local application of improvement and implementation science tools and measures will benefit any change projects that result from the development of the national guidance and critical bleeding bundle of care.

# Quality improvement informed by data analysis/intelligence

A key goal of the critical haemorrhage project is to identify high-risk patients for haemorrhage and audit their outcome following application of a nationally agreed care bundle to their treatment. NZTR data will be combined with data from the ANZ-MTR,[[57]](#footnote-57) the NZBS data on transfusion, and the pre-hospital data sets from St John Ambulance and Wellington Free Ambulance services. This expanded data set will be used to determine metrics that identify the key attributes of a critically bleeding trauma patient and their care, which will then inform activity aimed at improving that care.

The other main area of data collection and analysis will be related to adherence to a critical bleeding bundle of care (although this bundle is yet to be agreed, see below), and the variance from key indicators of delivery of blood products and medications to the patient, whilst delivering the patient to a place of definitive surgical or radiological care.

The data collection will be divided into three sections related to the presence or absence of a system approach to the care bundle, the delivery of key therapies to the patient, and the progress of the patient through the care pathway to definitive care.

# The critical haemorrhage project

Overall, the critical haemorrhage project seeks to develop, promote and support the implementation of a nationally agreed best practice guidance, including review and improvement of existing MTPs and the development of a national critical bleeding bundle of care. This suite of tools will support both pre-hospital and hospital early identification and effective management of critical haemorrhage in trauma patients.

The ERG (see Appendix A) confirmed the project plan in June 2020. It includes the rationale and objectives for the project.

The following points summarise the rationale for the project.

* Trauma is the leading cause of death for New Zealanders aged 1 to 39 years.
* In the first 12 hours after injury, blood loss is the leading cause of death, even after reaching hospital.
* International research shows critically bleeding patients treated with a bundle of care that addresses bleeding and coagulopathy are more likely to survive.
* This bundle of care could prevent up to 100 deaths in New Zealand over five years.
* We also expect this bundle of care to reduce complications such as MOF in haemorrhage survivors, reducing hospital stay length, potentially with financial savings in terms of hospital resource use and blood product consumption.

The objectives for this project include building on the work that’s been done in the sector to date to ensure that:

* the national best practice guidance and associated bundle of care covers all crucial aspects of critical haemorrhage management, including but not limited to:
  + early recognition and control of bleeding (including pre-hospital recognition and control and advance warning to receiving hospital)
  + pre-hospital intervention (eg, whole blood where this is possible)
  + rapid transfer (from ED) and intervention
  + appropriate process-level (eg, CC or similar activation), system-level and education elements that must be in place to ensure best practice
* all hospitals implement:
  + the national best practice guidance in a way that fits with their size and context
  + an agreed, nationally consistent best practice MTP, with some variation for hospital size and context
  + a nationally agreed critical bleeding bundle of care that integrates with each hospital’s acute trauma response system
  + system and resource improvements that result in patients getting what they need at the time that they need it, and avoid inappropriate or wasteful use of limited resources
* gaps in education and skills are understood and addressed
* equipment (eg, VEM) and blood products are fit for purpose, with a focus on simplifying and improving access
* hospitals work closely with the NZBS to achieve all the above.

The theory of change diagram in Appendix C outlines the linkages between system outputs and desired outcomes to achieving the project aim of eliminating avoidable deaths from haemorrhage and MOF in trauma patients by 2025. It also indicates a number of workstream activities that the project plans to focus on.

# How to get involved

The Commission and Network project team welcome your input; we need the advice and input of experts and key stakeholders, which is why the project is being informed by a core ERG (Appendix A) in consultation with a wider reference group (Appendix B).

If you would like to contribute, please email [help@majortrauma.nz](mailto:help@majortrauma.nz).

# Appendix A: Core expert reference group

The core expert reference group (ERG) was formed in early 2020 and had its first meeting in March 2020.

Its terms of reference define its purpose as being: ‘a “safe” group that the project team can consult and debate with, in confidence. It will also be an “expert” group and members have been appointed because their knowledge and skills are recognised in the sector (both locally and internationally). Finally, it will be a group that champions the project and its deliverables in the sector, both during their development and during their implementation.’

The Health Quality & Safety Commission and the National Trauma Network would like to thank the core ERG members for their efforts and enthusiasm in guiding the work to improve trauma care for critically bleeding patients. The members include the following:

|  |  |  |
| --- | --- | --- |
| **Name** | **Role** | **Organisation** |
| Andy Swain | Medical director | Wellington Free Ambulance |
| Caroline Gunn | Consumer representative | N/A |
| Chris Jephcott | Anaesthetist | Waikato DHB |
| David Drower | Quality improvement advisor | Health Quality & Safety Commission |
| David Lang | Emergency medicine specialist | Nelson Marlborough DHB |
| David O'Byrne | Emergency medicine specialist | Hutt Valley DHB, Wellington Free Ambulance |
| Dominic Fleischer | Emergency medicine specialist | Canterbury DHB |
| Dr Kerry Gunn (Chair) | Clinical lead, critical haemorrhage project (anaesthetist) | Health Quality & Safety Commission |
| Gabrielle Nicholson | Project manager | Health Quality & Safety Commission |
| Ian Civil | Clinical lead, National Trauma Network (vascular and trauma surgeon) | National Trauma Network |
| Jack Hill | Māori representative (anaesthetist) | Auckland DHB |
| James Moore | Intensivist | Capital & Coast DHB |
| Orla Fowden | Right Care advisor | St John Ambulance Service (South Island) |
| Paul McBride | Data scientist | Health Quality & Safety Commission |
| Renate Donovan | Trauma nurse | Capital & Coast DHB |
| Richard Aickin | Paediatric emergency medicine specialist, Starship Children's Hospital and representative for the New Zealand Resuscitation Council | New Zealand Resuscitation Council |
| Richard Charlewood | Transfusion medicine specialist | New Zealand Blood Service |
| Sandy Ngov | Project coordinator | Health Quality & Safety Commission |
| Susan Mercer | Transfusion nurse specialist (intensive care unit) | New Zealand Blood Service |
| Tony Smith | Medical director | St John Ambulance Service |

# Appendix B: Wider expert reference group

Also crucial to the successful delivery of the critical haemorrhage project is the wider ERG, with which the project team consults via email to ‘sense check’ deliverables and proposals prior to them being publicly communicated.

The Health Quality & Safety Commission and the National Trauma Network would also like to thank the members wider ERG for their support of the core ERG and the project. The wider ERG members include the following:

|  |  |  |
| --- | --- | --- |
| **Name** | **Role** | **Organisation** |
| Andrew Holden | Head of interventional radiology, Auckland City Hospital | Auckland DHB |
| Angus Jennings | Orthopaedic surgeon | Nelson Marlborough DHB |
| Annemarie van der Slot-Verhoeven | Blood bank scientist | Wellington Blood Bank |
| Anthony Buddle | Trauma clinical lead, Southland Hospital | Southern DHB |
| Christopher Harmston | Surgeon | Northland DHB |
| Claire Hitchcock | Trauma coordinator | Nelson Marlborough DHB |
| Dean Bunbury | Anaesthetist/air retrieval | Paediatric anaesthetist at Middlemore Hospital (Counties Manukau DHB) and prehospital retrieval medicine (PHRM) in Auckland |
| Emma Patrick | Anaesthetist | Chair Hospital Blood Transfusion Committee, Taranaki DHB |
| Fiona King | Transfusion nurse specialist | New Zealand Blood Service Wellington |
| Grant Christey | Surgeon | Waikato DHB |
| James La Ferve | Emergency medicine | Auckland Rescue Helicopter Trust |
| James McKay | Trauma surgeon | Canterbury DHB |
| Jim Faed | Transfusion medical specialist/haematology | Southern DHB |
| Kaylene Henderson | Trauma team training | UniServices |
| Krishna Badami | Sponsor ANZ-MTR | New Zealand Blood Service |
| Laura Young | Haematologist | Auckland DHB |
| Mark Friedericksen | Emergency medicine specialist | Auckland DHB |
| Michael Kalkoff | Intensivist | Northland DHB |
| Mike Hunter | Surgeon | Southern DHB |
| Murray Cox | Vascular surgeon | Taranaki DHB |
| Paul Blakemore | Emergency medicine specialist and prehospital physician | Tauranga emergency department and Auckland Rescue Helicopter Trust |
| Sarah Morley | Chief medical officer | New Zealand Blood Service |
| Scott Robinson | Anaesthetist | Waikato DHB |
| Tracey Clark | Blood bank team leader | New Zealand Blood Service |

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# Appendix C: Theory of change diagram

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