Modelling Red Blood Cell Provision in Mass Casualty Events

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Research Associated Publications and Presentations

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Thesis Abstract

Traumatic haemorrhage is a leading preventable cause of critical mortality in mass casualty events (MCEs). Treatment requires the rapid provision of high volumes of packed red blood cells (PRBC) to meet the surge in casualty demand these events generate. The increasing frequency of MCEs coupled with the threat of more violent mechanisms risks overwhelming hospital based transfusion systems. The overall objective of this research was to improve understanding of blood use in MCEs using a mathematical modelling approach.

A computerised discrete event simulation model was designed, developed and validated using civilian and military transfusion databases, a review of historical MCEs and discussion with experts involved in all aspects of in-hospital MCE PRBC provision. The model was experimented with across increasing casualty loads to optimise event outcomes under varied conditions of: stock availability, laboratory processing procedures and individual PRBC supply.

The model indicated even in events of limited size the standard on-shelf PRBC stock level was insufficient to adequately meet demand amongst bleeding casualties. Restocking during an event allowed for equivocal treatment results if performed early following an event and this would be most effective if activated by central suppliers. Modifications to transfusion laboratory processing procedures were found to be of limited benefit in improving outcomes due to the principally automated nature of the techniques they employ. Conversely, the use of restricting excessive individual provision of both overall PRBC and emergency type O PRBC to individual casualties did show potential for managing scenarios where only a finite supply of stock existed or an accurate estimation of expected casualties was available.

The application of simulation modelling to the problem of blood planning for MCEs was found to be a financially and logistically efficient method for providing greater insight into a complex system, offering potential solutions for optimising outcomes from these challenging events.

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List of Applied Abbreviations

ACIT II	Activation of Coagulation and Inflammation in Trauma Two
AHP	Analytical Hierarchy Process
AHRQ	Agency for Healthcare Research and Quality
AIS	Abbreviated Injury Scale
AMED	Allied and Complementary Medicine Database
APACHE	Acute Physiology and Chronic Health Evaluation score
ASCOT	A Severity Characterization of Trauma Score
ATC	Acute Traumatic Coagulopathy
ATD	Adult Therapeutic Doses
BASE	Bielefeld Academic Search Engine
BMS	Biomedical Scientist
BNI	British Nursing Index
BPMN	Business Process Model and Notation
CARS	Compensatory Anti-inflammatory Response Syndrome
CASP	Critical Appraisal Skills Programme
CBRN	Chemical, Biological, Radiological and Nuclear
CCU	Critical Care Unit
CDC	Centers for Disease Control
CI	Confidence Interval
CINAHL	Cumulative Index to Nursing and Allied Health
CNS	Central Nervous System
CRED	Center for Research on the Epidemiology of Disasters
Cryo	Cryoprecipitate
DCR	Damage Control Resuscitation
DCS	Damage Control Surgery
DES	Discrete Event Simulation
ED	Emergency Department
EMBASE	Excerpta Medical Database

ERIC	Education Resource Information Center
FFP	Fresh Frozen Plasma
FIFO	First In First Out
GCS	Glasgow Coma Score
GDP	Gross Domestic Product
GPSS	General Purpose Simulation System
GSW	Gunshot Wound
H_0	Hypothesis
HEMS	Helicopter Emergency Medical Service
HMGB1	High Mobility Group Box 1 Protein
HMIC	Health Management Information Consortium
IBM	International Business Machines
IED	Improvised Explosive Device
INFORMS	Institute of Operational Research and the Management Sciences
IQR	Inter Quartile Range
IRA	Irish Republican Army
ISPOR	International Society for Phamacoeconomics and Outcomes Research
ISS	Injury Severity Score
IV	Intravenous
JTTR	Joint Trauma Theatre Registry
KCH	King's College Hospital
LAS	London Ambulance Service
LIFO	Last In First Out
LIMS	Lab Information Management System
MAP	Mean Arterial Pressure
MCE	Mass Casualty Event
MeSH	Mapped Subject Heading
MH	Major Haemorrhage
MHP	Major Haemorrhage Protocol
MI	Major Incident
MOF	Multi-Organ Failure
MOI	Mechanism Of Injury
MT	Massive Transfusion

MTC	Major Trauma Centre
MVC	Motor Vehicle Collisions
NBS	National Blood Service
NCBI	National Centre for Biotechnology Information
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NISS	New Injury Severity Score
NYAM	New York Academy of Medicine
OR	Operational Research
P	Priority Score
PC	Personal Computer
Plt	Platelets
PRBC	Packed Red Blood Cells
PT	Prothrombin Time
PTT	Partial Thromoplastin Time
R3	Role Three
RAND	Research and Development Corporation
RBC	Red Blood Cells
RLH	Royal London Hospital
RR	Respiratory Rate
RTS	Revised Trauma Score
SBP	Systolic Blood Pressure
SC	Structural Collapse
SGH	St George's Hospital
SIMAN	Simulation and Analysis
SIRS	Systemic Inflammatory Response Syndrome
SMDM	The Society for Medical Decision Making
SMH	St Mary's Hospital
T	Treatment Score
TI	Trauma Index
TIC	Trauma Induced Coagulopathy
TRISS	Trauma Injury Severity Score
TS	Triage Sort

TXA	Tranexamic Acid
U	Units
UML	Unified Modelling Language
VBA	Visual Basic for Applications
VIMS	Visual Interactive Modelling Systems
VIS	Visual Interactive Simulation
WHO	World Health Organization

CHAPTER ONE

Introduction

1.1 A Disease Description of Trauma

1.1.1 Definition of Trauma

Trauma from the Greek word meaning wound may be defined as any form of physical injury sustained from an external source. As such, it may involve any or every part of the human body without regard for the anatomical boundaries common to other disease states (1). The depiction of trauma as a disease was first described in Scientific America in 1983, showing trauma to have an epidemiology, aetiology, pathophysiology, management and prognosis common to other classical disease states (2). As such, the treatment of trauma requires a disease specific approach to its management with specialist trauma teams, equipment and hospitals, practiced through a best evidence based approach. Best evidence in trauma care has been highlighted as a disproportionately under resourced area of research compared to the disease burden, which was estimated to cost the world economy in excess of $500 billion annually in the RAND report of trauma care in 2011 (3, 4).

1.1.2 Epidemiology & Aetiology of Traumatic Disease

Traumatic injury occurs in all communities everywhere in the world and is therefore an epidemic disease (5). Trauma can be generally divided into intentional and unintentional harm resulting from various mechanisms of injury (MOI) as described by the World Health Organization (WHO). The most common MOIs include: Road trauma, poisoning, falls, fires, drowning, violence and war as shown in Figure 1.1 (5). An individual's risk for a traumatic insult is related to their exposure to these mechanisms and therefore their age, gender, occupation, socio-economic circumstance and geographical location (5, 6). Whilst any age

group can be affected by trauma, it is primarily a disease of the young with the prevalence in this population increasing globally (6, 7). However, although those aged between one and 34 are more likely to suffer traumatic injury, trauma associated fatality remains highest in the elderly population (5, 6). Overall males are almost two and a half times as likely to suffer a traumatic injury compared to females, although the rate of interpersonal violence against women is on the increase worldwide (6). Certain occupations expose individuals to a much greater risk of traumatic injury including farming, fishing, mining and construction. The WHO reported in 2005 that the last of these - construction, led to a fatality every ten minutes and the global financial burden of non-fatal occupational injuries consumes approximately four percent of the world's gross domestic product (GDP) (5, 6).
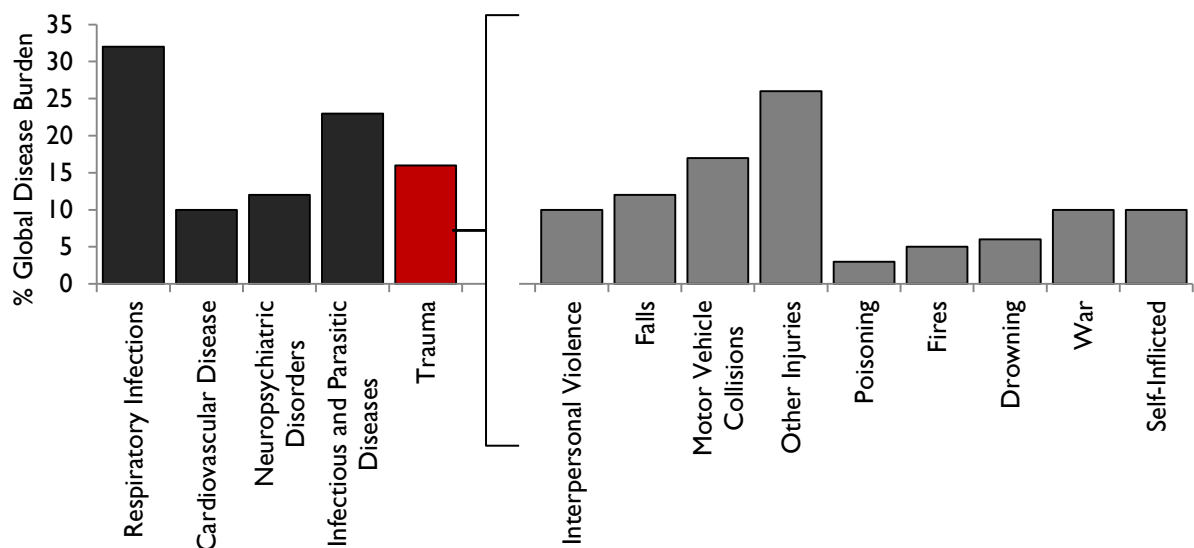
Figure 1.1 The five principal global disease burdens and the mechanisms contributing to the overall impact of traumatic disease in terms of overall percentage global morbidity and mortality.

Whilst trauma is endemic to all continents its prevalence and origin is variable. Increased global industrialisation has led to a rapid expansion of the automotive and technology industries over the last century and this has been accompanied by a substantial rise in trauma rates, with road traffic fatalities expected to increase from the 11th leading cause of global death to the third by 2030 (6). This is in part due to the failure of safety mechanisms and infrastructure to keep pace with industry expansion, especially in less developed countries. For example, the estimated road traffic death rate per 100,000 of population reported by the WHO in 2010 was 18.3 in India versus 3.7 in the UK. This discrepancy is expected to widen over the coming decades with 90% of motor vehicle collisions (MVC) occurring in the developing world (3, 5). Despite this, MVCs fall behind interpersonal violence and war as the leading causes of injury in the developing world, with around 60 million people injured worldwide as the result of conflict since the 1940s, primarily during dispute within individual nations (5, 6).

1.1.3 Pathophysiology of Trauma

1.1.3.i Macroscopic Description of Injury

Trauma can affect all tissue types in any region of the body, it involves a patient host and a vector (MOI) through which harm propagates (3). The type and degree of tissue disruption is dependent upon the nature, location and magnitude of the forces acting on the host as result of the vector and therefore the energy transferred between them; this can be mechanical (kinetic and potential), thermal, chemical, electrical, radiation or a combination (6). Mechanical energy is the most common mechanism of traumatic injury and can be precipitated through blunt or penetrating means. Blunt trauma occurs when a person is subjected to mechanical forces causing either rapid deceleration of the body or acceleration of an entity towards the body, the impact of which does not breach superficial tissue barriers directly, but instead leads to injury through shearing, rotational, distraction or compression of tissues internally or externally (5, 6). In contrast, penetrating trauma is the result of the direct division of tissues in anatomical order from superficial to increasingly

deeper layers. The energy transfer in penetrating injury and therefore the impact on tissue architecture is related to the causative agent and its rate of travel, this may be described as low, medium or high velocity. Examples of these include knife, blast projectile and gunshot wounds respectively (6).

Irrespective of mechanism, the trauma impact results in a primary injury to organ, skeletal or soft tissues, following this and depending on the type of insult, secondary damage occurs. The secondary injury can be early or delayed and involves factors both endogenous and exogenous to the host (8). Early secondary injury most frequently occurs through hypoxia or haemorrhage causing reduced tissue perfusion and eventually shock, which if unabated, leads to organ failure and death. Delayed secondary injury occurs predominantly through iatrogenic means in the form of any necessary emergency or elective surgery or through host infection involving either direct exposure or increased susceptibility to environmental pathogens (9). The endogenous response to both the primary insult and any second hit phenomena involves a spectrum of inflammatory responses. The magnitude of this response is proportional to the magnitude of the injury and ranges from local changes at wound sites to widespread Systemic Inflammatory Response Syndrome (SIRS) affecting distant organ systems (10-12).

The diverse extent of injuries that can occur following trauma can be categorised using a number of different tools specifically designed to provide an anatomical or physiological description of injury following trauma. Amongst the most commonly applied of these are: the Trauma Index (TI), the Injury Severity Score (ISS), the New Injury Severity Score (NISS), the Trauma Injury Severity Score (TRISS), A Severity Characterization of Trauma Score (ASCOT) and the Acute Physiology and Chronic Health Evaluation score (APACHE) (13-18). The most frequently used tool in reporting multiple trauma is ISS due to its correlation with hospital length of stay, morbidity and mortality following injury (6). The ISS system is based on the Abbreviated Injury Scale (AIS) which scores each injury by the threat it poses to life (19). Each injury is categorised by anatomical site and scored for severity from one point indicating a minor injury, through to six for an unsurvivable event. The ISS uses the sum of the squared highest AIS scores for the three most severely injured body regions to

give an overall score from zero, indicating no injury, through to a maximum of 75 signifying an irreconcilable injury load (6).

1.1.3.ii Microscopic Description of Injury

Following trauma the host mounts a systemic biological defence to maintain function, limit the propagation of injury and initiate tissue repair (20). In minor uncomplicated tissue trauma this response is mainly limited to the confines of the injury site involving a local inflammatory reaction followed by cellular proliferation and eventual remodelling of the tissues architecture. However, as the size and severity of tissue damage sustained increases with major and polytraumatic injury, there is a proportional increase in the activation of the host's wider defensive mechanisms with a systemic haemodynamic and inflammatory response observed (9, 11, 21). Early haemodynamic changes are primarily due to shock, in which there is a failure to adequately perfuse and oxygenate tissues. Shock in trauma can be from a single or multitude of causes with haemorrhage being the most common, this loss of circulating volume causes a compensatory tachycardia, increased cardiac contractility and peripheral vasoconstriction through neurohumoral mediators to preserve perfusion of central organs (22, 23). The failure to adequately perfuse peripheral tissues and therefore provide oxygenation leads to energy failure at a mitochondrial level, lactic acidosis, cell damage and eventually cell death. Unless this process is interrupted, compensatory mechanisms are eventually exhausted, organ damage ensues and finally multiorgan failure (MOF) occurs (22-24).

The inflammatory response to trauma is multifactorial and entails interactions between the host's hormonal, metabolic, and immune systems, the activation of which correlates with the injury magnitude (9). Direct tissue injury and reduced cellular perfusion initiates an acute stress response mediated through the neuroendocrine release of catecholamines, cortisol, glucagon and other acute stress hormones (9, 23). These hormonal mediators contribute to the acute metabolic reaction following trauma, this involves an acute hypo-metabolic phase prior to resuscitation and a post resuscitative hyper-metabolic phase lasting days or longer, in patients lacking physiological reserves such as the elderly or those with

chronic disease states (3, 9, 23, 25, 26). The course of metabolic changes following trauma maybe further altered through the occurrence of secondary insults as discussed above, with emergency surgery and infection both prolonging the hyper-metabolic state (9).

The hormonal and metabolic responses described following trauma both interact with, and are propagated by immune system derived mediators released following tissue injury. The immune system is activated locally and systemically in response to injury through an early generalised innate immune response and later via a specific adaptive immune processes (9). The local tissue damage and cell necrosis releases active mediators including kinins, arachadonic acid and high mobility group box 1 protein (HMGB1) (9, 23). Concomitantly the complement system is also triggered through the alternative pathway and interactions with the coagulation cascade. The complement system stimulates the degranulation of mast cells and histamine release, together with other local mediators these cause increased vascular permeability and the aggregation and activation of innate immune cells at the injury site including neutrophils and monocytes (9, 10, 27). The monocytes and local endothelial cells propagate the innate response further through the release of vasoactive nitric oxide, oxygen free radicals and both pro and anti-inflammatory cytokines (9, 10, 23).

The delayed adaptive immune response is predominantly T-lymphocyte driven, producing an immunomodulatory response through cytokine mediated anti-inflammatory processes (9, 23). The interplay between the pro and anti-inflammatory cytokines and the effector cells of the immune system balances the inflammatory response in trauma. When this equilibrium is disturbed for example during secondary injury, the host risks developing a systemic inflammatory response syndrome (SIRS) and further organ damage through an exaggerated pro-inflammatory response (9, 10). Conversely, a compensatory anti-inflammatory response syndrome (CARS) may also occur, with immune suppression and therefore increased risk of infections and the development of sepsis (8, 23).

1.1.4 The Management of Trauma

The management of trauma has evolved over many centuries, with the majority of advances in civilian trauma care adopted from innovations developed during periods of conflict and war (6, 28, 29). The principles behind trauma care are to treat the patient in order of greatest threat to life, maximise tissue and organ oxygen delivery and prevent secondary harm through a systematic approach (3). Mortality following trauma has been classically described as occurring in a tri-modal distribution since 1982 (2). The first peak in mortality distribution occurs almost immediately following injury and is generally the result of cardiorespiratory failure from severe central nervous system (CNS) disruption or cardiac or great vessel rupture. The second peak occurs within minutes or hours of injury, and is primarily the result of uncompensated shock or worsening CNS lesions leading to cardiorespiratory failure. The third and final mortality peak occurs in the weeks following injury and is most often due to sepsis and organ dysfunction (3).

The causes of instant traumatic deaths are largely untreatable and the focus of interventions for these cases lies primarily in the prevention of trauma through measures such as stringent occupational health and safety measures, public education and reduction in interpersonal violence and crime (6). In contrast, the mechanisms of the second and tertiary peaks in mortality offer far greater opportunity for intervention and patient salvage if recognised and acted upon early in the passage of care (3). In order to achieve a reduction in this mortality and the morbidity associated with trauma, many countries have developed specific trauma systems designed to match patient needs to available resources and provide optimal care in a cost-effective manner (6).

Central to the success of trauma systems is the ability to provide early and effective resuscitation of casualties rapidly following injury followed by definitive care to restore normal anatomy and physiology. A trauma system therefore must include pre-hospital care sub-systems, acute care facilities, surgical and intensive care units and rehabilitation services (6, 23). This approach has shown significant improvements in patient outcomes following

trauma especially with severe trauma treated at the highest level centres such as, level one trauma centres in North America and major trauma centres (MTCs) in the UK. (30-32). As a result, the tri-modal distribution of mortality has seen a shift in recent decades towards a bimodal pattern with immediate and acute mortality merging to form a single acute mortality peak followed by the classic delayed rise in mortality (33-35).

1.1.5 Prognosis Following Trauma

The mortality of trauma requiring hospitalisation is approximately 10% with around 5.8 million deaths a year worldwide occurring due to injury (36). Globally those aged under 44 years old are statistically more likely to die due to trauma than any other disease process (7). However, despite the predominance of disease in this young population, those over the age of 55 who suffer traumatic injury are more likely to die due to less physiological reserve and higher rates of chronic disease compared with the younger population (3). The mortality rate in trauma is accompanied by a significant level of morbidity amongst survivors (5). The number of individuals surviving trauma and requiring a medical intervention exceeds tens of millions and accounts for 16% of the overall global population disability burden (Figure 1.1) (36). Importantly, these statistics are likely to be underestimating the full extent of the impact of the disease, given that there is marked under reporting of trauma episodes in lower income countries where the prevalence of trauma is known to be higher (5).

1.2   Traumatic Haemorrhage

1.2.1   The Significance of Haemorrhage in Trauma

Haemorrhage is a leading cause of early mortality and the foremost cause of preventable death following traumatic injury (37, 38). In the pre-hospital setting haemorrhage has been shown to be responsible for between 33 and 56% of deaths and accountable for around 40% of total trauma mortality (33, 38). The in-hospital mortality rate from trauma haemorrhage peaks early in the chronology of the disease with the majority of all trauma deaths in the first hour and approximately 50% of deaths in the first 24 hours being due to bleeding (33, 38). After the first day the mortality reduces significantly with only a small proportion of deaths due to exsanguination occurring after this time period, when CNS damage, sepsis and MOF become the predominant threats to life (3, 33, 38). Despite haemorrhage no longer being the direct cause of mortality at this later stage, those suffering haemorrhagic shock pre-hospital or at admission have a greater association with the development of infections and MOF with rates of 39% and 24% respectively (38).

1.2.2   The Clinical Manifestations of Bleeding in Trauma

Traumatic haemorrhage causes a reduction in intravascular volume reducing cardiac diastolic filling pressure and therefore cardiac output and blood pressure. Vascular signalling pathways and neuroendocrine mediators respond to these physiological changes through vasoconstriction and the diversion of blood volume away from ischaemia-tolerant tissues to maintain critical end-organ perfusion (39). Ongoing haemorrhage or the persistence of an inadequately low volume state system leads to shock, cell death, profound metabolic

acidosis and organ failure (3, 23, 39). As shock worsens it manifests clinically through a series of haemodynamic changes and external signs indicating decompensation of homeostatic mechanisms, these include: tachycardia, narrowing pulse pressure, increased respiratory rate, reduced blood pressure, reduced cognition and deteriorating urine output (3, 39).

Alongside the direct ischemic effects of reduced cell and tissue perfusion occurring during traumatic haemorrhage, it has been shown that prolonged systemic hypotension is also associated with derangement of the coagulation system and in particular the prolongation of partial thromboplastin time (PTT) and prothrombin time (PT) (40). This acute traumatic coagulopathy (ATC) is thought to be a direct result of trauma induced shock and has been found to be present in up to a quarter of trauma patients at time of hospital admission (41). ATC and other well documented endogenous and exogenous precipitants of coagulopathy including: haemodilution, hypothermia, acidosis, hyperfibrinolysis and platelet dysfunction contribute to an overall hypocoagulable state which is collectively termed trauma induced coagulopathy (TIC) (40-43). This condition maybe further influenced through patient specific factors such as co-morbidities, genetics and concurrent medications (37, 44, 45). Irrespective of cause, the presence of TIC early in the clinical course appears intrinsically linked to the degree of trauma and has been shown to have a positive correlation with the severity of injury (46).

The integrity of the coagulation system is a necessary requirement for the reduction, cessation and prevention of haemorrhage, however, it also exerts a significant influence on the host's ongoing systemic reaction to trauma with continued effects even after haemostasis and volume resuscitation have been achieved (47, 48). As discussed previously the initiation of the coagulation pathway following trauma plays a significant role in immune activity following injury and there exists a complex reciprocal relationship between inflammation and coagulation mechanisms following injury (40, 43, 49). Casualties who are discovered to be coagulopathic on hospital admission have been found to have an eight fold increased risk of mortality in the first 24 hours of care and be at greater risk of: end organ damage, thromboembolic events, sepsis, MOF and prolonged stays in critical care (47, 48,

50). The restoration and maintenance of an intact coagulation system is therefore critical for both haemorrhage control and the prevention of TIC associated morbidity and mortality.

1.2.3 Management of Trauma Haemorrhage

The treatment of haemorrhagic shock centres around early recognition and control of active bleeding, restoration and optimisation of normal physiology and the prevention of secondary harm (38, 51). The structured approach to simultaneously achieving this is referred to as damage control resuscitation (DCR) (28). DCR encompasses the delivery of damage control surgery (DCS) alongside haemostatic resuscitation (28, 29, 52). DCR begins in the pre-hospital setting with the reduction of overt haemorrhage through techniques such as splints, pressure bandages, haemostatic agents and tourniquets (3, 29, 38, 51). These are however only temporising measures, which allow time to transport the casualty to a definitive care facility capable of managing major haemorrhage (MH) such as an MTC. MH is challenging to define and in the past has been arbitrarily described as the transfusion of one to one and a half times a patient's total blood volume in the first 24 hours. An alternative and more applicable definition in the initial stages of care maybe any haemorrhage which is life threatening (53, 54).

The in-hospital provision of DCS and haemostatic resuscitation occurs simultaneously. DCS for active MH is essentially concerned with early transfer to the operating theatre and crude control of haemorrhage through the ligation, clamping, packing and shunting of active sites of bleeding, whilst minimising the risk of contamination (55, 56). Casualties are often then maintained under anaesthesia on the critical care unit (CCU) following surgery with cavities left packed and open for definitive repair at a later stage (56, 57). The rationale for the technique is to minimise the tissue trauma insult when physiological reserves are already reaching exhaustion and allow further resuscitation to a homeostatic state prior to repeat surgery and the restoration of normal anatomy (28, 29, 51). Haemostatic resuscitation

occurs before, during and after DCS, it aims to judiciously restore intravascular volume and coagulation status whilst allowing for a permissive degree of hypotension until definitive haemorrhage control is achieved (28, 29, 51, 52, 58). The process of haemostatic resuscitation is multifaceted and the optimum strategy for its delivery has undergone widespread debate in recent years (58-69). The method is driven by three main therapeutic approaches:

1. Volume replacement: This is achieved primarily through the infusion of high numbers of packed red blood cell (PRBC) units in order to restore the blood's oxygen carrying capacity, correct metabolic imbalance and maintain end organ perfusion (37). Casualties suffering MH will often require a massive transfusion (MT) of ten or more units of PRBC in the first 24 hours and whilst the rates of MT are around 3% and 8% in the civilian and military trauma populations respectively, a single patient alone can consume as much as a 100U of PRBCs in instances of severe injury (28, 69-73).

2. Maintenance of coagulation mechanisms: The threat of ATC in severe injury as well as the evolving risk of developing TIC through other mechanisms such as high volume PRBC infusions which provokes the haemodilution of clotting components, mandates early incorporation of high dose coagulation therapy during the passage of care (37). The principal components of coagulation treatment are fresh frozen plasma (FFP), platelets (Plt) and cryoprecipitate (Cryo) given in near equal ratios of units compared to PRBCs transfused (59, 60, 62, 74-77). Alongside direct coagulation therapy adjunctive measures are also employed to prevent TIC developing or worsening, these include: maintenance of core body temperature, optimising ventilation, administration of Tranexamic acid (TXA) and monitoring treatment response through laboratory and viscoelastic testing (37, 51, 52, 78)

3. Permissive hypotension: Prior to definitive control of haemorrhage, maintaining a below physiological normal blood pressure which continues to preserve tissue perfusion has been shown to improve outcomes in both animal models and human studies (58, 65, 66,

68). This practice limits the degree of blood loss from active bleeding sites through a reduction in mean arterial pressure (MAP) and prevents excessive pressure on established blood clots which could become dislodged. The loss of a formed clot will not only further exacerbate haemorrhage but will also further consume clotting components potentiating the risk of developing TIC (3, 37, 51, 52).

1.2.4 Outcomes in Trauma Haemorrhage

A quarter of all trauma patients receive at least one unit of PRBCs and therefore they exert a significant effect on national blood stock demands (79). For example in North America approximately three to four and a half million units of PRBCs are used to treat victims of trauma every year, this represents between 10 and 15 percent of the nationwide annual PRBC consumption (73, 79). From the 25% of trauma cases receiving at least one PRBC unit, a quarter will go onto require a MT, which is predominantly delivered within the first few hours of admission (61, 73, 79-81). Despite the significant resource and financial burden of those suffering MH, the use of multiple MTs can be rationalised through reports of encouraging outcomes following substantial blood use. Overall, survival of MT has been shown to be as high as 74% in civilian trauma and 86% in military trauma populations, with certain studies also describing survival rates of around 43% and 33% following transfusions of over 75U and 100U of PRBCs respectively (70, 72, 73, 77, 82).

The initial treatment of severe haemorrhage mandates the use of type O universal emergency donor PRBCs for resuscitation until a patient's blood group can be determined. The significant positive skew of blood consumption over the timeline of patient care results in considerable use of emergency blood, with anything from 11-18% of PRBCs transfused in the first 24hours being emergency type O units (73, 82). In an effort to improve the early delivery of blood, rapidly transfer to group-specific components, reduce wastage and ensure coagulation dysfunction is confronted early in patient care; many trauma systems have

adopted specific major haemorrhage protocols (MHP). The activation of these protocols has been shown to reduce overall PRBC use, increase early clotting component delivery and encourage goal directed therapy using repeated coagulation testing. The overall result is a more cost-effective system capable of saving thousands of dollars through reduced wastage without effecting mortality (69, 83).

1.3 Mass Casualty Events

1.3.1 Introduction and Terminology

Single and multiple casualty trauma is a manageable and regular occurrence at MTCs or equivalent units (84). The principles of trauma management remain the same for each individual and the capacity of the unit to absorb multiple injured casualties is only limited by the resources at its disposal. However, with increasingly larger and more complex emergencies involving greater numbers of casualties the ability to respond to an acceptable level is challenged. Definitions and terminology describing such emergencies are often applied interchangeably and interpreted differently between countries, industries and organisations (85-87). For the purposes of consistency in this study, the following common and accepted definitions will be applied:

1. Major Incident (MI): 'Any occurrence that presents serious threat to the health of the community, disruption to the service or causes (or likely to cause) such numbers or types of casualties as to require special arrangements to be implemented by hospitals, ambulance trusts or primary care organisations' (88).

2. Mass Casualty Event (MCE): 'Single or simultaneous event(s) or other circumstances where the normal major incident response of one or several health organisations must be augmented by extraordinary measures in order to maintain an efficient, suitable and sustainable response' (85).

3. Disaster: 'Serious disruption of the functioning of a community or a society causing widespread human, material and economic or environmental losses which exceed the ability of the affected community or society to cope using its own resources' (89).

The first and last of these classifications are not patient load or healthcare specific and may describe situations related to events which require intervention from other emergency services or organisations (87). When referring to a medical response, these classifications follow a central theme related to the burden they exert on available resources. The declaration of an MI by emergency services occurs when an event threatens to exceed routine operational capability, requiring the instigation of additional measures but not exceeding resource capacity. Depending on the type of incident this may then evolve into an MCE with local resources becoming overwhelmed by casualty numbers. Alternatively a disaster ensues if the scale and impact of the event increases so as to affect infrastructure and the ability to mount any form of local medical response without copious external resource assistance, also termed an 'uncompensated event' (87, 90). The exact scale of the incident is often not known for hours or even days following the initial event, therefore, the term MI is often used initially until the scale of its consequences can be fully appreciated.

1.3.2 Prevalence, Trends and Significance of Disasters and Mass Casualty Events

Disasters and MCEs have become increasingly common in recent years (89, 91). The last decade (2000-2009) saw over 7000 disasters reported worldwide affecting over two and a

half billion people at a global cost of just under one trillion U.S. Dollars (92). Compared to the period 1990-1999, this era has seen a rise in disaster related deaths of 23%, with over one million lives lost and a 15% increase in the number of people affected (92). The upward trend in prevalence has been attributed to numerous factors, including: an increase in the global population, greater migration both permanent and temporary, the increased urbanisation of our population, an increase in the production and movement of hazardous material, ongoing climate change and greater civil unrest across the world (86, 92).

Events can occur in many forms and can be classified according to whether their origin is natural or man-made, they can occur suddenly as a single 'big bang' event or develop over time, a so-called 'rising tide' (85, 93, 94). Natural disasters consisting of meteorological, hydrological, climatological, geological or biological mechanisms predominate in the developing world (90%), they are associated with a mortality ten times greater than man-made events and cost three times as much in insured losses (95-97). Man-made events in contrast are more familiar to developed nations and commonly result in MCEs (89, 90). Although less when compared to that of natural disasters, these events still exert a significant human and financial impact with approximately 100,000 deaths excluding violent or conflict related mechanisms reported between 2000-2010 and insurance costs totalling around eight billion dollars a year (95, 97). In addition to the overall increase in prevalence of all disasters and MCEs, the proportion of man-made events contributing to this total increased by 25% alone in the latter part of the 21st century and was also accompanied by a five percent increase in event mortality (89).

The genuine prevalence of MCEs is likely to be far greater than actually reported, as due to their magnitude compared with natural disasters such as tsunamis or earthquakes, they are less likely to be registered by international emergency databases and often occur in low or middle income countries where reporting is less robust or well established. Estimates have suggested that there are 20 smaller emergencies occurring for every disaster recorded in recognised registries (98). Despite this, to-date the principal focus on disaster and MCE management research has been on natural disasters. This is in part due to the recognised potential to prevent, avert or intervene with their course of action. In contrast, there has

been comparatively minimal attention afforded to man-made disasters and MCEs, particularly with regard to the hospital based management of casualties (4, 90, 99).

1.3.3 The Mass Casualty Event Response

Natural disasters often lead to an uncompensated medical disaster following failure of transport, communications and infrastructure along with countless casualties. This is far rarer in man-made incidents which are more likely to result in major incidents and MCEs (87, 90). Man-made MCEs can develop from structural failures, industrial accidents, fires, mass gatherings, transportation accidents and episodes of conflict and interpersonal violence (87, 90, 93). Irrespective of mechanism, these events generate a high number of traumatically injured casualties in need of rapid assessment and treatment that is out of proportion to the resources available, threatening to restrict the delivery of an optimal level of care (85). The relative frequency and experience of these events demands that established healthcare systems have in place full emergency preparedness plans in order to ensure resilience and mount an effective response (87). MCE emergency preparedness involves strategic planning, implementation of proposed measures, dissemination of information and training. All services and organisations required for a response should be involved in this process (87, 100, 101).

The diversity of MCE mechanisms mandates a generalised initial response by emergency services to manage the incident scene through command and control of the area, communication between service providers, scene assessment, triage and the transport of casualties to an appropriate unit of care (87). In the UK a three-tier command system operates under the categories of: Gold, Silver and Bronze. This hierarchy is used both locally at the incident site and within hospitals to manage the event. Gold command represents the highest level of command and controls the strategic response; it is far removed from the immediately active response areas, whether that is the hospital's emergency department (ED) or the scene of the event itself, allowing overseeing of the

entire incident. Silver command is the tactical command centre, tasked with coordinating and implementing the response plan and therefore located nearby the actual areas of response. Bronze is the operational arm of the response and is active within the incident or hospital itself, ensuring the processing and delivery of care to casualties (87, 101).

1.3.4 Systems of Care

1.3.4.i Pre-hospital Care

The long held mantra of the overall MCE response is to provide 'the greatest good for the greatest number' (84, 87, 102). The basis of achieving this is effective casualty triage in order to sort casualties by priority (P) or treatment (T) needs. The T score is generally applied in the military environment whereas the P score is more familiar to the civilian setting and therefore will be applied for the remainder of this study. The 'P' and 'T' classifications are essentially equivalent with the exception of expectant casualties as shown in Table 1.1, although it should be noted that the term P4 is often also used interchangeably with 'P1 Hold' in civilian dialogue (85, 87, 103).

Table 1.1 The Priority and Treatment Casualty Classifications

Priority	Treatment	Description	Colour Code	Time To Treat
P1	T1	Immediate	Red	<1 Hour
P2	T2	Urgent	Yellow	2-4 Hours
P3	T3	Delayed	Green	>4 Hours
P1 Hold	T4	Expectant / Dead	Blue	Expectant Only if Resources Allow

Adapted from: Major Incident Medical Management and Support: The Practical Approach at the Scene, Mackway-Jones K.. John Wiley & Sons; 2012.

Although triage is a fluid process it usually takes place at three specific points during an event (Figure 1.2). The first triaging of casualties occurs during an initial rapid scene assessment immediately after emergency services have gained access to the incident,

commonly the triage sieve system is used due to its speed of application. This system grades patients as P3 if able to walk and delineates between P1 and P2 casualties using respiratory and pulse rate, other casualties are labelled dead or expectant (P1 Hold / P4) depending on available resources (87).

Upon extraction of casualties to a clearing station a repeat and more detailed triage sort (TS) is performed, this is primarily used to ensure casualties are transported to a suitable location to manage their needs and prevent where possible, overwhelming a single centre. TS employs a modified version of the Revised Trauma Score (RTS) and classifies patients by assessing Glasgow Coma Score (GCS), systolic blood pressure (SBP) and respiratory rate (RR) to confirm or modify their 'P' category (87). The third triage assessment is performed on arrival at hospital to determine if the clinical state has altered during transport, it therefore determines the most appropriate area for treating casualties. This triage process is normally undertaken in the receiving bay of the hospital by the most senior surgeon or emergency medic and may use a range of triage systems including the Manchester, Canadian or Australian triage tools for a rapid one to two minute priority assessment (104).
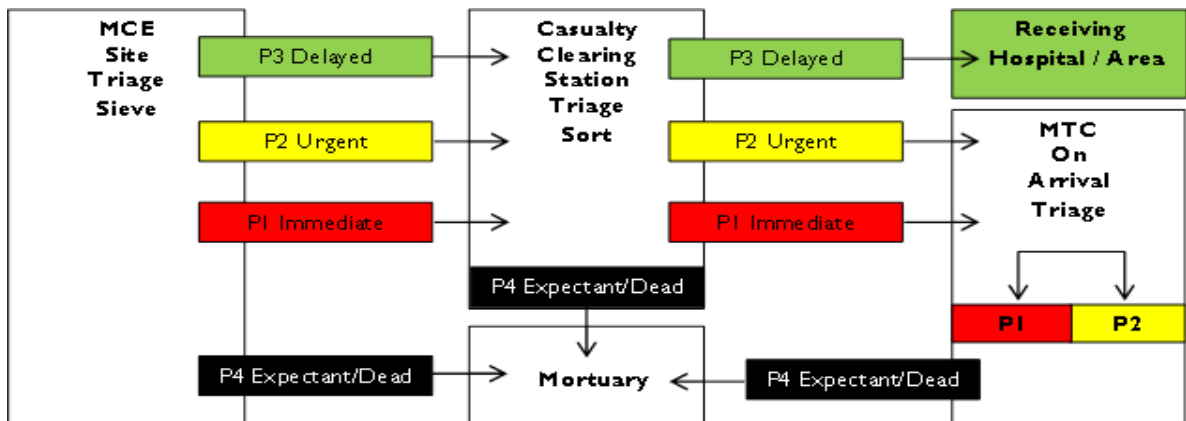
Figure 1.2 Triage locations and processes following an MCE.

.Adapted from: Major Incident Medical Management and Support: The Practical Approach at the Scene, Mackway-Jones K., John Wiley & Sons; 2012.

1.3.4.ii In-hospital Care

The overall hospital response to an MCE can be described as having four distinct phases: An initial response or crisis phase, a consolidation phase, a recovery and a restoration phase (105-107). The crisis phase follows immediately after an event is declared. Whilst pre-hospital teams are managing the MCE scene and triaging casualties, hospital staff have a limited timeframe in which to make preparations for their arrival and maximise casualty capacity, some of the fundamental strategies include:

- Ensuring all staff and departments are aware the MCE management plan has been instigated.
- Calling additional staff in to assist in the response and ensuring all staff are aware of roles.
- Organisation of a casualty receiving area for the front door triage of arriving casualties.
- Clearing of designated areas required for casualty assessment and treatment.
- Cancelling of all elective procedures and limiting any urgent procedures wherever possible including radiology and surgery.
- Transfer or discharge of appropriate in-patients.
- Distribution of essential resources to areas of expected need.
- Preparation of additional areas for management of uninjured patients, relatives and the media (87, 103, 108-110).

The time available to action the above will depend on the type of incident precipitating the MCE, the ability to transport casualties and the distance from scene to hospital. P1 and P2 casualties are by definition urgent and require management at an MTC or equivalent facility, these casualties require rapid extrication and transfer to hospital to reduce mortality. This therefore creates a surge in casualty arrivals at receiving hospitals early in the event timeline which peaks within the first few hours. As 50-80% of these casualties are received during this time, this presents the period of greatest risk for the available resources to become

overwhelmed (Figure 1.3) (111-113). Should the number or rate of casualties arriving exceed the resource capabilities of the treating unit it is said to have reached surge capacity (112).

Following the surge of casualty arrivals there is a period of consolidation in the hospital response as the rate of P1 and P2s received reduces (113). During this phase further information regarding the incident becomes available and although the full extent of the event is unclear, a more accurate estimate of expected casualties may be made, aiding informed decision making on resource allocation (99). As casualties continue to be processed through the system the burden on essential areas of trauma care continues to increase with particular strain placed on operating theatres, CCUs, radiology units, pharmacy and the blood bank. This may lead to bottlenecks developing in the system delaying patient flow and therefore impacting on patient care delivery (99, 114-118).
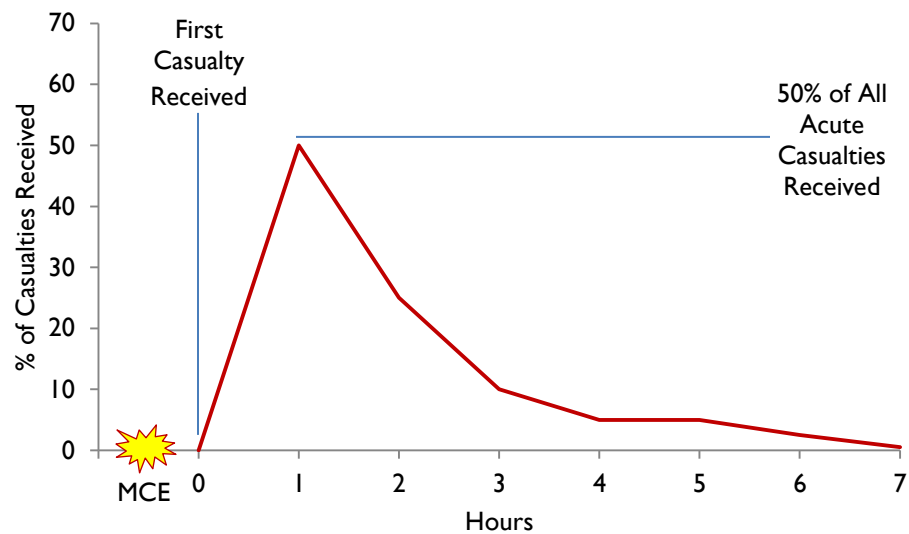
Figure 1.3 Surge in casualty arrivals at receiving hospitals following an MCE.

Adapted from: The Center for Disease Control online emergency preparedness Mass Casualties Predictor, Accessed November 2011 at http://emergency.cdc.gov/masscasualties/predictor.asp

The recovery phase begins once all casualties have been received and the event is well defined (99). This period may last from days to weeks, during which there is ongoing pressure on staff and resources as patients who underwent initial DCS are returning to theatre for definitive procedures. CCU may now be at capacity, minor injuries require assessment and treatment, and community healthcare also begins to return back to normal operational levels (93, 99, 119). Additionally, consumable hospital resources such as blood products will also need replenishing during this stage to manage demand and ongoing deficits. The public donations of blood which often occur following MCEs are the primary source for ensuring this, as well as the restoration of regional and national blood stocks back to their normal acceptable levels (118, 120, 121). The final phase of the MCE is the restoration phase which can last from months to years depending on the circumstances of the incident. This may involve a thorough investigation and public enquiry into the event including legal proceedings, analysis of service performance and identification of improvements for future MCE management (93, 106).

1.3.5 Traumatic Haemorrhage and Mass Casualty Events

Casualties from man-made MCEs suffer almost exclusively traumatic injuries, the exception to this is unconventional acts of terrorism involving chemical, biological, radiological or nuclear (CBRN) materials (122). As a result haemorrhage is a common cause of preventable morbidity and mortality following these events (118, 123-127). Casualties suffering significant haemorrhage by definition will be included in the P1 and P2 cohort and therefore will require treatment at an MTC or equivalent facility (4, 128). These patients are at risk of requiring a MT as a part of DCR and although they represent a small percentage of the total number of injured, have been shown to consume the majority of all PRBCs transfused following an event, the bulk of which are consumed within the first 12 hours (124). The timely availability and appropriate delivery of blood products in MCEs is therefore essential to improve critical mortality in these severely injured patients (118, 129, 130).

1.4 The Provision of Blood in Mass Casualty Events – A Case Study

1.4.1 Introduction

In 2005, London was the focus of the largest UK peacetime MCE for over a century (119). Despite decades of terrorist activity on the UK mainland during the Irish Republican Army's (IRA) campaign from 1969-2000, an attack of this manner and size had not been previously experienced (131). At the time, the capital's morning rush-hour saw around 800,000 commuters accessing the London transport network on an average weekday (132). On the morning of the 7th of July that year, just before nine o'clock and at the peak of the morning commute, three terrorist suicide bombers detonated improvised explosive devices (IEDs) on the London underground during a calculated and coordinated attack (119, 133) This was followed within an hour by a fourth bomb detonated aboard a central London bus. The attacks resulted in over 700 casualties and 56 deaths. The events of this day along with those the previous year in Madrid and on September the 11th 2001 in the USA, underlined the shift in modes of terrorism in recent times towards tactics more familiar to warfare than the civilian environment (119, 131).

1.4.2 A Major Trauma Centre Response

The Royal London Hospital (RLH) is one of four MTCs in London and received the most severely injured casualties on the day of the event. On the morning of the attacks the RLH was hosting a monthly governance meeting for the Helicopter Emergency Medical Service (HEMS) for which the hospital is the base unit; this resulted in a larger than usual number of

pre-hospital trained providers being available to assist in the response (132). The train bombs were detonated at the three separate inner city locations over a fifty second window at 08:51hrs. The London Ambulance Service (LAS) were made aware of confirmed fatalities and casualties suffering from smoke inhalation within minutes and alerted HEMS at 09:07hrs (132). This was followed later by notification of a London wide MI at 09:23hrs.

The most senior biomedical scientist (BMS) at the RLH assumed control within the transfusion laboratory just prior to the confirmation of the major incident and was made aware by the RLH's Gold Command that the hospital would be the first casualty receiving unit. Following this declaration; the ED was cleared of all non-urgent cases, available bed space was increased through the discharge of suitable inpatients, all elective surgery was cancelled and non-urgent blood transfusions were restricted. The lead BMS dispatched staff to the ED to oversee provision of emergency blood prior to arrival of the first casualties, shortly after which, the fourth and final bomb was detonated aboard a central London bus at 09:47hrs. At 10:05hrs, the first high priority casualty arrived in the ED, 69 minutes after the first explosion. The peak in casualty arrivals at the RLH was reached between two and three hours after the first explosion with a rapid decline in seriously injured casualties presenting thereafter (Figure 1.4).
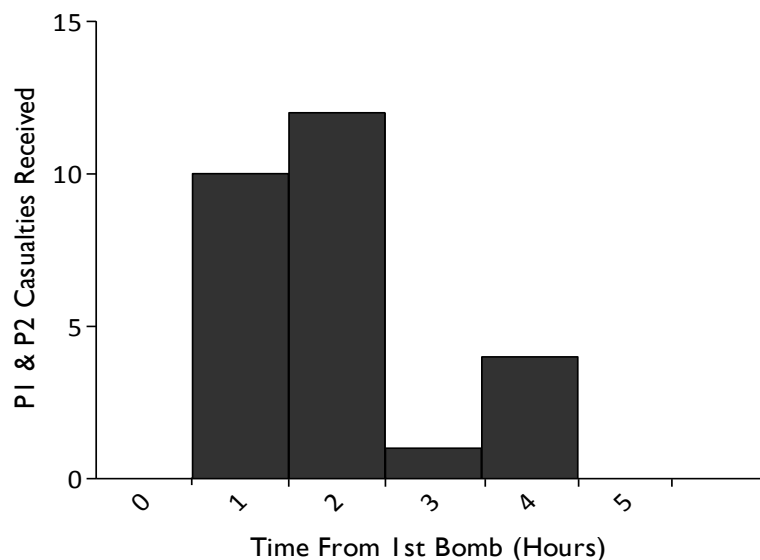
Figure 1.4 Histogram of casualties received per hour at the RLH on the 7th of July 2005.

The initial estimates from silver command at the incident sites were that casualties would number in the order of hundreds. This led to the decision to transfuse Type O negative PRBC to all casualties of unknown gender and women under the age of sixty, all others would receive Type O positive PRBCs until group-specific blood was available. The blood stock inventory at the hospital on the morning of the event was approximately 306U of PRBCs, 168U of FFP, 20U of Cryo and 4 adult therapeutic doses of Plt (1 ATD = 4 buffy coats). In addition to this, further blood supplies were requested from the National Blood Service (NBS) to cope with the expected increased demand. The first of these requests occurred at 10:32hrs and was one of three PRBC requests made by the RLH on the day of the attacks (Figure 1.5).
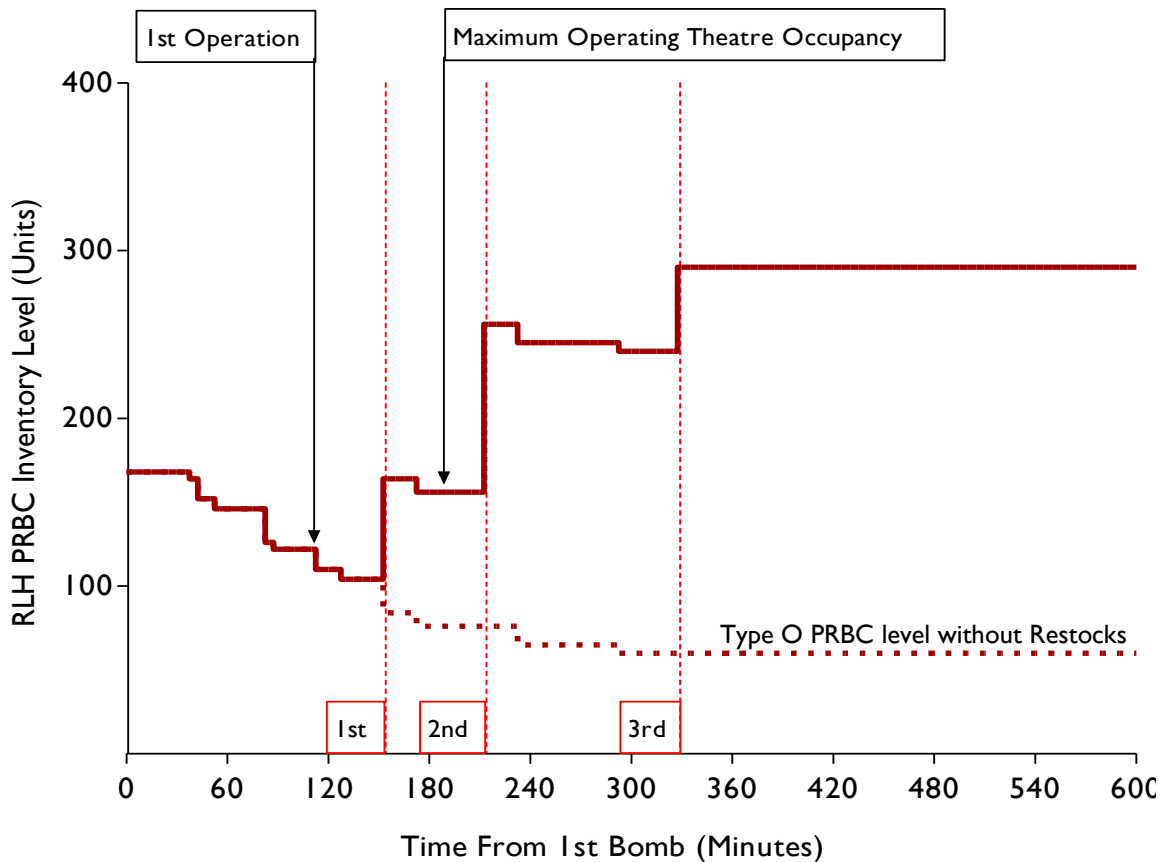
Figure 1.5 A timeline of type O PRBC use at the RLH on 07.07.2005. The times of the 3 PRBC deliveries which occurred during the event are shown by the reference lines (---).

The clinical case-mix encompassed all body regions with signs of all four echelons of blast injury, including: perforations, amputations, haemorrhage, fractures and burns through both penetrating and non-penetrating mechanisms (134). The first operation for one of the victims of the attack commenced at 10:45hrs and theatres reached maximum usage within 75 minutes as further casualties arrived (Figure 1.5). Incident Gold command informed the RLH to expect a second wave of casualties at midday on top of the 175 casualties the hospital had already processed. This second wave fortunately did not materialise and the major incident at the RLH was declared over at 12:40hrs. Despite this, the impact of the event continued to have repercussions for the rest of the day and the weeks that followed. The final delivery of PRBCs was received at 14:20hrs with a further delivery consisting of only Cryo, Plts and FFP received at 18:20hrs. By 19:45hrs the RLH had admitted 28 casualties of priority one and two status. Seven of these required critical care, 19 warranted admission to a general ward and two had died, one in the ED and one in theatres, where eight operations were still taking place.

1.4.3 The National Blood Service Response

The NBS is a division of The National Health Service Blood and Transplant (NHSBT) special health authority. The NBS provides approximately two million units of blood to 304 hospitals in England and Wales every year with a stock level of around 55,000 red cell units, this equates to approximately an eight 'standard' day supply of PRBCs (135). Operational databases record all blood issued to National Health Service (NHS) hospitals across England and Wales. This maintains a real-time strict audit trail of all blood components released by the system. The emergency NBS system was activated at approximately 09:35hrs on the day of the bombings and stood down at approximately 18:30hrs the same day.

On the morning of the attacks, the NBS blood and blood component stocks were running at average levels. The mean number of normal operational days that the NBS blood stocks could satisfy in 2005 ranged from 8.3 days-worth of blood for low-use hospitals through to 4.6 days-worth for high-use teaching hospitals such as the RLH. Following the confirmation of the bombings the message that emergency donations of blood were not required was made clear by the NBS both internally to staff and externally to the public at donation centres and via the media. Despite this July 7th saw its highest ever-recorded total of calls for one day. In total 10,046 attempts were made to contact the NBS – three times the normal volume for the time of the year. At its peak, 66 calls were received every minute.

The first emergency orders for blood were placed within 30 minutes of the first bomb. Eight NHS Trusts placed emergency orders; however two did not require the blood ordered. One major receiving hospital did not order emergency blood and managed from existing stocks. All blood bank managers from the trusts involved had written procedures for a MI, including blood ordering, in place prior to the attacks. The total demand from hospitals for the event was 1,455 units of blood and components, this was based on expected casualties and stock levels at the time and included: 978 units of PRBCs, 36 ATDs of Plts, 141 units of FFP and 300 individual doses of Cryo (136).

The number of PRBC units requested far exceeded that of similar past events (Table 1.1). The breakdown of the individual groups issued by the NBS is shown in Table 1.3. Three hospitals ordered group O as a priority whereas the other five ordered a mix dependent on their stocks. From the total volume of PRBCs requested 71.7% were group O with 23.3% being O negative. In contrast, the average proportion of group O and group O negative blood ordered in a standard delivery is 48.0% and 11.5% respectively (137).

Table 1.2 The NBS Response to Previous UK MIs

Incident	Year	PRBCs Requested (U)	Number of Deliveries
Southall Rail Crash	1997	215	3
Soho Bombing	1999	260	4
Paddington Rail Crash	1999	388	2
Selby Rail Crash	2001	297	6
Potters Bar Rail Crash	2002	160	4
London Bombings	2005	978	18

Table 1.3 Breakdown of Blood components by group issued by the NBS to the requesting hospitals

	O+	O-	A+	A-	B+	B-	AB+	AB-	Total
PRBCs (U)	473	228	165	30	70	12	0	0	**978**
Blood group (%)	48.4	23.3	16.9	3.1	7.2	1.2	0	0	
FFP (U)	55	0	35	10	5	0	25	9	**139**
Blood group (%)	39.6	0	25.2	7.2	3.6	0	18	6.5	
Platelets (ATD)*	32	4	0	0	0	0	0	0	**36**
Blood group (%)	88.9	11.1	0	0	0	0	0	0	
Cryoprecipitate (ID)**	100	60	50	30	30	0	30	0	**300**
Blood group (%)	33.3	20	16.7	10	10	0	10	0	
Neonatal FFP(U)	0	0	0	2	0	0	0	0	**2**
Blood group (%)	0	0	0	100	0	0	0	0	

*ATD – Adult therapeutic dose = 2.4×10^{11} per bag, **Individual doses.

The five main responding hospitals all ordered NBS blood to manage the approximate 360 casualties they received. In total 18 deliveries were made to the various units, at least three times the number seen in similar past events (Table 1.2). In total 338 units of PRBCs were transfused to 23 patients by midnight on the 7th of July. Two further patients received transfusions over the following days. Other receiving hospitals reported no blood use for the victims on the day of the bombings. These figures give an initial mean use of 14.7 red cell units per patient transfused with a total mean of 17U (range 2 – 91U) for the whole

event. The amount of blood ordered was therefore three times that initially used. In total 54 of all units issued by hospitals (16%) were used as emergency group O blood.

The proportion of emergency group O units issued varied from one hospital to another with a range of 0-21%. Patients requiring a MT received early replacement of components, with use until midnight on the 7th totalling: 103 units of FFP, 235 individual doses of cryoprecipitate and 31 adult therapeutic doses of platelets. The mean component use per patient and a description of patient demographics is shown in Table 1.4. A few of the hospitals who ordered blood components and then largely dealt with patients with burns and smoke inhalation did not need to utilise the majority of components provided. The greatest consumption of blood products appears to be associated with traumatic amputations as part of their injury profile, with one patient requiring up to 50 units of PRBCs by midnight on the first day.

Table 1.4 Patient demographics and mean blood component use during initial admission

Criteria	Range (Mean)
Age	2-63yrs (36yrs)
Gender	13 Male, 11 Female, 1 Unknown
Red blood cells	2-91 units (17 units)
Fresh frozen plasma	0-24 units (7 units)
Cryoprecipitate	0-40 units (18 units)
Platelets	0-7 doses (9 doses)
Outcomes	13 Survived, 2 Died, 2 Transferred, 8 unknown

(Number =25)

There were no reports of cell salvage being instigated in the emergency departments during the course of the event, nor of the employment of factor XIII or fibrinogen concentrates in the treatment of victims. The latter two, remain strategies which are not currently widely available in the UK system. However, rFVIIa (Novo Seven, Novo Nordisk) was used in five patients as part of the management of massive haemorrhage. Four of these patients survived their injuries.

Although the highest daily transfusion burden occurred on the first day of the attacks, transfusions for the treatment of victims continued for many more months. Figure 1.6 shows the timeline of transfusions received by the victims during their length of stay. Two smaller peaks in transfusion rate can be seen to follow the initial surge on days four and six. This likely corresponds to patients returning to the operating theatre for definitive treatment having been initially cared for using damage control surgical techniques. One individual required over 91 units of PRBCs with a variety of other blood components during their inpatient stay. The total number of PRBCs required to treat all victims from admission to discharge was approximately 440 units. However, some patients transferred to secondary units as part of their on-going care may have received further transfusions which were not included in the data.
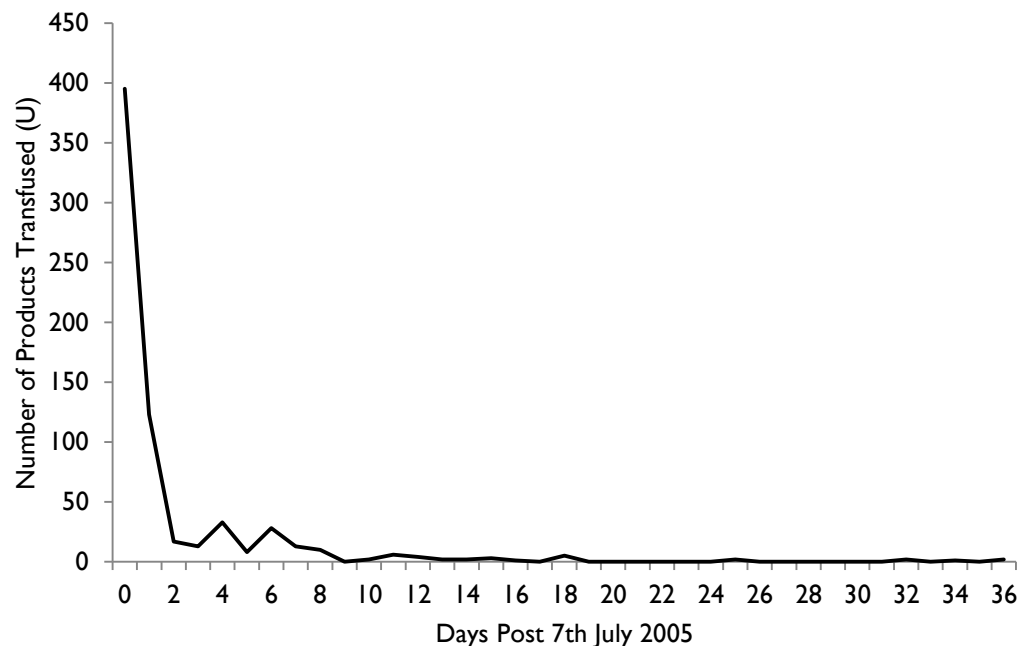
Figure 1.6 Number of blood product units transfused per day following the attacks at all London hospitals.

1.4.4 Lessons Learnt From The 7th July 2005

On the day of the attacks almost 1000 units of PRBCs were ordered over an eight hour period. The actual clinical demand on this occasion was only one third of the blood ordered. Receiving hospitals are unlikely to know their actual demand and planners should assume that over-ordering might occur. However, over-ordering may lead to pressure on both total stocks and supply of vulnerable groups such as O negative PRBCs. Group O negative blood has a distribution in the UK donor population of about eight percent, as the 'universal blood group' for PRBCs; as such, it is a precious resource in emergencies. Therefore, priority for its use is given to females under 60 years of age in order to prevent complications related to pregnancy, with group-specific blood introduced as soon as a patient's blood group has been confirmed (3).

The hospitals involved identified a number of reasons for the additional use of group O blood when group-specific would have been appropriate. These included; the incompatibility of the MI numbering applied within the hospital Blood Bank system and a lack of gender documentation on patient blood samples. This resulted in the approach of giving group O negative blood to all patients of unknown gender and women <60 and group O positive to all others.

These issues are longstanding and were also reported by Darvall in 2002 following the Bali bombings (138). She identified the need for a group O blood bank and highlighted the problems associated with patient identification and sample labelling. Dann et al have previously emphasised the risks of mis-transfusion due to labelling and collection errors (139). One method employed in Israel to minimise labelling errors is the requirement to send two samples for processing but the effect this has on processing time is unclear (124).

1.4.5 Contingency Blood Planning for Mass Casualty Events

Planning blood provision for health services involves a business continuity element to ensure service delivery under standard operating conditions and an emergency response element to ensure service resilience during an acute surge in demand such as an MCE. In the UK, NHSBT operates a demand planning group to specifically monitor and regulate blood supply across its service. The group's primary aim is to minimise waste and reduce costs whilst also ensuring the adequate availability of blood to meet the variable and evolving needs of the population. Ensuring business continuity involves daily system review with local redistribution of blood stock, as well as prediction and preparation for longer term forecasting of service demands. The latter involves consideration of a number factors including; historical trends, demand data, seasonal fluctuations in both supply and demand, changes in practice and policy, the availability of new products and modifications to national clinical service guidelines. These elements are combined to inform a multivariate prediction tool from which national blood stock requirements can be managed.

Emergency response blood provision is more challenging, threats to business continuity afford planners more time in which to respond and allow a considered response to stock management at almost entirely a central level of the transfusion service. However, emergency events demand an immediate reaction both centrally and at a local hospital level where there is less flexibility within the system. Despite this heightened threat to service provision MCE transfusion service contingency planning is poorly reported in the literature (140-145). This is in contrast to the attention afforded to other blood planning emergencies such as pandemic influenza and seasonal blood shortages (146-149). MCE blood planning must encompass preparation for both anticipated and unanticipated events. Anticipated events occur during periods when there is a known heightened risk of an event occurring such as planned mass gatherings, sporting events and national celebrations, whereas unanticipated events occur without any warning such as in a catastrophic transport system failure or large industrial accident (87).

Conventional terrorist attacks which often involve the use of high energy weapons and explosives span both categories, with random attacks occurring alongside assaults on high profile events such as the Olympics or a city marathon, occasions which present an ideal opportunity for delivery of widespread and devastating attacks which will be witnessed across the world (140-145). The latter as well as other anticipated events do afford a degree of preparation, and some blood services such as in Israel and the US military have adopted methods utilising pre-tested walk-in donors. This approach facilitates the provision of fresh whole blood rather than stored individual components for trauma victims. However, the current policy in the UK and many other nations for blood donation in times of civilian disaster is to hold sufficient on-shelf stocks to deal with incidents, rather than accept emergency donations (118, 150-152). The main tension in planning blood provision for MCEs whether anticipated or not, is therefore based on managing the balance between holding sufficient blood stocks in the right place to meet a sudden or expected surge in demand, versus avoiding the unnecessary waste of valuable blood donations.

Historical experience of blood use in MCEs has indicated held stocks of RBCs have been adequate for a hospitals' capacity to deliver them to casualties, however, despite this, there have been continued reports of the burden placed on blood banks, the need for emergency restocking during an event and the use of emergency public donation following MCEs which may challenge this popular zeitgeist (118, 124, 126, 129, 153). In addition to this, the nature of MCEs and the management of trauma continue to evolve. There have been significant increases in the frequency of all types of disasters and major emergencies in recent decades, growing urban population densities accompanied by the greater transport and housing infrastructures required to support them has increased the risk of MCEs, an issue further confounded by a continued and growing global threat of terror activity which itself specifically has not only grown but also evolved in its methods (89, 92, 154-158).

The USA September 11th attacks in 2001, the Madrid bombings of 2004, the London 2005 attacks and the Boston bombings of 2013 are just a few examples of how there has been a shift in the paradigm of terrorism, with translation of high energy mechanisms causing widespread severe injury from a more familiar battlefield setting across into the

unprotected and unprepared civilian environment (90, 131, 145). The previously unimaginable events of September 11th 2001 have been described as a 'catastrophic casualty anomaly' due to the disproportionate relationship between the resulting number of dead and the number of severely injured casualties. The argument has been postulated that if this relationship had been the reverse scenario, medical systems would have struggled to cope and the available medial infrastructure including blood provision therefore require greater attention (87, 90, 129, 153).

More recent years have seen a further migration of warfare style mechanisms making their way into the civilian terrorists' arsenal. The use of automatic weapons in Mumbai in 2008, Oslo in 2011 and Paris in 2015 illustrate an alarming threat which has the potential to create widespread high energy injury, generating an ongoing burden of critically injured casualties suffering major haemorrhage (159-161). Such events can also last for a protracted period of time, building to a crescendo over hours or even days (159). During this time emergency care systems may be hampered in their response, including the ability to restock local blood supplies and keep pace with the ongoing demands of arriving casualties.

In order to improve the emergency blood response and therefore optimise outcomes from future MCEs we must focus on several factors: avoiding the re-learning of lessons from past events, developing our understanding of the hospital blood system under such surge conditions, and anticipate the required responses for future scenarios which we have not previously experienced or even imagined possible. A systems analysis study using a modelling approach may offer a logistically and financially viable option for tackling these challenging issues and establishing an optimum response for blood provision during MCEs.

1.5 Systems, Models and Mathematical Solutions

1.5.1 Systems

The provision of blood following an MCE involves various systems which themselves are part of an overall health system providing care to the victims of these events. A system can be defined as any group of parts organised and interacting together towards a common purpose (162). Systems can be divided into those of natural occurrence or human creation. Human created systems have three subtypes: abstract, activity and physical (163). Examples of abstract and activity systems are concepts such as mathematical theory and political strategies respectively, whilst examples of physical systems include factories, vehicles and other human engineered or designed entities such as hospitals or health systems. An MTC is a complex system with a large number of interacting parts and people. Performing a system study allows us to understand complex systems better and improve or predict their performance under varied conditions. This can be achieved either through experimentation with the actual system or with the aid of a model of the system of interest (164).

1.5.2 Models

Experimentation during a live MCE is not possible; however, real hospital system experimentation under MCE conditions is common and continues to be undertaken across the world as a part of emergency preparedness drills. The advantage of these drills is they allow the full emergency plan to be conveyed to, and practiced by, all responding hospital staff. This ensures they are familiar with roles, protocols and the dynamics of the MCE response in the actual environment within which they work (87, 103, 165). The role-play

nature of these experiments is also particularly useful in identifying logistical issues such as conversion to unfamiliar hospital MCE specific documentation. The disadvantages of this approach are the requirement to close certain clinical areas during such an experiment as well as the need to divert resources and personnel away from regular public healthcare services (93, 165-167). The financial implications and impact on community healthcare provision often make such an experiment a rare or unviable option and whilst these drills have been shown effective in terms of training personnel for an MCE response, their role in improving planning for events remains unclear (165).

The alternative solution to real hospital experimentation is to carry out an investigation using a model of the system. A model in its most basic form is a simplified representation of reality (163, 168). Developing a model allows: description, interpretation, prediction or explanation of a phenomenon of interest (169). The type of model developed to investigate the system depends on the type of system being modelled. The process of identifying the type of system being considered, the various components from which it is formed and their relevance to the particular area of interest is termed a system analysis (170). A complex system such as an MTC which involves both human and non-human factors can be modelled both physically or mathematically (164).

A physical modelling approach could involve the creation of a mock-up hospital in a suitable building removed from the hospital or in a large open space where an MCE response could be acted out. A mock-up hospital experiment reduces the service disruption experienced during real in-hospital studies, whilst maintaining the ability to communicate plans and roles to staff. The primary disadvantages of this approach are that it still requires substantial diversion of expensive resources, and similar to real hospital experimentation, is restricted in terms of the volume and type of experiments which can be run during the time available (165, 171, 172).

An alternative approach to physical modelling of MCEs is to perform a series of table-top exercises using 2-D schematics of the hospital with a round-table expert discussion group playing out and analysing events (93, 99, 164, 165). This exercise allows for more scenarios

to be considered and with only a few lead figures involved, avoids any significant service disruption. Compared to real hospital or mock-up simulations, table-top planning can include multiple scenario considerations at a much lower cost as well as maintaining a focus on planning initiatives as opposed to staff training. The current UK NHS requirement of all hospitals is to perform both types of these physical models on a regular basis to ensure MCE plans are effective, robust, well communicated and practiced across all responding hospital staff levels (93).

These physical models offer an attractive tactile insight into how the MTC system responds during an event, however, as described, the experimentation yield of these models will always be constrained by the time, cost, and resource burden they demand. Another limiting factor in their use for MCE planning is the level of complexity that can be achieved in a purely human operated physical model, as all inputs and outputs must remain manageable and interpretable at a human level of understanding. Mathematical models offer a more time and financially efficient approach to system modelling. These models consist of a system under study, a question which relates to that system and a set of mathematical statements which may be applied in order to answer the question posed (170). As such they use quantitative relationships to demonstrate the input and output behaviour of a system. These relationships are described using equations, constants, functions and other mathematical expressions as building blocks, allowing improved understanding of complex systems through the analysis of numerical products (173, 174).

A mathematical model can be constructed through a black-box or white-box modelling approach. A black-box model is one built on describing a system through the direct relationship of experimental data inputs to their subsequent outputs, without consideration of intermediate relationships. This model type therefore maintains a purely implicit relationship between the data and the system being modelled and is best suited to experimentation of a largely incompletely understood or inaccessible system (169, 175). In contrast, a white-box model involves building a model which imitates the actual interacting components of the system and therefore maintains an explicit relationship between the model and experimental data. The level of approximations built into the model are

determined by the model purpose, the degree of *a priori* knowledge and the accessibility to the system of interest (169). The investigation of an MTC blood system during an MCE lends itself more towards a white-box modelling approach as it allows understanding and optimisation of individual processes within the system, as opposed to purely describing input-output relationships. Following construction of a black or white-box model, the model can then be solved in order to answer the questions proposed.

1.5.3 Mathematical Solutions

Solving mathematical models broadly requires either an analytical or simulation based approach. Model analysis involves numerical computation of the model's equations or algorithms to arrive at a derived solution, from which, observations and conclusions can be made regarding a system's performance (176). This method may involve techniques which include linear programming, queuing theory or differential equations to provide an exact solution to the model (174). As system models become more complex the mathematical techniques required to solve them analytically become more demanding, the computational time required to solve them increases and the likelihood of being able to find an exact analytical solution reduces (176).

The alternative method of model solving is through the use of simulation, which can be defined as the act of imitating a system (163). Solving a model using simulation involves the execution of repeated runs of the mathematical model to provide a series of model solutions, which collated together as a set of statistics can be interpreted to measure system performance and solve the model (176). Simulation models can be classified by several separate domains (177):

- Deterministic or Stochastic - Deterministic simulation involves no random or probability distribution based variables in the model, therefore the output is fixed

once the input parameters are inserted into the model. A stochastic simulation model in contrast contains variability in its construct based on known or estimated probability distributions. There is therefore variability in the outputs even when fixed input parameters are applied (164, 177).

- Static or Dynamic - Static simulations describe a system in a fixed state and are independent of time, whereas dynamic simulations are time-dependent and model a system as it changes through time (164, 177).

- Continuous or Discrete - When a simulation model measures constant changes in the state of its component variables it is referred to as a continuous simulation. Whereas, if the model measures variable state changes only at a fixed or interval based time points throughout a simulation run, it is referred to as discrete (164, 177).

The decision to model using these different methods is not fixed, but determined by both the type of system being modelled and the overall objective of the simulation project (164). In contrast to analytical techniques, simulation can reduce the experimentation time for complex models, incorporate and account for variability in the system and can manage uncertainty in a system through the application of assumptions in order to solve the model (163, 164, 176).

1.5.4 Mathematical Modelling in Healthcare

Mathematical modelling studies for the purpose of improving or solving problems in industry form part of a number of techniques employed within the overall framework of Operational Research (OR). OR takes its roots from World War II when the techniques it encompasses were used to solve logistical challenges associated with the war effort.

Following the end of the war, OR continued to grow in the context of emergency response with a shift in focus towards more public sector applications including healthcare (178). The increased popularity and perceived benefits of OR led to greater uptake and application of the practice amongst other industry sectors with OR now used by almost every business and governmental organisation in the world (179).

OR using mathematical models has seen diverse application in the context of the healthcare response to MCEs and disasters through a range of mathematical methodologies. The majority of these models have been developed within the remit of the pre-hospital care response, examples include: scene management using a scheduling and clearing model, triage decision making approached through linear programming and fluid models, emergency vehicle routing using mixed integer and constraint programming models, pre-hospital care team performance and casualty distribution studies using optimisation modelling, and scene casualty decontamination and resource capacity assessment using simulation models (178, 180-186).

Comparatively, the investigation of in-hospital based care during the response to MCEs through mathematical modelling is less abundant. One of the earliest examples being a study of surgical resource utilisation following urban terrorist bombings by Hirshberg et al in 1999 (187). This study used computer simulation to analyse and optimise the surgical care based elements required when responding to these types of event. The study identified mathematical simulation modelling as a beneficial and powerful adjunct to hospital based planning for MCEs. Specifically, this study found the assessment of a hospital's capacity to accept casualties from an event at that time as being overly optimistic. The reasons for this were found not to be due to bed availability as was expected, but in fact, a result of a limited number of the specialist personnel which would be required to care for them. Furthermore, the authors were able to use the developed model to illustrate the major bottlenecks arising in the hospital system during an event response. These primarily occurred in the queue to access the CT scanner and be transferred to one of the available shock rooms in the case of treating the most severely injured casualties (187).

One area of overestimation in the understanding of a required response at the time was that of operating theatre use. Whilst it was thought this resource would be of such demand only the most critical casualties could be permitted access to it, the simulation study showed this not to be the case and in fact non-immediately life threatening injuries could be operated on at an earlier stage in the event response. The results of this investigation were translated into hospital procedure for future events with an increase in the number of shock rooms and greater appreciation amongst stake holders of the expected availability of resources during such events (187). The ability to model variability and make the generalised assumptions necessary for planning such events is what allows a mathematical modelling approach to be applied across a wide range of scenarios and problems, providing quantitative results which can be interpreted and translated into real life practice.

Over the years which followed this initial application of mathematical modelling to in-hospital MCE response, there have been several other studies which have employed this methodology to develop our understanding of planning in MCEs. Hirshberg himself revisited in-hospital simulation of MCEs in 2005 with a study investigating the relationship between casualty load and the level of overall trauma care which could be provided to the victims. Here he and his colleagues identified the surge capacity of a responding unit and offered a quantitative definition of an MCE in terms of the overwhelming of a hospital's capacity to cope. The study showed the rate of casualty arrival as a principal determining factor in the ability to adequately treat casualties as opposed to an absolute resource or asset number (188). The rate of casualty arrivals following an MCE was also modelled through simulation by a group from Kansas State University in the USA (189). They describe mathematical modelling as a particularly powerful and effective tool in its application to MCE planning and preparedness. The findings of this study echoed those of Hirshberg et al in 2005, identifying the variation in a healthcare institution's ability to cope with the fallout from an MCE to be a related to the arrival pattern of the resulting casualties (188).

The specific investigation of consumable resources in MCEs using mathematical modelling has only been studied a finite number of times. Abir et al at the University of Michigan designed a mathematical model, again using a simulation approach to predict surge capacity

bottlenecks for burn mass casualties at hospitals (190). They found medical units in this case would be limited early in the course of such an event through their bed capacity, followed by consumable treatments such as Sulfadiazine, albumin and importantly, type AB PRBCs. This is the only mathematical model in the context of MCEs which discusses resource consumption in terms of blood products and does so solely in the context of mass burns casualties. Interestingly, other factors which were modelled as a part of this study which would be expected to provoke concern earlier than blood products when considering resource needs in an MCE setting, such as ventilator availability, were found to be adequately available for the needs modelled (190).

Other models of resource consumption and requirements include functioning generic prediction tools by the Chicago Department of Public Health and a surge model by the Agency for Healthcare Research and Quality (AHRQ) (191, 192). These provide an estimate needs assessment of resources based on the size and type of event by means of interactive stand alone or web-based programs respectively. Whilst providing an overall approximation of resource needs they do not consider the state of supplies available already at responding centres, neither do they map the consumption of these supplies as casualties are treated over time.

Although the predominant methodology of mathematically modelling MCEs in hospital has been through simulation studies, other rarer techniques have also been employed. A group in Israel developed a fluid network model to minimise mortality following an event by determining the most appropriate allocation of available surgical personnel between various treatment areas (193). As found by Hirshberg's group, this study by Cohen et al recognised the application of mathematical modelling to be a viable decision support tool which provides quantifiable results translatable to the real life system of interest (193).

1.6 Chapter One Conclusion

As traumatic mechanisms encountered and their frequency has evolved in both MCEs and conventional trauma, so have the techniques developed to manage them. New methods for; controlling active haemorrhage, implementation of pre and in-hospital trauma systems, and early instigation of major haemorrhage protocols through high dose coagulation therapy as a part of DCR, have all resulted in greater survival and an increase in casualty blood demands, both initially, and throughout hospital stays (28, 30, 41, 60, 78, 194, 195). The importance of blood in potentially reducing mortality from these MCEs therefore demands that future emergency preparedness strategies must include evidence based blood planning to improve outcomes.

This need for improved MCE blood planning has also been echoed elsewhere. The Centers for Disease Control (CDC) has described an uneven balance between the large amount of pre-hospital care research following these events and the comparative lack of hospital care based research (99). The Research and Development Corporation (RAND) carried out a landmark report in 2011 investigating complex trauma research in the UK. This report found trauma research to be underfunded compared to the burden of disease and identified several key areas of improvement which were required, these included: increased collaboration between military and civilian care providers and greater international dialogue to improve learning and share ideas, greater attention to strategic based thinking, further use of medical simulation in research activities and the need for disaster response modelling as a priority for future care improvement (4). The following study works to address some of these key issues and develop this under represented area of healthcare research using novel techniques common to other industry sectors.

1.7 Objective and Aims of Thesis

The overall objective of this study was to improve understanding of blood use in mass casualty events (MCEs) and develop strategies to improve packed red blood cell (PRBC) provision to casualties across a range of event sizes and applied conditions using a mathematical modelling approach. This was approached through the following six aims:

Aim One: **A Review of the Literature** - Investigate the use of blood in MCEs from a historical perspective to understand the challenges and controversies associated with casualty blood provision.

Aim Two: **Creating a Model** - Design a working mathematical model of the in-hospital provision of PRBCs to casualties following an MCE, in order to develop a greater understanding of the system and the effect a range of conditions and constraints have on outcomes across increasing sizes of event.

Aim Three: **Appraising the Model** - Evaluate the model using industry accepted standards and practices to ensure the developed tool is fit for purpose and suitable for experimental analysis.

Aim Four: Investigating PRBC Stock Management - Determine the effect variations in the management of in-hospital PRBC stock has on outcomes across event sizes in terms of the following experimental hypotheses:

Hypothesis 4A (H_{4A}) – There exists a critical ratio of MTC held PRBC stock levels to the casualty load received, below which, the ability to treat bleeding casualties effectively, becomes overwhelmed.

Hypothesis 4B (H_{4B}) – Outcomes following an MCE are greatest when a restock of an MTC's held PRBC volume occurs at the earliest opportunity in the timeline of an event.

Aim Five: Varying Laboratory Processing - Through the following hypotheses, investigate the influence on outcomes across event sizes following modifications to the transfusion service's protocols for processing and providing group-specific PRBCs:

Hypothesis 5A (H_{5A}) – Outcomes from an event can be improved by prioritising the laboratory processing of P2 casualties to provide group-specific treatment whilst preserving emergency type O PRBCs solely for P1s.

Hypothesis 5B (H_{5B}) – In addition to prioritising the blood group analysis of P2s, overall outcomes from an event can be further improved through restricting the processing of bleeding P1 casualties altogether, providing their treatment exclusively through the use of type O emergency PRBCs.

Aim Six: **Limiting PRBC Provision** - Identify by means of the following hypotheses effective strategies for improving outcomes when restocking of PRBC supplies at an MTC is not possible for MCEs of increasing magnitude:

Hypothesis 6A (H_{6A}) – Limiting individual casualty overall PRBC provision can improve overall outcomes following an event.

Hypothesis 6B (H_{6B}) – Overall outcomes can be further improved through additionally limiting all P1s to one 6U pack of emergency type O PRBCs, whilst also denying P2s treatment with this particular resource altogether.

CHAPTER TWO

Blood Use in Mass Casualty Events:

A Review of the Literature

2.1 Introduction

The first chapter illustrated the importance of blood in minimising mass casualty event (MCE) morbidity and mortality, as well as highlighting some of the potential challenges facing MCE blood planners today. Blood provision for future events will require development of transfusion services capable of ensuring adequate system resilience in order to cope with modern day casualty blood demands resulting from an ever evolving climate of civilian MCEs. The aim will be to maintain the equilibrium between sufficient on-shelf blood stock inventory levels, capable of satisfying blood demands across a range of events and scenarios, whilst simultaneously minimising the waste, costs and associated loss of public confidence related to the overstocking of blood banks. Transfusion practices must therefore be built around evidence-based figures of blood demand and provision. Similar to business continuity planning, such processes in part require the consideration of historical blood use data from previous MCEs from which future MCE blood management may be based.

Past blood demand prediction tools in trauma have focused predominantly on early individual casualty physiology and laboratory results to predict a dichotomous outcome of whether or not a massive transfusion (MT) will be required (196-199). Whilst applicable to individual casualties where information may be in abundance, in an MCE scenario such detail is often unavailable, both at planning stage and early in the course of the event. Predicting blood demands in this instance therefore requires broader population based descriptors of the casualty load. Studies of events, both in the military and civilian setting have previously suggested quantifying packed red blood cell (PRBC) requirements by units used per casualty, or per hospitalised casualty, however, these have always been based around single centre experiences and focused purely on events of a terrorist nature (124, 139, 200). In conjunction with this, transfusion strategies in trauma have evolved significantly in recent years with the advent of damage control resuscitation (DCR) utilising early high dose

coagulation therapy alongside PRBCs to prevent and treat coagulopathy, the effects of which on MCE management have not been clearly established (28, 41, 60).

The objective of this chapter was to investigate the provision and use of blood in MCEs based on historical events in order to better understand blood consumption in MCEs and further inform future planning strategies. This was performed through the following four sub-aims. The first was to assess the degree and adequacy of the reporting of blood provision and utilisation across a full range of civilian MCEs. The second was to determine whether a predictive relationship exists between blood use and available casualty profiles. The third sub-aim was to determine whether any existing relationship is affected by the nature of the event itself. The fourth and final sub-aim was to investigate the effect that current trauma transfusion practices would have had on blood demands during previous events.

2.2   Methods

A comprehensive literature search was performed reviewing blood use in civilian MCEs over the last hundred years. A more standard methodology of performing a systematic review based around a specific question and using the mapping of search terms to such headings as: population, interventions, outcomes and effects, as applied in other literature based studies was not appropriate for this particular investigation (201). This was primarily due to the nature of the information the search aimed to provide. Whilst there maybe numerous reports of MCEs in the literature, assimilating all available descriptions of blood provision during these events is challenging. This is because although the data may be recorded within a specific MCE report, it might not have formed the primary or even secondary focus of the article. A more protracted methodology was therefore employed in order to maximise the degree of applicable qualitative and quantitative data included in the

study, whilst also maintaining the best-practice search selection and appraisal of evidence methods common to a more typical systematic review (202).

The comprehensive literature review included a search of eight electronic scientific databases: PubMed, Medline, The Cumulative Index to Nursing and Allied Health (CINAHL), the Excerpta Medical Database (EMBASE), the Allied and Complementary Medicine Database (AMED), the Health Management Information Consortium (HMIC), the British Nursing Index (BNI) and the Health Business Elite archive. The databases were accessed via two web-based portals: National Health Service (NHS) Evidence (www.library.nhs.uk) and the National Centre for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov). The search was performed over a 100 year period from the 1st November 1911 through to the 31st October 2011. Search terms were identified in relation to two subject headings, one regarding the population of interest, this being victims of MCEs and one regarding the intervention of interest, which was the provision of or requirement for blood by a casualty. The search terms applied across the databases included the use of free text terms as well as mapped subject headings (MeSH headings) when available.

The database search was complemented by a search of the grey literature to identify unpublished data, as well as official governmental and non-governmental organisational reports of both past events and MCE planning procedures. These were searched for via academic search engines including: Google Scholar, the Education Resource Information Center (ERIC), the Bielefeld Academic Search Engine (BASE) and the New York Academy of Medicine's grey literature (NYAM) report. A full list of all applied search terms, strings and application of Boolean operators is provided in the detailed description of the search strategy and its results in Appendix I.

All search results were collated and their individual titles examined for any article which described MCE planning strategies or discussed the response to either collective or individual events. The wide international and regional variations in the definition and description of MCEs required an adaption to the MCE definition provided earlier in order to ensure an all-inclusive search of the literature. For the purposes of this comprehensive

review an MCE was therefore defined as; any incident producing many injured patients and creating either a resource burden for the responding healthcare facilities or involving injury to at least ten casualties (89, 203). A number of additional criteria also needed to be satisfied in order to be included in the study, these were as follows:

1. Studies had to relate only to human subjects.
2. Articles had to be written or translated into in English.
3. Any discussed 'event' was required to be 'man-made', thus excluding natural disasters, which as discussed, can result in the unpredictable loss of infrastructure affecting the ability to mount any sort of medical response.
4. All discussed 'events' had to be predominantly civilian in nature, therefore reducing data confounders such as body armour or a likely narrow population in terms of physiology as seen amongst military cohorts. However, this did not preclude civilian MCEs which either occurred in a military environment or were reported by a military organisation.

Following the application of these limitations and removal of duplicate citations, the titles of all collated results were screened for subject relevance and shortlisted for further review of the associated abstracts. The selected article abstracts were interrogated by two independent reviewers to establish a final list of articles for which the full-text article was sourced. All articles selected by both reviewers were included in the full-text review phase of the search. The full-text articles were assessed and critically appraised for study relevance using the principles laid out by the Critical Appraisal Skills Programme (CASP) (www.casp-uk.net/). Those articles unavailable in electronic format were requested as hard copies from the relevant publishing institution or accessed through alternative local resources including university and national libraries. The range and breadth of the literature search was further widened through the inspection and where applicable, collection of all the relevant articles referred to within the reference sections of the reviewed articles.

Reports of events were collated and analysed for data regarding casualty profiles and respective blood product utilisation. The following definitions were applied to produce consistency in reported values; an 'event' was considered to be a single entity if it was reported as such or occurred on the same day in the same geographical location. The mechanism of injury (MOI) was taken as the primary event that occurred with other major causes of injury also mentioned if likely to contribute to immediate patient morbidity or mortality. The number of injured was the reported number of people involved in the entire incident and reported as injured or requiring medical attention. If no other figure was available the number of patients reported on was used. This did not include the number of immediate deaths or deaths pre-hospital. The number of casualties hospitalised was the number of living casualties received by the reporting hospital or hospitals. The number of casualties admitted included all those admitted to the hospital beyond the emergency department and finally, the number of severely injured casualties was the total number of casualties classified as having an Injury Severity Score (ISS) greater than 15 (14).

In terms of blood descriptors, the general term red blood cell (RBC) units (U) was used to encompass all PRBC units or equivalent and whole blood units in order to account for variation in service provision and the evolution of transfusion services over the search period. RBC use, as with all other products considered (Fresh Frozen Plasma (FFP), Platelets (Plts) and Cryoprecipitate (Cryo)), was the number of units used within the first 72 hours of the event. The 72 hour time period was selected to account for delayed and repeat procedures during the recovery phase of an event and to ensure the capture of blood use related to casualties arriving over prolonged periods. This timeframe also allowed insight into the need for restocking of blood and encompassed the period during which restocking would be most challenging. If the blood use was reported over a longer period, it was noted but not used in the graphical data or further analysis, if not stated it was assumed to be within this immediate timescale. One unit was taken as a standard measure for all products and not volume adjusted for between individual institutions or countries. It was also assumed that unless stated all blood delivered and discussed was required and transfused.

Examination of events and blood use required the collaboration of several reports of individually named incidents to improve completion of the dataset and provide an overall account of each MCE. This was only possible when the datasets correlated, for example, individual reports of the same event from the same hospital or authors. When there were discrepancies in the reported values between individual authors, the primary source data was used. When there were two or more primary sources the mode value was selected, or the arithmetic mean if only two reports were available. The collated data was later grouped into type and associated MOI to investigate potential correlations between events of a similar nature or outcome and blood requirements. Events were divided into four groups: terrorist attacks of any type, bombing incidents (inclusive of summaries of events where bombing was the dominant MOI, but excluding events involving a structural collapse), non-terrorist related MCEs and events involving a structural collapse as a primary or secondary event.

The effect of current transfusion practice on the blood demands in MCEs was investigated by comparing actual MCE blood use, with the equivalent use, had current trauma haemorrhage protocols been in operation at the time. A 1:1 ratio of RBCs to FFP, Plts and Cryo based on current guidance was applied to individual MCEs with component requirements based on the original RBC use during the event (60, 77, 204). Due to the nature of blood reporting in these events it was necessary to make the general assumption that all patients requiring initial transfusion would have qualified for activation of a current major haemorrhage protocol (MHP) and therefore, high dose coagulation therapy based on RBC demand. This was done with the aim of illustrating potential effects modern transfusion strategies may have on future events and is not suggested as a predictive method. All data analysis was performed in Microsoft Excel (Microsoft Corp. Redmond, WA, USA). Unless stated, a p-value of <0.05 was considered significant in all statistical analysis.

2.3   Results

The initial literature search identified 31,263 citations across all of the databases searched. From these results and following the application of the study limitations as well as the removal of any duplicate citations, 1,592 article abstracts were suitable for assessment by the two independent reviewers. The interrogation of the collated abstracts provided 262 full-text articles discussing specific or collective MCEs. 28 (10.7%) described quantitative blood consumption in single or multiple MCEs and seven (2.7%) focused on blood use and supply as a primary objective (118, 119, 124, 126, 127, 129, 139, 140, 205-224). The 28 articles combined with collaborative accounts (84, 121, 133, 158, 225-236) provided a total of 34 reports of individual MCEs with documented RBC consumption (Figure 2.1). Three reports were further excluded from the data analysis: one had reported blood use in excess of the 72 hour defined period, the other two were summaries of events, from which the MOI could not be ascertained, or whether they individually met our designated criteria for a MCE (118, 219, 220). The final analysis therefore included 31 reports covering 51 MCEs occurring over a 30 year period and giving as a minimum, initial casualty numbers and their corresponding RBC consumption (Table 2.1).

The reporting of casualty numbers and injury severity for all events was considered initially. The median number injured per event was 55 (inter-quartile range (IQR) 42-195) across all events and of those, a median of 38 (IQR 23-158) were taken to hospital. The median number of casualties admitted beyond the emergency department (ED) was 36 (IQR 18-84). Details of casualty injury severity was available for 61% of MCEs, with ISS recorded for 50% of the events, a triage priority score for eight percent of events and both scoring systems provided for just four percent of events (119, 213, 237). The median number of casualties termed as severely injured per event was 25 (IQR 8-31) and 18 (IQR 7-26) where ISS >15 classification was applied. Overall the 51 MCEs discussed in the study involved a total of 11,821 casualties of which at least 211 were severely injured.
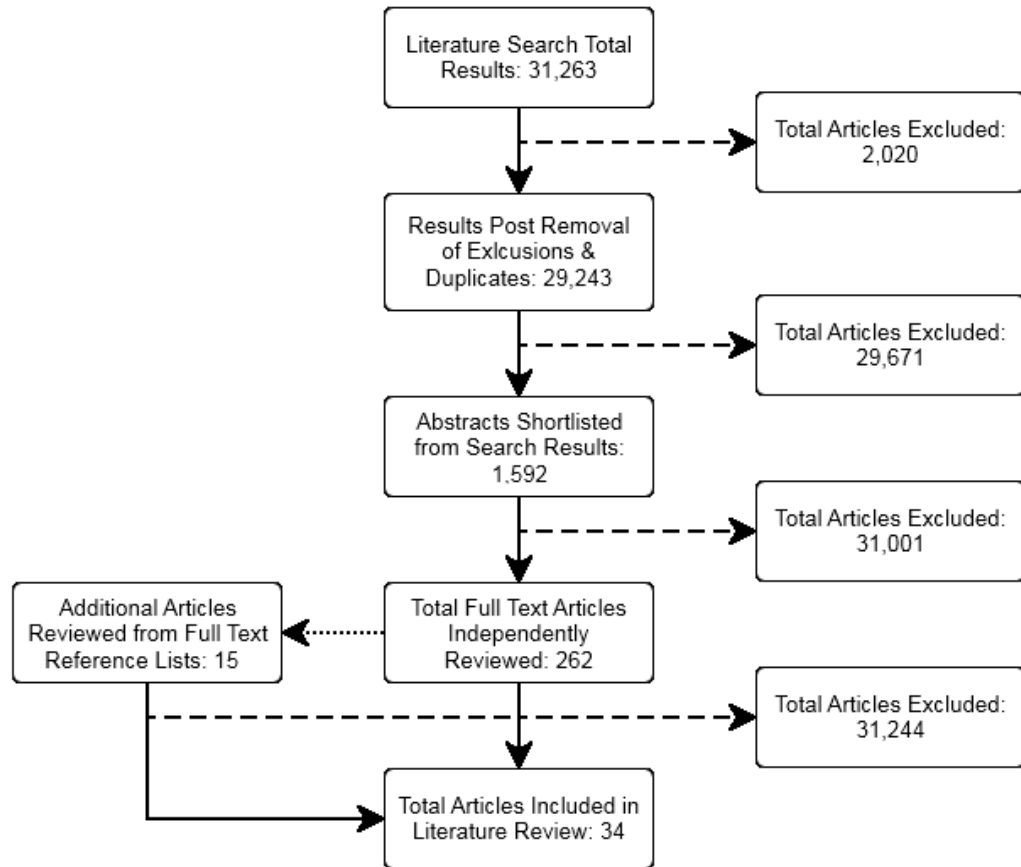
Figure 2.1 A flowchart representation of the search strategy and results for each stage of the comprehensive literature review.

All MCE reports included in the study described RBC use within the first 72 hours of an event. During this period the total RBC use for all events was 3,455U, with a median use per event of 38.0U (IQR 15.5-137.5U). The transfusion of packed RBCs was specified in 71% of events, whereas eight percent reported the delivery of both whole blood and RBCs. Only one event in 1989 was documented as using exclusively whole blood for all transfusions (208). 20% of events were reported using solely the term 'units of blood'. Reporting of blood usage at more than one time point during the initial 72 hours of an event was provided for two thirds of events. From these events, 11 (22%) reported transfusions within four hours and at 24 hours showing that between 62% and 74% of the total RBC requirement in the first 24 hours occurred within the first four (139, 209, 216). The majority of red cell transfusions are therefore delivered within the first few hours of an

event. During this period prior to the availability of type-specific or fully cross-matched RBCs, type O emergency RBCs will form the mainstay of transfusions.

Type O RBC data was available for 53% of events (124, 140) with 27% (IQR 18-40%) of all RBCs transfused per event being type O. There is therefore a heavy reliance on emergency type O RBCs during the acute phase of the MCE response. Individual hospital stocks of RBCs by blood group were provided by only two reporting units from the 51 events, one described holding on average 57U of type O and 110U of other blood groups whilst the other stated an inventory of 189U of type O and a 145U mix of other groups (124, 139).

Transfer of large numbers of casualties from emergency type O RBCs onto group-specific or fully cross-matched RBCs requires adequate staffing levels in the transfusion laboratory to manage the surge in sample processing required. Fully quantitative transfusion laboratory staffing levels were provided by just two of the reporting units across all events. One unit described utilising a staff of eight to manage all sample processing for the event, whilst the other reported a range of staff availability during the nine events it responded to numbering between two and six depending on the time of day (139, 219). Adequate staffing levels are critical to managing blood provision during MCEs, particularly in ensuring timely transfer of casualties onto group-specific blood products in order to conserve levels of emergency type O RBCs.

Table 2.1 MCE casualty statistics and blood component use within the first 72 hours

Blood products expressed in units, (MVC) Motor Vehicle Crash, (SC) Structural Collapse

Year	Country	MOI	Injured	Hospitalised	Admitted	Severe	RBC	FFP	Plt	Cryo
1977	USA	Train Crash (205)	178	175			25			
1978	USA	Plane Crash (205, 225)	175		22		6			
1980	Italy	Bomb / SC (84, 207)	218	218	181	25	100			
1981	USA	SC (129, 205)	188	188			126	23	32	10
1984	USA	MVC (140)	51	17	10		14.5			
1989	UK	Plane Crash (208, 227, 236)	88	86	84	26	596	59	91	
1989	USA	Plane Crash (129, 226)	185	185			119			
1991	UK	Bomb (209)	51	30	30		226			
1994	Argentina	Bomb / SC (84, 210)	202	84	41		201	97	63	76
1995	USA	Bomb / SC (84, 121, 129, 228, 229)	593	434	83		300			
1996	Israel	2 Bombs (211, 230)	86	17	17	15	29			
1997-2005	Israel	16 Bombs & 2 Shootings (124)	986	498	251	50	332	92	72	148
1999	USA	Shooting (129, 231)	30	30			105			
1999	UK	Bomb (212, 222, 224)	84	40			150	69	29	31
1999	India	Train Crash (223)	800	103			17			
2001	Serbia	Bomb (213)	21	13		4	25	5		
2001	USA	Plane Crash / SC (84, 129, 153, 232, 233)	3922	1103	139	55	224			
2001	USA	Plane Crash / SC (129, 153, 215, 234)	106	106	49		34			
2001	Israel	Bomb (139, 158)	38	19			38			
2002	Israel	Bomb (139, 158)	34	30			27			
2002	Israel	Bomb (139, 158)	52	10			16			
2002	Israel	Bomb (139, 158)	44	44			14			
2002	Israel	Bomb (139, 158)	40	11			9			
2003	Israel	Bomb (139, 158)	36	36			64			
2003	Israel	Bomb (139, 158)	50	31			15			
2004	Spain	10 Bombs (126, 216-218, 235)	1885	312	90	26	145	60	75	
2005	UK	4 Bombs (119, 133, 221)	722	194	27	10	130	46	11	70
2005	Israel	Bomb (139, 158)	37	33			15			
2005	Israel	Bomb (139, 158)	67	21			6			
2006	India	7 Bombs (139, 158)	817	76			175			
2008	Iraq	3 Bombs (127, 206)	50	50	50		172	190	114	

Prediction of RBC needs in MCEs is reliant on broad casualty descriptors to be effective. In order to inform future planning, the relationship between all available descriptors of casualty populations and RBC use was investigated to identify which casualty profile most closely associates with subsequent RBC use. RBC consumption as a function of the number of casualties injured, hospitalised and admitted in each MCE is shown in Figure 2.2 A-C respectively. Median RBC use was 0.3U (IQR 0.2-1.0U) per injured person, 0.8U (IQR 0.5-2.0U) per hospitalised casualty and 1.7U (IQR 1.4-4.5U) per admitted casualty. No correlation was found between these casualty profiles and RBC use per event. Based on the findings here these broad casualty profiles do not appear to offer a predictive benefit in planning blood needs for MCEs.

Previous MCE studies show the majority of severely injured patients arrive in the first four hours, which corresponds to the observed time of maximal RBC use in this study, the decision was therefore taken to investigate whether this narrower population correlated with RBC need during an event (111, 119). The median and upper quartile RBC use per severe casualty was 5.9U and 8.2U respectively (IQR 4.0-8.2U). There appears to be a better association between RBC use and number of severely injured casualties than seen with other casualty profiles, however, this did not reach statistical significance (r^2 = 0.2, p = 0.23). Overall pure numbers of casualties and their injury severities seem to be poor predictors of subsequent red cell usage.

Together with casualty profiles, the impact type of event and associated MOI may have on blood use in MCEs was also investigated. The median RBC use for related MOI and casualty profile is shown in Table 2.2. Terror events made up over 86% of the data set and therefore the relationship between blood use and casualty profiles within this cohort was investigated further. The correlations between number injured (r^2 = 0.26, p = 0.01) and hospitalised (r^2 = 0.34, p < 0.01) with RBC use in terrorist events alone, were better than when all events were considered collectively. There was also a close and significant relationship (r^2 = 0.75, p = 0.01) with a median RBC use of 5.6U (IQR 4.0-6.5U) per severely injured casualty across these terrorist events (Figure 2.2 D). A lack of data prevented analysis of casualty

profiles with other MOI, although, the combination of severely injured casualties and MOI appears to offer potential as a predictor of RBC needs in MCEs.
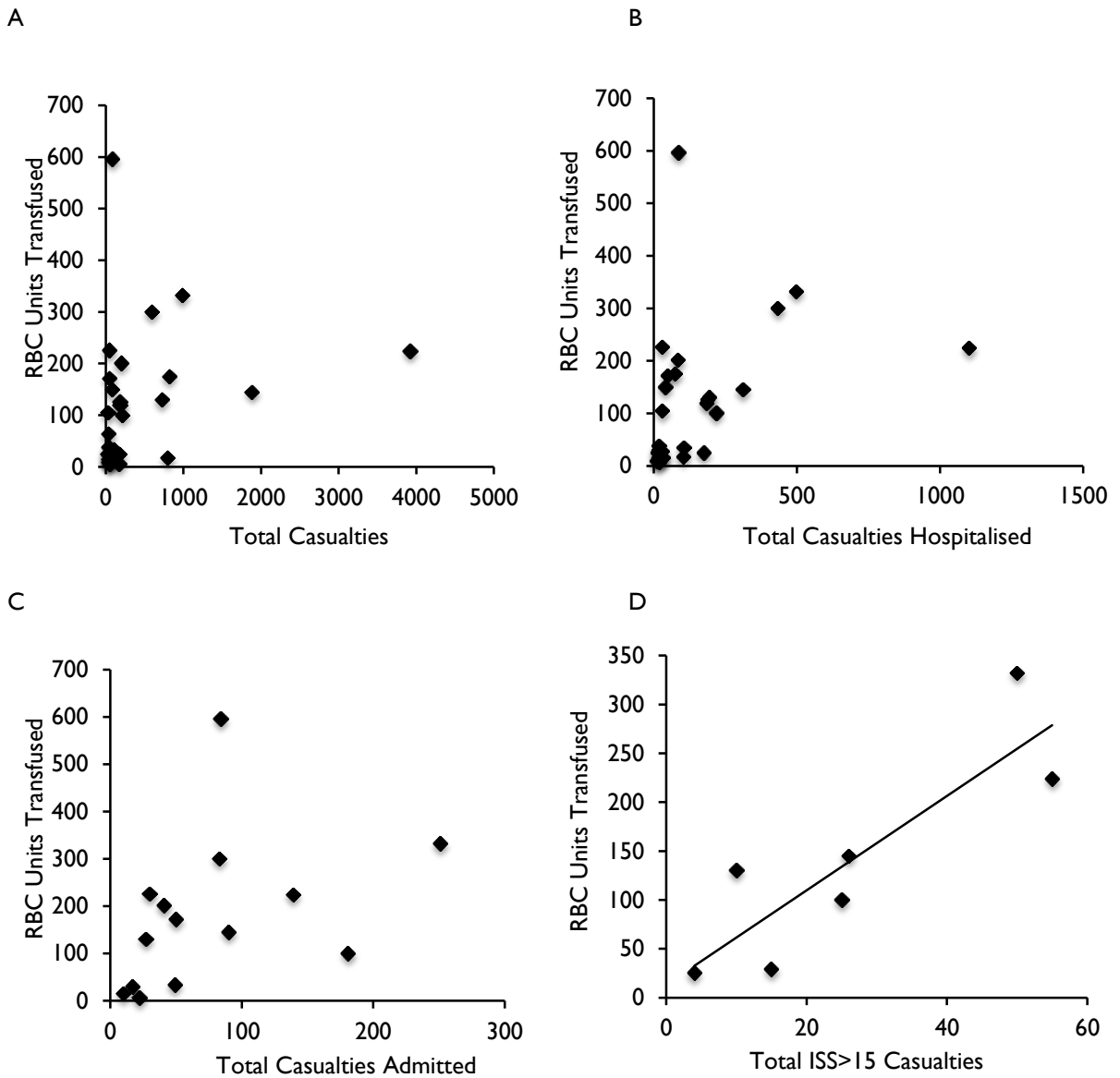
Figure 2.2 RBC Units transfused in relation to casualty profiles. A: Total injured patients per MCE against total RBCs transfused. B: Total hospitalised patients per MCE against total RBCs transfused. C: Total admitted patients per MCE against total RBCs transfused. D: Total number of ISS>15 casualties per Terror related MCE against total RBCs transfused (r^2 = 0.7453). RBC units included all types of red cell transfusion including whole blood. Correlations where presented are significant at p<0.05.

Table 2.2 Median RBC use per casualty profile by mechanism of injury

Casualty Profile	Terror Events	Bombing* Events	Non-Terror Events	Structural Collapse Events	All Events
Injured Patient	0.4 (24)	0.3 (18)	0.3 (7)	0.5 (6)	0.3 (31)
Hospitalised Patient	0.9 (24)	1.3 (18)	0.7 (6)	0.6 (6)	0.8 (30)
Admitted Patient	1.7 (11)	2.6 (6)	1.5 (3)	1.6 (5)	1.7 (14)
Patient with ISS >15	5.6 (7)	6.3 (5)	22.9 (1)	4.0 (2)	5.9 (8)

*(Number of observations). *Excluding any structural collapse. All values expressed in units (U).*

Current damage control resuscitation (DCR) strategies demand much higher volumes of blood components alongside RBCs than previously used. Ensuring adequate supplies of these products for MCEs could be argued as being equally important for planning as RBC supply. All three of the components (FFP, Plts and Cryo) were reported for fewer than half of the events. FFP was the most reported product with data available for 55% of events, Platelet use was recorded for 53% and Cryo transfusions available for 43% of events. The ratio of these products used during the event was specified for just two percent of MCEs (127, 206). Overall, component use in all events totalled 641U of FFP, 487U of Plts and 335U of Cryo with median use per event of 60.0U of FFP (IQR 46.0-92.0U), 67.5U of Plts (IQR 31.3-79.0U) and 70.0U of Cryo (IQR 31.0-76.0U). In terms of relationship with casualty profiles, there was no correlation between number of injured or hospitalised patients and component use, and too few observations were available for the remaining profiles, including severely injured casualties. Ratios of components based on RBC predictions maybe the only option for planning component needs given the data currently available.

How DCR in future MCEs may affect component supply and demand has yet to be investigated. Whilst data for component use in severely injured MCE patients was lacking in the literature review, there was still some overall individual event data available. The hypothetical effect a 1:1 ratio of RBC to FFP and Plts would have, if employed during these

previous events based on the RBC usage at the time was therefore considered. This study required the assumption that all those requiring RBCs would also require component therapy (Figure 2.3 A & B). The median ratio of FFP to RBC was 0.4 (IQR 0.2-0.4) and Plts to RBC was 0.2 (IQR 0.2-0.4). Taking one event as an example – the skywalk collapse in a Kansas hotel in 1981, the responding hospitals would have required availability of an additional 103U of FFP and 94 units of Plts to achieve a 1:1:1 ratio with RBCs transfused, this is four and three times respectively what they actually used and indicates the significant shift which DCR has brought about in component use. One event reviewed did in fact state the use of a current 1:1:1 strategy, and delivered a ratio of 1:1.1:0.6 (127, 206). Employing current DCR methods would appear to have required far greater availability of components to meet demands in past events based on RBC use.

A

B
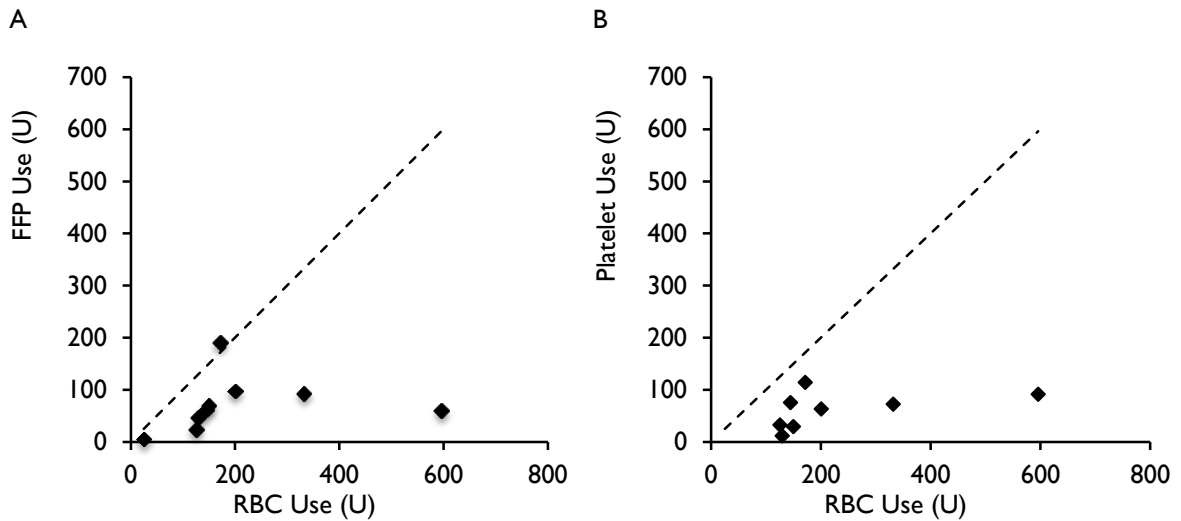
Figure 2.3 Blood component use in relation to RBC Units transfused per MCE (---). A: FFP use as a function of RBCs transfused per MCE. B: Platelet use as a function of RBCs transfused per MCE.

2.4 Discussion

This was a comprehensive study of reported blood use in MCEs spanning 100 years. While the quality and consistency of reports has improved over time, there is a clear need for improved reporting of blood use and casualty statistics in MCEs. RBC consumption was shown to be greatest early in the course of events and requires significant on-shelf RBC stocks in order to satisfy the surge in demand. The number of severely injured casualties was most closely associated with RBC use, particularly for terrorist events; unfortunately, there was little information on the use of blood component therapy. Despite this, utilisation of FFP and other components was significantly lower than recommended by current DCR strategies. In order to provide DCR under surge in MCEs, hospitals would need to hold adequate stocks of all blood products in their inventory or decide to target lower ratios in order to conserve resources for the largest number of casualties.

No report has previously looked at the standards of blood reporting across all types of man-made civilian MCE. Previous studies have been limited to single countries or single hospital experiences (124, 129). Blood has been shown to be a key resource in MCE management and a lack of availability impacts directly on patient care. In the last 30 years, over 6000 'man-made' disasters have occurred worldwide (97). However, the literature search produced just 51 events with blood use availability, indicating the overall inadequacy of reporting in this area. In addition, the level of reporting and detail provided differs widely between reports. Centralised reporting of disasters as carried out by organisations such as the World Health Organization (WHO) collaborating Centre for Research on the Epidemiology of Disasters, whilst effective in providing general data and event overviews, remain third party investigators (97). They are therefore precluded from adequate access to blood use and casualty profile data. The onus must be on centers responding to incidents to adequately report this data, and guidelines are needed to ensure this is conducted in a standardised manner.

A relationship was identified between severely injured casualties and RBC use in terrorist MCEs. The median RBC requirement for severe casualties in terror events was 5.6U and the upper quartile was 6.5U, which is similar to the 6.7U per moderately and severely injured casualty suggested by Shinar and colleagues in their review of terrorist events in Israel (118). These severe casualties classically present within the first four hours and our study illustrated that over two thirds of RBC use was transfused in this time. This is consistent with a previous study where over half of RBCs used in the first 48 hours were administered in the first two hours (124). There is a clear need for designated receiving hospitals to hold adequate RBC stocks at all times as restocking within this timeframe would be challenging.

The DCR approach and our understanding of coagulopathy in trauma require that greater consideration is given to components such as FFP, Plts and Cryo during MCE planning (62, 238, 239). The reporting of these blood products also needs to be improved. In previous reports existing blood supplies are usually declared to have been sufficient. Whether this remains true given modern transfusion practices is unclear (205). This study demonstrated the significant effects of applying current transfusion protocols to previous MCEs. Unfortunately, it was not possible to ascertain if supplies would have been exhausted during these events under these protocols. Whilst appreciating it is a generalisation that all casualties requiring RBCs would require coagulation therapy and achieving a 1:1:1 ratio may be unnecessary (62), component demand will almost certainly still increase and the importance of this demands greater attention in the reporting of these events.

2.5   Limitations

This study was limited in a number of ways. Firstly, was the assumption that a unit of blood was of equal volume when considering data from different countries and at differing time points. This information was not made available by individual articles and definitions of blood use prevented sourcing the information from elsewhere. Secondly, evolution in transfusion practice and local protocol changes could not be applied with any certainty and may have affected blood use over the 30 years reported. Third and finally, apart from the low number of reports overall, the reliability of reporting given the nature of MCEs may have led to inaccuracies in the dataset.

2.6   Chapter Two Conclusion

The reporting of blood use in MCEs clearly requires improving in order to better prepare for future events. The combination of the changing nature of MCEs, a DCR approach and new traumatic haemorrhage control strategies are likely to place a major strain on all blood component stocks. Both clinical and transfusion services will need to develop new strategies to manage this demand for future events. Relationships appear to exist between casualty statistics and RBC requirements which offer potential as a future guide to stock needs, however, the limited data currently available to planners and the complexity of the system, demands the consideration of an alternative method for blood planning beyond a straight forward units per casualty approach.

Furthermore, the heavy reliance on blood supplies in the initial stages of an MCE, especially type O PRBCs indicates any alternative planning approach would need to focus on stock

management as well as in-hospital on-shelf blood levels. In the past other areas of transfusion service planning have been investigated and seen improvements through the application of a system modelling approach (240, 241). However, this methodology has not previously been explored in the context of MCE blood management. Based on this assessment, the overall study objective of creating a mathematical model with which system resilience and operating procedures can be tested across a range of event sizes and conditions, appears valid. This chapter has satisfied the first aim of the thesis, identifying the key challenges and controversies in providing casualties with blood following these events. The chapters that follow describe the development and evaluation of the mathematical model for exploring in-hospital provision of PRBCs to casualties following an MCE.

CHAPTER THREE

Modelling Strategy & Development

3.1   Introduction

3.1.1   Best-practice in Healthcare System Modelling

The review of literature performed in Chapter Two provided a foundation for the development of the mathematical model required to meet Aim Two of this study. This chapter and the one which immediately follows sought to satisfy these aims through a fully accountable and transparent process based on recognised industry standards. In 2011 the International Society for Phamacoeconomics and Outcomes Research (ISPOR) and The Society for Medical Decision Making (SMDM) formed a joint task force (ISPOR-SMDM). This entailed widespread representation both internationally and from a multitude of industry sectors comprising experts in the application of modelling to complex problems. The aim of the joint task-force was to set out a number of best practice guidelines for the development of healthcare models designed to inform medical decision making and the allocation of scarce healthcare resources (242). These guidelines therefore formed the basis for the design and development of the study's model.

The ISPOR-SMDM identifies the first step in any mathematical modelling process to be the conceptualisation of the model. This is performed through a statement which encompasses a description of the following factors: the overall objective of the simulation study, model constraints, its rationale, the analytical perspective, the target population, outcome measures, planned interventions, various data input sources, a time horizon and the application of the model (242). The conceptualisation process is designed to ensure there is clarity regarding the model in terms of its purpose, the level of complexity and detail it will involve as well as the boundaries of the system within which the model must remain. Following this process allows the investigator to establish the modelling technique which

provides the best-fit for the study's structure and constraints and ensures the model remains fit for purpose (242, 243).

3.1.2 Conceptualising the Model and Selection of Modelling Style

- Statement of Model Objective – The model objective was to satisfy Aim Two of this study:

  'Design a mathematical model for developing strategies to improve packed red blood cell (PRBC) provision to casualties across a range of mass casualty event (MCE) sizes and applied conditions.'

- Model Constraints - The model was limited to a single generic UK based major trauma centre (MTC) and included only the systems involved in the provision of PRBCs to casualties suffering, or at risk of traumatic haemorrhage. Due to the relatively recent changes in component use within damage control resuscitation (DCR) and the comparative lack of data in the literature regarding blood component use outside of PRBCs it was decided to concentrate primarily on PRBC management in the initial model. The model could then be modified at a later date depending on the success of this original study. The basic process flow map of the conceptual model is shown in the Business Process Model and Notation (BPMN) diagram below (Figure 3.1)

- Rationale - There has been a well described increase in the frequency of MCEs, especially involving conventional terrorist activity. The financial and resource burden required in order to develop adequate response plans suggests a mathematical model would be advantageous over alternative planning solutions.
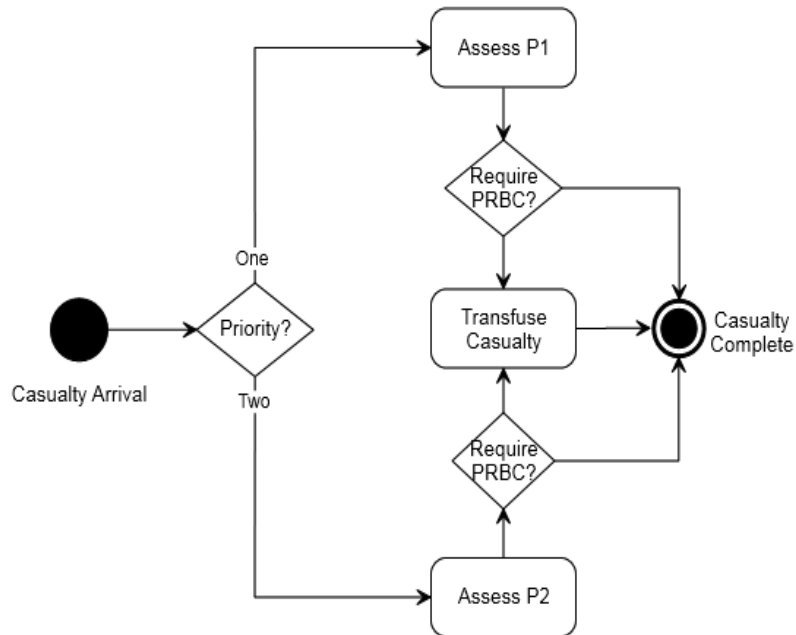
Figure 3.1 BPMN diagram of the conceptual model.

- Analytical Perspective - Societal, based on achieving the greatest good for the greatest number (84, 87, 102).

- Target Population – All priority one (P1) and two (P2) casualties resulting from an MCE. The priority system was chosen as it is specific to MCEs and by definition only P1 and P2 casualties would suffer from traumatic haemorrhage likely to require a transfusion.

- Outcome Measures - The two principal outcome measures were:

  1. The percentage of bleeding P1 and P2 casualties receiving their required level of transfusion within the time allocated by their triage category (within one hour for P1s and four hours for P2s).

2. The time point at which emergency type O PRBC inventory levels were exhausted (a surrogate for the inability to treat and therefore receive further bleeding casualties).

- The Interventions - The various interventions will focus on the three key areas as laid out in Aims Four, Five and Six of the study and respectively included:

  1. Varying the quantity of held PRBC stock at the MTC prior to the event as well as the ease of restocking these supplies further following during an event.
  2. Modifying the protocol for processing casualty blood samples for the provision of group specific PRBCs as well as the distribution of emergency type O PRBCs based on a casualty's severity of injury.
  3. Limiting the provision of PRBCs to casualties both overall and with respect to emergency type O PRBCs.

- Data Sources - Input data with which to inform the model were derived from a number of primary complimentary sources, including:

  1. The comprehensive literature review of blood use in MCE performed in Chapter Two.
  2. Discussion with all established MTCs in the Greater London area of the UK.
  3. Interrogation of available civilian and military trauma datasets where required and if deemed applicable to the study.

- Time Horizon -The model covered the first 72 hours from the time of the first P1 or P2 casualty arrival at the MTC. This time period therefore encompassed the crisis, consolidation and start of the recovery phases of the MCE, during which time blood is in greatest demand (105-107).

- Model Application - The model was designed to be adaptable to global health systems operating with equivalent trauma system setups. Input data applicable to the local population and service protocols can therefore be used to inform the model and the outcome interpreted specifically for the society being served.

3.1.3 Selection of Mathematical Modelling Methodology

The ISPOR-SMDM joint task force recommends the use of simulation and specifically the use of discrete event simulation (DES) for mathematical models which involve the following components:

- Human and system interactions
- Individual patient modelling as opposed to cohorts
- Models covering a relatively long time horizon
- States in which the numeracy rapidly becomes intractable
- Determining the allocation of scare resources and resource competition problems
- Waiting lists or queue minimisation measures

The latter two components are problems which DES was specifically designed to confront and all of the above are factors common to this particular study model (242). Along with the inherent uncertainty and wide variability familiar to both MCEs and all human centred systems including healthcare provision, the evidence suggests a simulation technique would be the most appropriate method for solving this type of model. In addition, the investigation of the system over the time course of an MCE and particular interest in resource allocation suggests the DES methodology would be the most suitable and efficient method of simulation.

3.2 Appraisal of Discrete Event Simulation Methods

3.2.1 Introduction

Simulation modelling confers a number of advantages over the alternative modelling techniques available depending on the type of system being modelled. The advantages can be broadly described by the general benefits of a mathematical modelling approach over real-world experimentation and those specific to the practice of DES itself. There are also a number of limitations to simulation which both model designers and those interpreting a model's output must be aware.

3.2.2 General Advantages of Mathematical Modelling

- Specific System Understanding:

  Mathematical modelling permits the appreciation of why certain specific phenomena occur within a system through the recreation of a previously observed system state. The detailed examination of the system under such specific circumstances maybe impractical or impossible using real-world experimentation (243).

- System Exploration:

  Following development of a valid mathematical model the operator is allowed the freedom to experiment with the system without ethical, legal or resource constraints. New tried and

tested policies can then be implemented through translation to the real system, where such experimentation may be extremely limited or altogether unviable (243).

- Experimental Control:

In experiments investigating alternative system designs, a mathematical model allows the operator to control other experimental conditions and confounding factors to ensure a direct comparison can be made. Additionally, experimentation bias such as the Hawthorne effect of modified human behaviour based on awareness of their involvement of an experiment can also be prevented through such a model (163).

- Financial Efficiency:

Mathematical modelling is often significantly less expensive than real-world or physical modelling investigations in terms of the ratio of cost to information yield. As discussed previously, real or physical model experiments require resource acquisition and prolonged service disruption, both of which can be highly expensive. Mathematical studies such as simulation on the other hand, maybe limited only by software, computational power and design costs and typically cost less than one percent of the total expended during a system design or redesign project (163, 174, 243).

- System Modification:

A valid mathematical model can be altered with relative ease and at minimum cost to maintain continuity and relevance to changes in the real-world system's construct or operation. The model can therefore evolve with the real-world system to continue informing policy, whereas all past real-world experimentation studies would become less relevant to the actual system and eventually obsolete without costly and disruptive re-experimentation (163, 243).

- Conceptual Experimentation:

On occasion the system considered does not exist as yet and there is no option to perform real or physical model experimentation, in these instances the investigator has to develop a model to experiment with. Mathematical models allow for this abstract and flexible interpretation of the system (163).

3.2.3 Specific Advantages of a Discrete Event Simulation Modelling Approach

- Variability:

The ability to model variability is one of the main advantages to simulation modelling over other mathematical or physical modelling techniques. Modelling variability in real-world or physical models rapidly becomes a time exhaustive process even at low levels of change. Although some mathematical methods other than simulation can include variability, this dramatically increases their complexity and the computational time and power required to solve them, making the inclusion of system variability unviable (163).

- Time Management:

Simulation models can be run at varied speeds depending on need. Extremely slow runs may be performed to investigate high level detailed complex system interactions, or time can be compressed to investigate system change over much longer periods than is possible in real-world experiments such as weeks, months or even years (163, 243).

- Restricted Assumptions:

Simulation modelling allows complex systems to be simplified to a desired level through the use of assumptions. Insufficient data may require the use of probability distributions to satisfy one aspect of the system in a model, whilst other mathematical models such as queuing theory are restricted in the type of distribution which can be implemented, in simulation, any describable distribution can be used as long as the design software can accommodate it (163).

- Identification of Failures:

Real complex systems can have numerous interactions between contributing components making diagnosis of system failures and their impact on system performance challenging. Simulation modelling allows improved understanding of these interactions, identification of system bottlenecks and greater insight into ways of improving system performance (163, 243).

- Transparency and Communication:

In real experiments only certain areas or operations of a system maybe observed at any one time by any individual. A simulation model can be used to visualise the complete system; this allows improved understanding of how the system operates as a whole and the effects of change on performance. The intuitive nature of simulation models allows managers to comprehend the system visually, as opposed to attempting to understand it's complexity through a series of mathematical equations. This allows decision makers to gain more confidence in the relationship between the model's outputs and the real system (163).

- Design Efficiency:

In the development of a brand new untested system, the use of simulation in the planning design phase can be used to specify requirements of the system and ensures the real-world system is built for purpose and with maximum efficiency prior to initiating manufacturing. This can prevent costly errors and the unnecessary wastage of valuable or limited resources (163, 243).

3.2.4 Limitations of Discrete Event Simulation

- Expense:

Although significantly less expensive than many other experimental options, simulation studies still require some considerable financial outlay. Simulation software used to construct the model can cost thousands of pounds and require a suitably powerful computer or computers on which to run them. When many lengthy simulation runs are required computational power may exceed standard commercial personal computer (PC) capacity, requiring access to larger industrial super-computers with additional associated costs (163, 243).

- Development Time:

The process of simulation modelling can be lengthy, especially with complex systems. A simulation project must undergo several phases of development as discussed in the following chapters, this can take years to complete depending on availability of personnel, materials and expertise without a guarantee of a successful end-product (163, 243).

- Data Rich:

A simulation model is dependent on the data assumptions it is built on and therefore, requires a substantial amount of data to inform it in order for it to operate at a useful and satisfactory level. This large data pool must be accessible, as well as being cost and time effective in its collection (163).

- Expert Input:

Simulation modelling is a learning process often requiring expert experience to ensure proper execution. The availability of experts to assist or run the project may determine the complexity of the simulation and whether a simulation model is feasible at all (163, 243).

- Model Interpretation:

In real-world experimentation the results are often fairly simple to understand and interpret, however, simulation outputs are essentially a set of random variables which must be distinguished between whether they are system performance indicators or merely the result of random occurrences (243). Adequate understanding of both the system and simulation processes maybe required for appropriate interpretation of the results.

- Overconfidence:

One of the often reiterated warnings regarding simulation modelling is that those interpreting the results must remember they are the model's results and not actual real data. The use of system visualisation in simulation models can often mislead an observer into believing the model is real and the degree of validity of a model's results is crucial in their accurate interpretation (163).

- Overuse:

Simulation has become increasingly popular in recent years (174). The availability of user friendly software has made the practice much more accessible and the increased computing power now available allows most simulation programs to be run comfortably on just a family PC. This has in turn led to overuse of simulation when other far simpler mathematical models may suffice (163, 243).

3.2.5 Application of Discrete Event Simulation in Healthcare

The wide variability observed within healthcare systems and the large number of effects and interconnections between people and their departments over time, creates a complex system highly suited to investigation using DES techniques (244). The ability of these simulations to simplify complexity and improve resource efficiency has led to a significant increase in the application of simulation in the healthcare environment over the past few years (245-249). This surge in popularity has in turn been accompanied by improvements in study quality and the increased accessibility of the technique to today's medical researchers, brought about through greater commercial availability of DES software packages and more powerful computers on which to run them on as alluded to above (244, 246). The period 2003-2007 saw more than twice as many health based simulation publications compared to the period 1993-1997 and over seven times the number from 1973-1977 (248).

DES can be applied to a wide range of areas within the health sciences (244, 246, 248). These can be broadly categorised by sector with the most common areas investigated being: Health demographics and economics, EDs, surgery, CCUs, consumable resources and supply chains, general inpatient departments and outpatient clinics. In addition to the DES models discussed in Chapter One as a part of an overall review of MCE mathematical

modelling methods, a cross-section of examples of DES applied generally within healthcare are provided in Table 3.1 (244, 246, 248).

Table 3.1 Examples of DES applied in various sectors of healthcare

SECTOR	SIMULATION STUDY
Health Demographics and Economics	Ratcliffe et al 2001 (250), Pasin et al 2002 (251), Roderick et al 2004 (252), Paul et al 2006 (253)
ED	Fletcher et al 2002 (254), Takakuwa et al 2004 (255), Zeltyn et al 2011 (245), Ashton et al 2005 (256), Hoot et al 2008 (257), Sinreich et al 2005 (258)
Surgery	McAleer et al 1995 (259), Bowers & Mould 2002 (260), Vasilakis ET AL 2007 (261), Blake et al 1995 (262)
CCU	Ridge et al 1998 (263), Kim et al 2000 (264), Livvak et al 2008 (265)
Consumable Resources and Supply Chains	Reynolds et al 2011 (266), Couchman et al 2002 (267), Haijema et al 2007 (268)
General Inpatient Departments	Millard et al 1994 (269), Vasilakis et al 2005 (270), El-Darzi et al 1998 (271), Harper et al 2002 (272)
Outpatient Clinics	Guo et al 2004 (273), Harper & Gamlin 2003 (274), Eldabi et al 1999 (275)

The healthcare simulations referred to in Table 3.1 primarily aim to improve operational decision making and the planning aspects of care (244). Previous reviews of DES in health have found a preference towards facility specific and department specific studies with a lack of whole hospital encompassing simulations. This has been suggested to be due to the complexity and time required to model these complete systems which rapidly becomes unmanageable (246, 248). The majority of simulation studies in the past have also focused largely on EDs due to their accessibility and the time limited and operationally bounded processes that take place there (246). One review found only six percent of health DES studies investigated healthcare supply chains such as drug and blood provision, compared to the 66% which modelled other inpatient hospital services including the ED (248).

The investigation of a system through a DES 'what-if' approach provides an opportunity to improve and integrate blood system response plans for MCEs when other options available are either unviable or highly restricted in terms of their application (248). To date, there have been several simulations of out of hospital blood production and regional blood inventory management or collection systems (268, 276, 277). There have also been a number of studies applying DES to MCEs investigating: in-hospital routing of casualties, overtriage and mortality and the prediction of bottlenecks in casualty flow (190, 253, 278-280). However, there has yet to be a study applying DES in optimising a hospital's blood system under the surge conditions of a disaster or MCE and although there has been a sharp increase in application of DES in health systems, there remains a comparatively small increase in the translation of the practice into policy making. In terms of blood planning the lack of adequate or appropriate alternatives to planning provides a real opportunity for application of this methodology and the implementation of the results into actual policy (190, 253, 268, 276-278).

3.3 Simulation Methods and Software Selection

3.3.1 Methods of Simulation

A simulation study can vary from the use of very basic tools to the use of highly complex methodology. The simplest forms of simulation can be done by hand, for example in an early instance of what today would be referred to as a simulation experiment, Leclerc around the year 1733 used a table and the throw of a needle to estimate the value of π (174). Following the development of number tables and random number machines in the 1920s mathematical and statistical methods improved and by the 1950s analogue computers

were commercially available, this lead to the transition of simulation into computerised platforms (174, 281).

Since this time the development and advances in the practice of simulation have closely mirrored that of the computer. The initial use of the general programming language FORTRAN in the late 1950s was superseded by simulation specific programming languages such as SIMULA, SIMSCRIPT and International Business Machines' (IBM) General Purpose Simulation System (GPSS) during the digitalisation of computers in the 1960s. DES was then developed with its primary application being in operational research for business and industrial engineering (281-283). The programming languages used in simulation have continued to be developed throughout the 20th century with the release of second generation versions of the original languages, as well as the introduction of numerous alternatives including Java, Visual Basic, C++, SLAM and SIMAN to mention a few (174, 282).

Although these programming languages are highly powerful and versatile tools allowing the investigation of a wide range of systems and scenarios, they still require a significant level of user understanding and expertise to operate them effectively (174). The introduction of visual interactive simulation (VIS) in 1979 allowed users more intuitive access to simulation runs through observation of an animated representation of the model, a technique more suited to the human predisposition towards pattern recognition in problem solving (163, 283). VIS together with the greater access to faster PCs led to the production of high-level simulation software programs throughout the 1980s and 90s. These programs have continued to propagate and evolve in their capabilities with visual interactive modelling systems (VIMS) now allowing the non-expert access to advanced simulation methodology. These VIMS equipped programs include interactive menus and graphical templates pre-coded to provide a user friendly interface to the underlying complex programming language at a much reduced cost (163, 174, 176, 284).

The investigator should always aim to select the most appropriate tool for the complexity of the proposed study and the financial and time constraints under which it will be carried out. All available options should be considered from a common computer based

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mathematical spreadsheet package such as Microsoft Excel (Microsoft Corp. Redmond, WA, USA) to the development of a highly complex custom-designed pure programming language solution. In relation to this study the primary concerns were a model with an adequate range of application and flexibility to simulate a generic UK MTC, a relatively short software learning and build time and a high level of usability for validation and experimentation (163, 283).

3.3.2 Evaluation, Comparison and Selection of Available Software Packages

The wide variety of commercially available simulation software packages providing a VIMS-type interface creates a challenge for investigators to select the most appropriate program for constructing a model. Although there has been debate over the impact that software selection has on ensuring the success of a simulation project, the process of selecting the most appropriate software has been the focus of numerous studies (163, 285-288). The process of software selection involves four general steps: establishing the software demands of the model through the conceptualisation and planning phase, surveying the software and generating a short-list of potentially suitable programs in which to build the model, evaluating the shortlisted products' suitability based on a range of study-specific desired criteria and finally performing an overall comparison from which the best suited software is selected (163, 288).

The Institute of Operational Research and the Management Sciences (INFORMS) is the largest global body of its kind for professionals in the fields of management, analytical and operational research sciences. This not-for-profit organisation provides a biennial comprehensive simulation software survey covering a wide range of commercially available simulation software packages and offers a comparative profile of each vendor's product, describes the specific features the software includes and indicates possible areas suitable for its application. The long-list for software selection for this study was taken from the eighth edition of the INFORMS simulation software survey performed in 2011, it includes 56

simulation packages released through 29 separate vendors as listed in Appendix II (179). Short-listing was performed by identifying all software stated by the INFORMS survey which met the following essential criteria for this investigation and therefore reducing the package number to a manageable level for further comparative evaluation:

1) The software provided a suitable platform for performing DES without the need for additional software.

2) 'Healthcare' or an equivalent general term was referred to under the list of industries in which the software is primarily applied.

3) The software is compatible with a standard PC and the Microsoft Windows operating system (Microsoft Corp. Redmond, WA, USA).

4) The software offers a graphical construction process using pre-coded modules in the form of VIMS or an equivalent interface.

The shortlisting process produced a cohort of 11 packages suitable for this study including: Analytica 4.4, Arena Simulation Software, ExtendSim, Flexsim, MedModel Optimization Suite, Micro Saint Sharp, Patient Flow Simulator, SAS Simulation Studio, Simcad, Simio Express and Simul8. Suitable product comparison can be performed using various methodologies, among the most commonly applied techniques are the analytical hierarchy process (AHP), fuzzy set theory and the weighted average system (163, 285, 286, 289-292). The AHP system is a time consuming and complex process best suited to multi-dimensional comparisons with large number of criteria requiring consideration, whereas the fuzzy set theory is useful in instances where there is greater uncertainty on the part of the investigator regarding the importance of individual criteria (163, 285). For this study due to the moderate number of criteria considered, an understanding of each criterion's significance in the project and the relative ease of application of the technique, the weighted average system was preferred (285, 291).

The weighted average system as described here follows a similar structure as described by Collier et al form the proceedings of the 32nd Hawaii International Conference on System

Sciences (291). The process begins with the grouping of related criteria into distinct categories, each criteria is then weighted by its importance to the study being considered so that the sum of all criteria weights within a single category equals one. The categories are also weighted depending on their significance to the study with various ways of categorising the packages. This study used four main categories of equal weight, these are shown in Table 3.2 with the individual criterion considered and their investigator designated weighting in relation to this study (163, 285, 288, 291).

Table 3.2 The criteria and weighting for each category considered during software selection

Software Functionality (CW 0.25)		Simulation Execution Options (CW 0.25)		Output & Analysis Facilities (CW 0.25)		Vendor & Cost Options (CW 0.25)	
C	W	C	W	C	W	C	W
Compatibility with external software	0.20	Runtime debugging	0.20	Output analysis and data exporting	0.50	Training courses	0.20
Utilisation of multiple computer processors	0.20	Batch simulation runs	0.30	Optimisation	0.30	Support hotline	0.20
Customisation using programming language	0.20	Cost allocation of components within the system	0.20	Model sharing with external partners	0.20	Online discussion groups and literature availability	0.20
Input distribution options	0.40	Real-time animated run observation	0.30			License cost and trial or student options	0.40

CW – Category Weighting, C – Criteria, W - Weighting

The evaluation of individual software packages is performed by assigning a score for each of the listed criteria based on a comparison with a preselected reference software package. This reference package is assigned an average three for each criteria, if they are equivocal

the software package scores a three, if superior a four and if far superior a maximum of five. Whereas, if the software is inferior to the reference package it scores a two for that criteria and if far inferior, a minimum of one on the discrete scale (291). The category scores are totalled, weighted against the overall category significance and an overall weighted average is calculated for each software package using the formula:

$$E_i = \sum_i W_j \, T_{ji}$$

E_i The total evaluation score of software package i

W_j The weighting for the category j

T_{ji} The total comparative score for the category j for the software package i

(Adapted from: Simulation: the practice of model development and use. Robinson S.: John Wiley & Sons; 2004)

The software package Simul8 (Visual Thinking International, Ltd., Mississauga, Ontario, Canada) trial version 2011 was used to develop an understanding of simulation techniques, familiarise the investigator with the basics of simulation model construction and appreciate the significance of the criteria listed in Table 3.2 with respect to the study being undertaken. This software was therefore used as the reference package for comparison with the short-listed alternatives as shown in the evaluation results in Table 3.3, the score for each software package was assigned using a combination of data from the individual package vendors' website and the 8th biennial survey performed by INFORMS in 2011.

Based on the weighted average system, Arena simulation software (Rockwell Automation, Pittsburgh, USA) was selected for the study with the highest overall score of 3.73. A free trial evaluation license was initially obtained to ensure the software was suitable and to allow for the initial construction of the model prior to purchasing a one year academic fully operational license. The latest version: Arena Simulation Enterprise Suite version 14.0 was used to develop the model and perform the subsequent experimentation.

Table 3.3 Evaluation and overall weighted score for all short-listed simulation software packages considered for model development

Category and Criteria	Wj	Reference Package (Simul8)	Analytica 4.4	Arena Simulation Software	ExtendSim Suite	Flexsim	MedModel Optimization Suite	Micro Saint Sharp	Patient Flow Simualtor	SAS Simulation Studio	Simcad	Simio Express
Software Functionality:	**0.25**											
Compatibility with external software	0.20	3 (0.60)	1 (0.20)	4 (0.80)	3 (0.60)	4 (0.80)	4 (0.80)	2 (0.40)	3 (0.60)	1 (0.20)	3 (0.60)	4 (0.80)
Utilisation of multiple computer processors	0.20	3 (0.60)	3 (0.60)	3 (0.60)	1 (0.20)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)
Customisation using programming language	0.20	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	1 (0.20)	1 (0.20)	3 (0.60)	1 (0.20)
Input distribution options	0.40	3 (1.20)	2 (0.80)	4 (1.60)	3 (1.20)	3 (1.20)	4 (1.60)	2 (0.80)	4 (1.60)	3 (1.20)	1 (0.40)	3 (1.20)
Total	**1.00**	**3.00**	**2.20**	**3.60**	**2.60**	**3.20**	**3.60**	**2.40**	**3.00**	**2.20**	**2.20**	**2.80**
Simulation Execution:	**0.25**											
Runtime debugging	0.20	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)
Batch simulation runs	0.30	3 (0.90)	2 (0.60)	4 (1.20)	2 (0.60)	4 (1.20)	4 (1.20)	4 (1.20)	5 (1.50)	5 (1.50)	4 (1.20)	2 (0.60)
Cost allocation of component within system	0.20	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	1 (0.20)	3 (0.60)	1 (0.20)	3 (0.60)	3 (0.60)
Real-time animated run observation	0.30	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)	3 (0.90)
Total	**1.00**	**3.00**	**2.70**	**3.30**	**2.70**	**3.30**	**3.30**	**2.90**	**3.60**	**3.20**	**3.30**	**2.70**
Output & Analysis:	**0.25**											
Output analysis & data exporting	0.50	3 (1.50)	2 (1.00)	5 (2.50)	2 (1.00)	3 (1.50)	4 (2.00)	4 (2.00)	4 (2.00)	4 (2.00)	3 (1.50)	3 (1.50)
Optimsation	0.30	3 (0.90)	3 (0.90)	3 (0.90)	2 (0.60)	3 (0.90)	3 (0.90)	3 (0.90)	2 (0.60)	2 (0.60)	3 (0.90)	3 (0.90)
Model sharing with external partners	0.20	3 (0.60)	3 (0.60)	4 (0.80)	2 (0.40)	4 (0.80)	3 (0.60)	4 (0.80)	3 (0.60)	1 (0.20)	3 (0.60)	2 (0.40)
Total	**1.00**	**3.00**	**2.50**	**4.20**	**2.00**	**3.20**	**3.50**	**3.70**	**3.20**	**2.80**	**3.00**	**2.80**
Vendor & Cost:	**0.25**											
Training courses	0.20	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)
Support hotline	0.20	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)
Online discussion groups & literature availability	0.20	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	3 (0.60)	1 (0.20)	3 (0.60)	3 (0.60)
License cost & trial or student options	0.40	3 (1.20)	4 (1.60)	5 (2.00)	2 (0.80)	2 (0.80)	1 (0.40)	3 (1.20)	2 (0.80)	2 (0.80)	2 (0.80)	5 (2.00)
Total	**1.00**	**3.00**	**3.40**	**3.80**	**2.60**	**2.60**	**2.20**	**3.00**	**2.60**	**2.20**	**2.60**	**3.80**
Overall Weighted Average		**3.00**	**2.70**	**3.73**	**2.48**	**3.08**	**3.15**	**3.00**	**3.10**	**2.60**	**2.78**	**3.03**

Values given as Score per criteria and (Total), (Total = Score x Weighting)

3.4 Model Construction

3.4.1 Core Components in Discrete Event Simulation Software Architecture

Arena, along with the majority of other software packages available executes DES modelling through four core system concepts interacting over time. These concepts include entities, resources, controls and operations (243, 293). Time is managed via a simulation clock which begins at the initiation of a simulation run and undergoes discrete advancements whenever there is a change in the state of the system, these may be referred to as 'event times' (176, 243). Event times are the controlling factor for the simulation clock and therefore the discrete advances in time are determined by when events occur as opposed to pre-set identically separated time steps. The four core concepts referred to above are described in further detail below and referred to through specific examples in the model structure description which follows (3.5.2).

- Entities:

These are objects or people created at the start or during the simulation run; they flow through and interact with the system undergoing periods of activity. During these activity periods they perform or undergo a process or periods of delay whilst they wait for a specific set of conditions to be met (293). These entities may remain in the model until the simulation is complete or exit the system and be disposed of when they are either no longer required by the system or have completed their designated objectives. Entities consist of attributes which describe them and are specific to that individual person or object. These attributes may be fixed such as a person's gender or vary depending on the entity's circumstances within the system such as their degree of healthiness (243, 283).

- Resources:

These are system elements which serve an entity, the service may be temporary, after which the resource is available for another entity to occupy it, or permanent if the resource is consumed by an entity. The competition for resources by different entities requiring a service leads to queues and therefore delays in an entity's flow through the system. A system resource can be modelled to be unlimited (a non-constrained resource) or finite (a constrained resource) in its availability, depending on the study design and their importance within in the system and relation to the model's outcome measures (243, 283).

- Controls:

These are elements which alter the flow of entities through the system using a number of decision trees, variable condition states or defined rules which dictate the passage, timing and interactions an entity will undergo whilst within the system (243). Controls may be interactive during a simulation run or completely predetermined in the model's structure and design. An example of a control would be whether a patient entity is triaged as severely ill or moderately ill and hence forth continue within the system to either the resuscitation room or the majors area of the ED respectively. Other examples might be when entities are queuing for a resource, whether the queue operates on a first-in-first-out (FIFO) or last-in-first-out (LIFO) premise (174).

- Operations:

These are the activities performed on the entities or by the entities whilst they flow through the model. They are the steps an entity must take in order to complete its journey through the system (243). An example of a set of operations might be a patient's encounter with a hospital ED, they must arrive at the hospital (be created in the system), be triaged (occupy a resource in the form of a triage nurse), receive their treatment (occupy a resource in the form of a doctor) and be discharged (be disposed of from the system).

3.4.2 Description of the Model Structure

The conceptualisation of the model described earlier in this chapter provided a framework from which the most appropriate modelling methodology for achieving the study's objectives could be decided. Coding the model in the Arena software requires a clear description of the model and the real-world processes it encompasses and represents. The model structure was designed through reference to the extensive literature review performed in the previous chapter, observation of real-world MTC processes (specifically at the Royal London Hospital - RLH) and discussion with experts involved in blood provision and utilisation during MCEs. These experts included all relevant disciplines from transfusion scientists through to surgeons in order to ensure a broad opinion base and specialist knowledge for each component of the system.

The setting, as previously referred to, was based on a generic UK MTC's response to an unspecified MCE. The MTC itself represented the boundaries of the model and therefore the two terms are synonymous in its description. Events occurring outside of the MTC during an MCE were not included or considered during the simulation. In addition, only events involving the provision of PRBCs to casualties were considered in the model, additional aspects of casualty care were outside the scope of this study. The model had to include as a minimum, all the critical processes involved with processing PRBC provision to casualties from their arrival through to their complete receipt of their PRBC demand. This was essential to provide a sufficient link between the experimental factors and subsequent outputs generated (163). As such, the model was divided into three essentially distinct areas: casualty assessment, casualty treatment and the transfusion laboratory area. Although in a real MTC these 'areas' may involve several different departments, for example casualties may be treated in the ED, theatres, CCU or the wards, for the purposes of this transfusion specific model a simplified generic treatment area was assigned. The model design is presented in Figure 3.2 as a Unified Modelling Language (UML) Activity Diagram.

The simulation entities consisted of either P1 or P2 casualties which arrived at the MTC from the start of the simulation run already assigned a priority level. All arriving casualties were assigned a unique sequential hospital number which served as an individual identifier as they passed through the model and during analysis of the model results. Casualties were also assigned a blood group which was tested for at the time of their initial assessment. This initial assessment was performed by a medical team in the casualty assessment area, a control element ensured casualties were treated by a team appropriate to their triage category, reflected in the model by the time taken to assess them. This assessment was the first operational activity within the model. During this primary survey of their injuries their bleeding status was determined as either bleeding or not. If deemed not to be bleeding the casualty exited the model at this stage and was recorded as such, taking no further part in the simulation. Those casualties assessed as bleeding were assigned a PRBC demand volume again appropriately based on their priority, this PRBC demand had to be fulfilled in order for them to exit the simulation and be recorded as treated. The PRBCs of each blood group were set as a defined stock level and along with the staff and blood processing machines formed the model's resources element.

Following assessment the casualties requiring transfusion moved to the Treatment Area of the model, in parallel with this, a casualty specific blood sample was sent to the Transfusion Laboratory area of the model for processing and blood group determination. In the treatment area casualties initially received emergency type O PRBCs transfused by an attending medical team whilst they awaited their specific blood group to be determined. The volume of PRBCs provided at any one time was limited to single packs of a defined number of units. Having received their initial transfusion, casualties fell into one of three categories; those who had received their complete complement of PRBCs and therefore exited the model and were assigned as treated, those who were awaiting further PRBCs to meet their demand volume but who's blood type still remained unknown, and those who were awaiting PRBCs and had had their blood type confirmed. The latter went on to receive group-specific PRBCs if available, whereas those awaiting confirmation of blood type continued to receive packs of emergency type O until their PRBC demand was met or their group confirmed. PRBCs were provided in order of casualty compatibility and availability.

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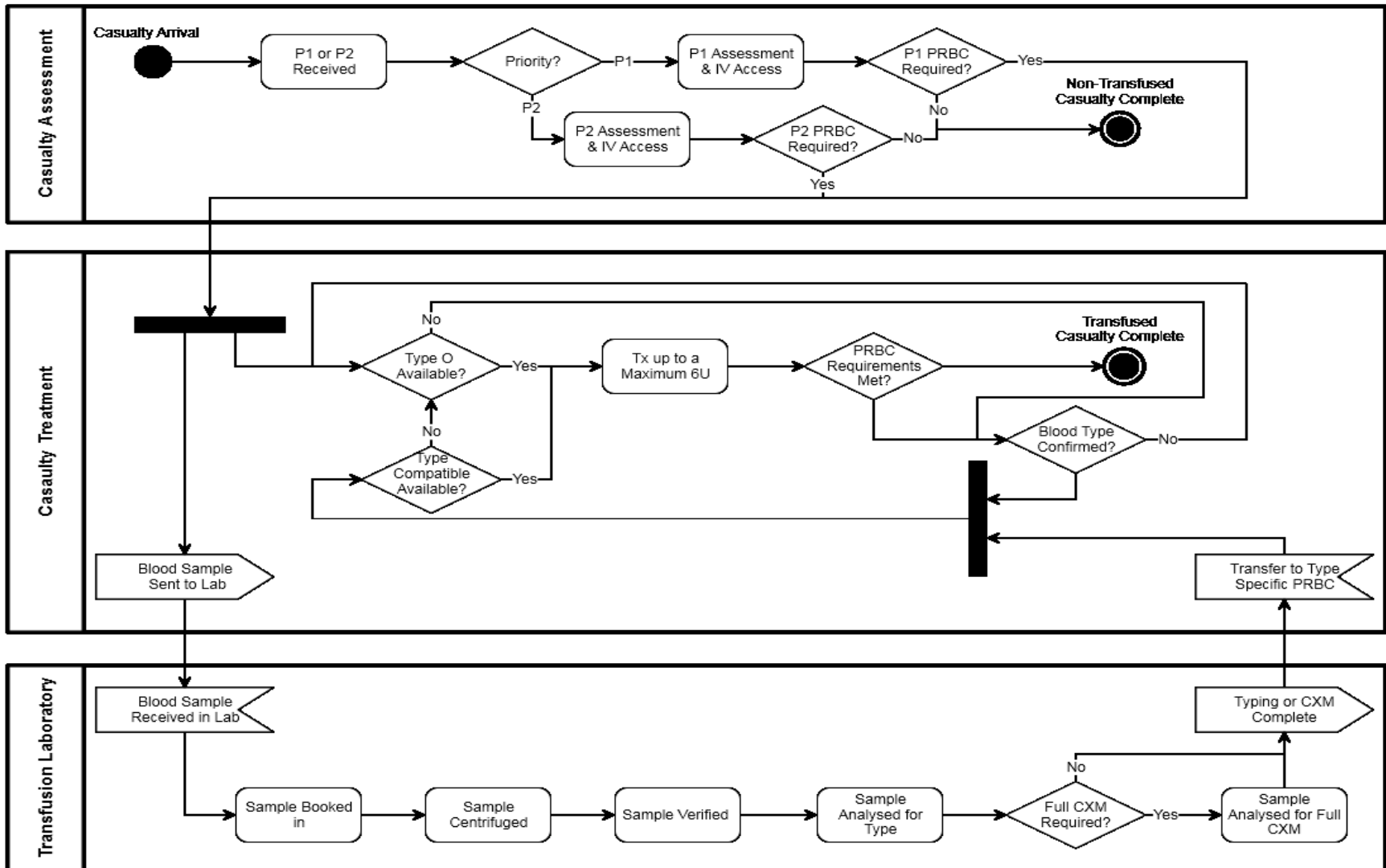
Figure 3.2 An Activity Diagram using UML of the model structure.

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The Transfusion Laboratory dealt specifically with the blood samples received from bleeding casualties. The samples were treated as entities as well in this part of the model which passed through the laboratory processing system and exited the model once the casualty's blood group had been determined. The sample held all the unique identifying information of the casualty it was sent from in order to match them together when processing was complete. On reception of a sample the laboratory staff verified and booked the sample into the transfusion computer system and then centrifuged the sample in preparation for blood group analysis. Once centrifuged, the sample was verified and loaded onto an automatic blood group analyser which provided both the blood group and of a more prolonged full antibody screen if required. Once the blood group was determined the sample was registered as grouped on the system and the corresponding casualty could then receive type specific or any compatible PRBCs available.

3.4.3 Assumptions in the Model Design

Following discussions with the expert panel consulted during the model design, several simplifying assumptions were made as listed here:

- The MTC was in a state of readiness for arrival of the first casualty with no other current casualty encounters in progress.
- Casualties were correctly triaged upon arrival and no variation in their triage priority occurred during the simulation.
- The triage description definitions of time to treat P1 and P2s were taken as time from their arrival into the model and not the time of the initial event.
- Only P1 and P2 casualties required transfusion and all P3 casualties were treated at a separate location to avoid impacting on care of those more seriously injured.
- No system failures or human errors occured throughout the simulation.
- All physical treatment resources aside from PRBCs and the components involved in PRBC provision to casualties were considered adequate for casualty care.

- All bleeding casualties were assumed to have a defined PRBC demand from admission which did not increase during their time in the model.

- Casualty blood samples did not require collection or delivery as they were transported by automatic pneumatic air tube systems.

- Emergency type O PRBCs were available for immediate transfusion from satellite blood fridges kept in most acute treatment areas whereas type specific units required collection.

3.4.4 The Arena Modelling Environment

Arena is programmed around the simulation specific language SIMAN (SIMulation and ANalysis) first developed by Dennis Pegden in the 1980's. The software uses a Microsoft Windows-type interface to graphically design models using drop-down menus and interactive toolbars. The investigator constructs the model in the modelling window where the building blocks of the model - termed 'modules' can be dragged and dropped from a project bar and connected to form a system flowchart or 'map' of the model through which entities travel during the simulation (Figure 3.3). The modules represent the control and operational aspects of the model, directing entities during the simulation and facilitating system processes. The project toolbar contains all the modules required to construct the model's flowchart categorised by type, from basic pre-programmed modules which require minimal investigator input, through to advanced technical modules demanding more extensive coding and therefore, allowing more customised process definitions (174, 176, 293).

The flowchart model construction is supported by the spreadsheet window (Figure 3.3). Whilst modules are coded to fulfil an array of general modelling tasks, they also depend upon user-defined inputs to inform the specific nature of their system interactions. The spreadsheet interface facilitates this module data input as well as housing the non-module

based elements of the model such as resources, control of queues and individual entity parameters, which unlike modules, do not have a graphical presence in the main modelling window. The user-defined fields in the spreadsheet window may be string inputs such as gender, or reference to an image file to represent an entity or they may be numerical, depending on the model element being defined. Data-based inputs available include: constants, expressions, reference to external data sets or probabilities. The last of these can be a specific probability or sampled from a defined distribution, this feature of the model building process is crucial for modelling the inherent variability common to the real life system. An example of data input fields for the Create module - used for generating a new entity for entry in to the simulation, is shown in Figure 3.4.

Each module type or data-only element consists of its own definable fields specific to its role in the simulation model. The components used in the construction of this study's model, a description of which follows, are shown in Table 3.4 along with an explanation of their action and a study-based example. Prior to a simulation run and once all the definable fields have been populated the final stage in the model construction is to determine the simulation run parameters. This includes: the time units applied during a simulation run, the length of the simulation, the number of replications that should be performed, the statistics collected during the event and the speed of the simulation run from a visual perspective.

As in other Arena elements there are a number of advanced settings which may be applied here when performing highly complex and detailed simulation studies, only those that are relevant to this investigation have been discussed here. The Arena simulation setup dialogue window is shown in Figure 3.5.
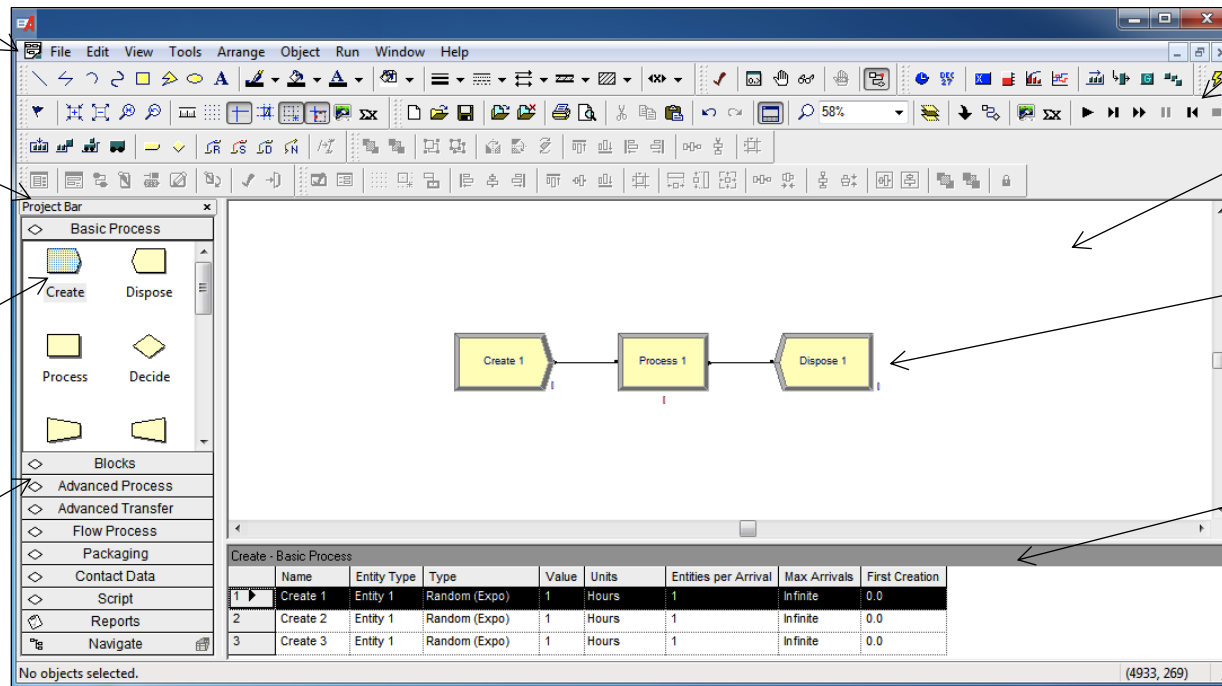
Figure 3.3 The Arena (Rockwell Automation, Pittsburgh, USA) simulation program user-interface.
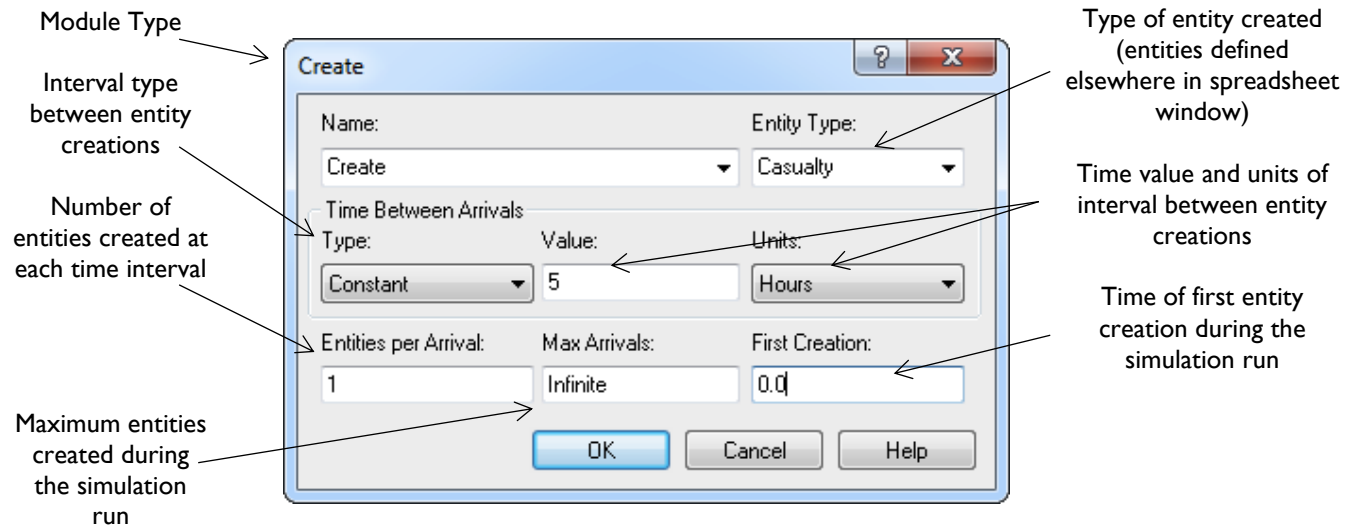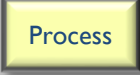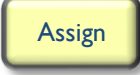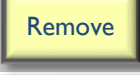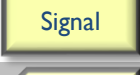
Figure 3.4 An example of a module input window in Arena (Rockwell Automation, Pittsburgh, USA) with the required definable data input fields.

Table 3.4 A description of the components involved in the study model's construction

Component	Description
Create	Inserts entities into the simulation at defined time points triggering an 'event time'. Although entities encounter prior processes in the real-world system such as a casualty's pre-hospital care, only system interactions from this point (at the MTC) are considered
Dispose	Removes entities from the simulation when all their tasks are complete. Although entities continue to undergo further processes in the real-world system such as a casualty's ongoing recovery, no further system interactions are considered from this point
Process	Performs an action on or by the entity such as the act of transfusing PRBCs to the casualty, this involves an 'event time' as the entity is delayed until the process is complete and may also involve sequestering an available resource such as a nurse to perform the process
Assign	Allocates, removes or updates an entity characteristic such as providing a hospital number to a casualty or updating their PRBC demand following a transfusion. These modules and the components which follow are informative only and as such will not trigger 'event times'
Decide	Controls the flow of an entity based on an entity's characteristics or a current system state. For example the module may divide casualties by their priority into separate processing arms or divert a casualty to a queue if a required resource is currently unavailable.
Separate	Splits entities into two with identical characteristics for situations where the entity undergoes two simultaneous processes. For example a casualty continues treatment with Type O PRBCs whilst their blood sample is simultaneously processed to determine their blood type
Hold	Delays an entity in the system until a condition is met elsewhere or a signal is given to release it. This can be used to 'hold' casualties until their blood group is known or an alternative becomes available
Search	Checks the system or a queue for a component which meets specific conditions, such as matching a casualty's hospital number to that of their processed blood sample in order to signal a casualty can progress from receiving type O PRBCs to type specific PRBCs
Remove	Extracts an entity from a point in the system such as the removal of a casualty from the queue for blood type availability once it has been confirmed
Signal	Alerts a system component a condition has been met as in the search example above
Record	Collects statistics on entities and the system state for simulation analysis and output measure results
VBA	Prompts a user-coded procedure performed in Microsoft's Visual Basic for Applications (VBA) system (Microsoft Corp. Redmond, WA, USA) after which the entity continues its system flow. This study uses the module to record system and entity statistics and write them directly into Microsoft Excel (Microsoft Corp. Redmond, WA, USA) during a simulation run
→	The module connection arrow shows the direction in which entities flow through the system model
Spreadsheet	A spreadsheet only component used for data inputting information regarding resources, queues, attributes and variables used by the entities as they flow through the system as well as defining general characteristics of different entity types. For example assigning an initial resource level at the start of the simulation, deciding if a queue operates a first-in-first-out (FIFO) system or not
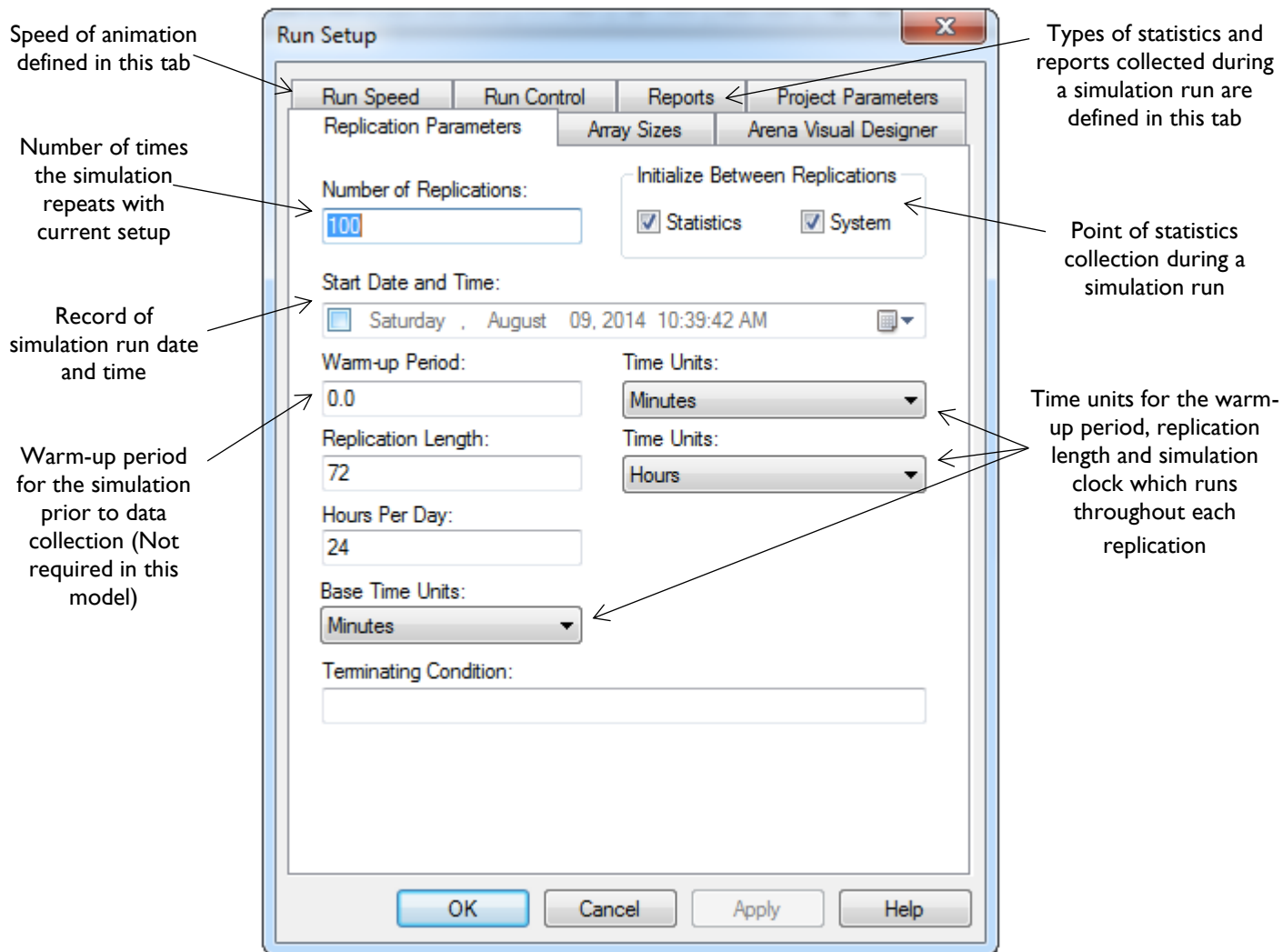
Figure 3.5 An example of the simulation run setup window in Arena (Rockwell Automation, Pittsburgh, USA).

3.4.5 Implementing the Model Design in Arena

Due to the large number of modules required to satisfy the intended logic of the model design, the model map can quickly become overwhelming in its complexity. In order to aid both the design and understanding of the simulation, the model was divided into sections through the addition of various sub-models which encompassed groups of related actions. The overall model map is shown in Figure 3.6 and each of its sub-models are discussed individually in the rest of this section, along with a detailed description of the events modelled. The data-based inputs such as probability distributions which populate the definable fields of each module, the resource parameters and the control decisions of the simulation are discussed in the following chapter.
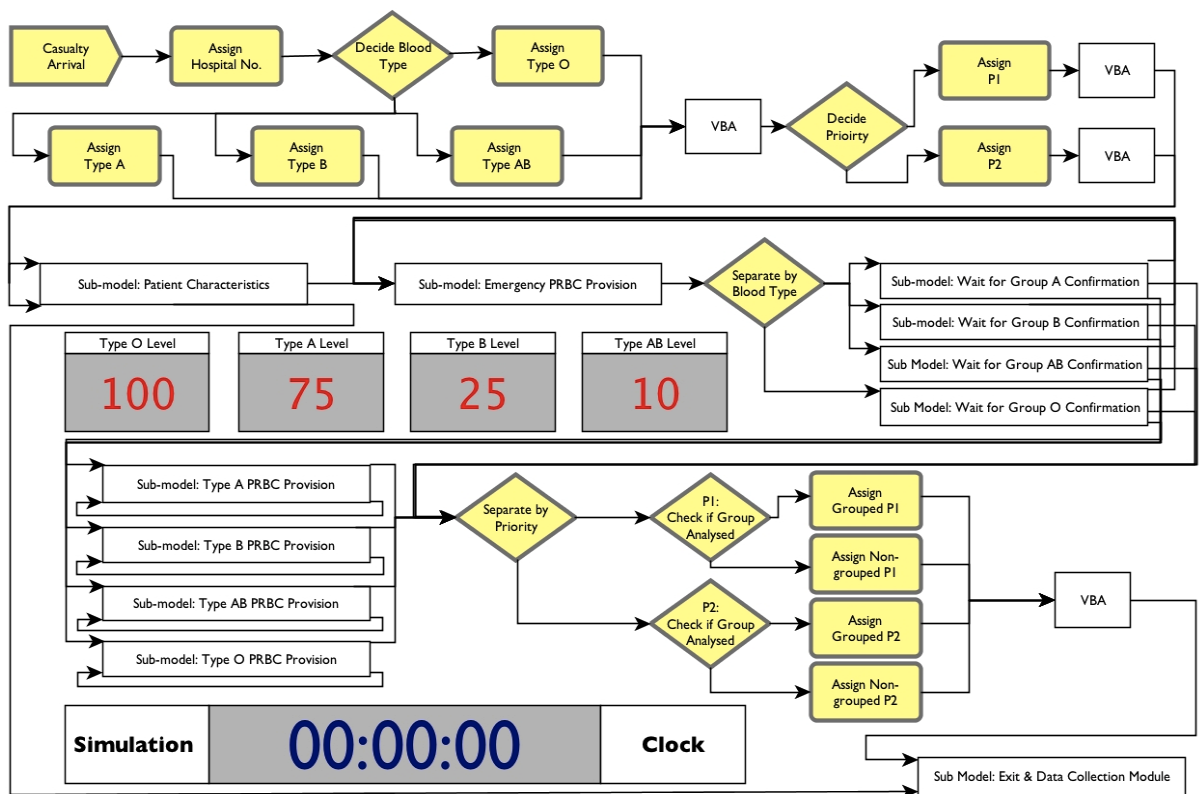
Figure 3.6 The overall model map including various sub-models and selected output displays active during a simulation run. This includes all group-specific PRBC inventory stock (in Units of PRBC) counters and the digital display simulation clock.

The model begins with a Create module where casualties are generated and enter the model. The arrival rate is sampled from the Create module's associated probability distribution based on a pre-determined approximate overall casualty load set within the module. The simulation clock which is displayed digitally in the main model map, shows the hours, minutes and seconds from the initiation of the simulation, starting from the arrival of the first casualty. Only one casualty is created and therefore arrives at any one time, however, there is no limit on the time interval between arrivals, which is governed by the random sampling from the aforementioned probability distribution. Having arrived, a casualty progresses to the 'Assign Hospital No.' module. As is the case for all Assign modules, this is an instantaneous occurrence and therefore does not represent a discrete event within the model. This Assign module serves to record a casualty's arrival time, provide them with a unique identification (hospital) number and record the total number of casualties which have arrived up to that point.

The next step is a Decision module, which similar to all Assign modules does not advance the simulation clock, as it is not a discrete event. This module is used to determine a casualty's blood group based on a four way probability of the four possible human blood groups A, B, AB and O. The casualty then passes to one of the four corresponding Assign modules which follow and is labelled with their determined blood type respectively. The group labelling is performed at this stage to simplify the model construct, however, the actual process of determining this blood group occurs at the appropriate stage later in the model as per the real life system. Having been assigned a blood group, all casualties converge to pass through a VBA module which instantly exports their assigned parameters, including arrival timings, to Excel for real-time data collection from that specific simulation run. Following this, they enter another decision module which applies a two-way probability to separate casualties into either P1s or P2s, which they are then labelled and recorded as in the subsequent corresponding Assign and VBA modules respectively. At this stage, whilst numerous modelling steps have occurred, casualties have essentially only undergone one time related process – their arrival at the MTC as a P1 or P2 casualty. The two groups

continue onwards separately as they enter the first sub-model – the Patient Characteristics sub-model shown in Figure 3.7.
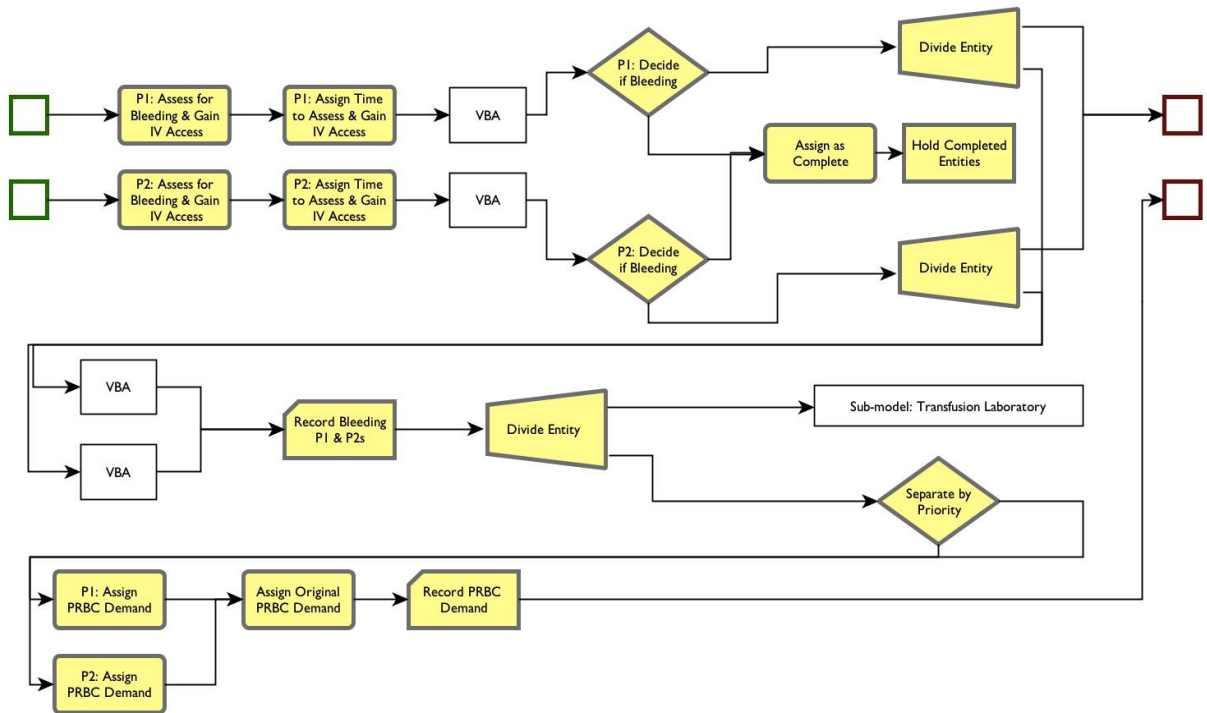
Figure 3.7 The Patient Characteristics Sub-model with Entry ☐ and Exit ☐ points linking it with the main model map.

Casualties arrive in the Patient Characteristics sub-model via the two entry points depending on their priority status. From here they are assessed for bleeding and intravenous (IV) access is gained for blood sampling and transfusion if required. This is done via a Process module and therefore constitutes an event, whereby the casualty is held in the module for the period of time taken to complete this action. The two priority groups are kept separate to represent the variation in resources afforded to them and therefore the length of time taken to carry out these two procedures. The time taken is sampled from a defined probability distribution in the module. During this process the casualty occupies a resource in the form of a 'generic medic' to perform the above tasks. This resource level was left unlimited for the purpose of this study and as such, a medic was always available to perform this task over the sampled timescale. The Assign modules which follow then label

the casualty with the time at which this process is complete. This is then recorded in the subsequent VBA modules.

At this stage, within their P1 and P2 groups, the casualties are separated via a Decision module into those found to be suffering haemorrhage and therefore requiring a transfusion, and those that are not. This decision is based on a two-way probability in accordance with their priority status. Those casualties found not to be suffering haemorrhage are assigned as such and held together in a Hold module which prevents them having any further interaction within the model. Casualties found to be bleeding enter a Divide module; this is not an event, but an Arena mechanism for creating an identical copy of an entity (casualty) including all the assigned information it holds at that point. The casualty copies leave the sub-model through the exit point returning to the main model map where they enter the 'Exit and Data Collection Module' sub-model. This sub-model, which is discussed in greater detail later, is used for further collating real-time data in Excel, including: priority, process and arrival timings, blood type and bleeding status.

The original casualties who are all deemed to require a transfusion enter a further VBA data collection module and then a Record module. The latter of these simply counts the entities passing through it and therefore is not an event in terms of the simulation time. The Record module, unlike the VBA modules, can be referred to by the Arena program when making entity routing decisions as a part of any simulation experimentation performed later.

Following this, the casualties are divided again to create another identical copy which is used to perform blood group analysis in parallel to casualties continuing their treatment. The copied entities which now represent an individual's unique blood sample, leave this sub-model to enter a further sub-model – the Transfusion Laboratory sub-model (Figure 3.8). The original casualties are split again by their defined priority through a Decision module. This allows their PRBC demand to be defined in the following Assign module based upon their priority state and therefore likely severity of haemorrhage. The P1 and P2 PRBC demand Assign modules define the individual casualty's need for PRBCs through random

sampling from a probability distribution, defined explicitly in each priority specific module. The subsequent Assign and Record modules are used by Arena for later calculating how much of a casualty's original PRBC demand has been met as they progress through the model. Prior to discussing the emergency treatment of casualties, the Transfusion Laboratory sub-model (Figure 3.8) is discussed.
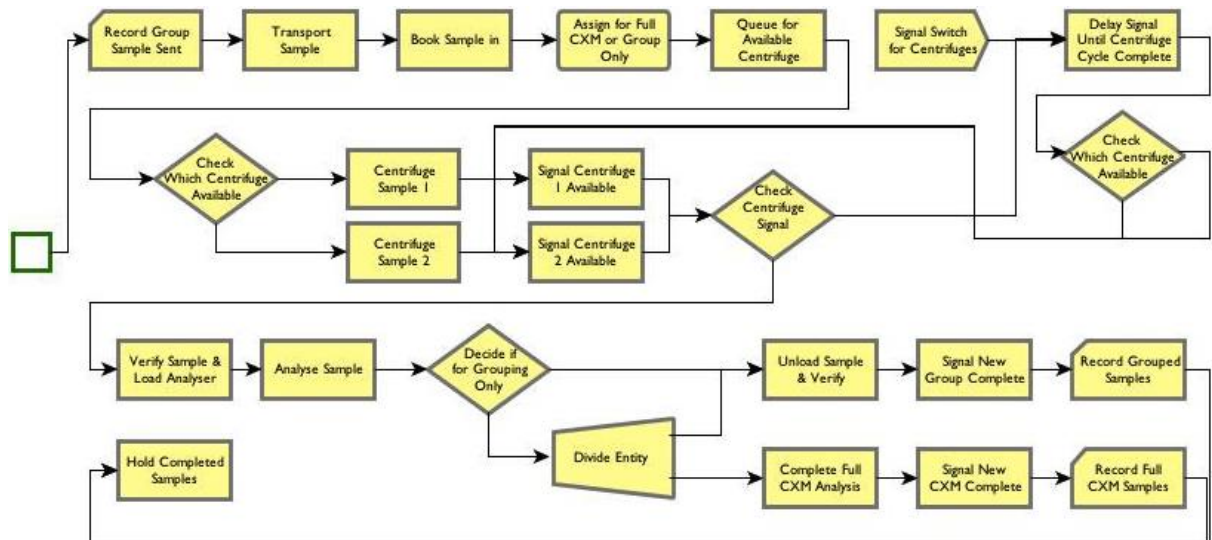
Figure 3.8 The Transfusion Laboratory sub-model with the Entry point ☐ from the Patient Characteristics sub-model.

The processing of samples for the provision of group-specific PRBCs to casualties is performed in the Transfusion Laboratory sub-model. As stated previously, entities in this sub-model represent individual casualty-specific blood samples as opposed to the casualties themselves. Firstly, the sample is recorded as being sent to the laboratory for Arena to monitor how many samples have been sent and received. The first discrete event follows, as the sample is transported from the casualty to the laboratory. This is assumed to occur through an automatic air-tube system common to most hospital environments and to consume a defined mean time period set within the module. Upon arrival, the sample is booked into the transfusion laboratory which requires one of a finite number of laboratory technicians (a model resource), who are occupied with this task for a defined time period.

Following this step, the sample is marked as allocated for a full antibody cross-match or simpler group analysis. This was added to allow flexibility in the model in any future experimentation. The assigned default setting was to perform group analysis only for all samples.

Once the sample is booked and assigned for processing, it waits for a centrifuge to be available to prepare the sample for analysis. The sample is held in a queue until this condition is satisfied. This queue is set to a default setting of prioritising P1 samples ahead of P2 followed by a FIFO arrangement. Centrifuges generally do not allow continuous loading, hence the spin cycle must complete prior to a new sample being added, however, they do allow the spinning of multiple samples at once, depending on the product used. An unlimited number of centrifuges can be included in the model. Figure 3.8 shows the use of two available centrifuges, the capacity of which is set within the Process module. The centrifuge Process module – 'Centrifuge Sample -1 or 2', delays the sample for a defined period of time also set within the module to simulate this process, following which, the entities pass through a Signal module. Signal modules are not time-dependent steps and serve only to indicate to queuing samples that a centrifuge is now free for use.

A separate Create module was added to the sub-model at this stage. This is required to trigger the signal of centrifuge availability at the start of the simulation when no samples are being processed and as a fail-safe to ensure samples do not wait in a queue when a centrifuge is available. The module creates a phantom entity at time zero which is held in a Hold module until a centrifuge is empty (as is the case at the start), at which point it is released to the Decide module. This module checks if a single or both centrifuges are free and sends the entity to the respective Signal module to ensure the release of the samples from the queue. The Hold module (which houses the queue of waiting samples) is set to release the maximum number of samples that can be accommodated by the free centrifuge(s). The Decide module which follows the individual centrifuge signalling modules, serves to recycle the phantom entity in this section of the sub-model, it therefore forms a closed repeating process loop with no discrete event effect on the simulation.

The samples themselves continue in the model following the centrifuge process. They are verified and loaded into the automatic blood sample analysing machine through a time-dependent Process module, this additionally occupies a resource in the form of a laboratory technician for a defined time scale. The loaded samples are processed by a continuously loadable analyser with a defined capacity and a defined processing time set within the module. As analysers are generally continuously loadable, instead of adding further analysers to the model, the capacity of a single module can be increased to represent additional machines as required. The processing procedure is interrupted at this stage to allow the decision as to whether the sample is for grouping only or full cross-match analysis as assigned earlier in the model. If it is for full cross-match analysis, the sample continues instantaneously into a further cycle of analysis by way of a Divide module which allows a replica sample to progress for parallel provision of group-specific PRBCs. The timescale for the full cross-match process is determined by random probability distribution sampling within the module and uses the same machine as for group analysis. The sampling distribution is applied to represent the variation in antibody profiles of the population's blood and thus the time required to establish a full compatibility characterisation.

The samples for which the basic blood group has been established are unloaded and verified as per the loading module. A signal is then released in the model confirming that the corresponding casualty can now receive group-specific PRBCs wherever they are in the system at that point in time. Finally the samples are recorded in Arena as complete and held in a Hold module which prevents them having any further interaction within the model. The full cross-match samples undergo the same processes upon completion of their full analysis. As all samples eventually terminate within this sub-model there is no required exit for returning to the main model map, all signals are transmitted automatically within the entirety of the model.

Meanwhile, during blood sample analysis, casualties continue to be treated in parallel elsewhere in the model. The casualties leaving the Patient Characteristic sub-model (Figure 3.7) enter immediately into the Emergency PRBC Provision sub-model (Figure 3.9) via the

main model map (Figure 3.6). This sub-model is constructed through a series of Decision modules which act as logic gates to ensure the specific casualty receives emergency type O PRBCs (universal donor PRBCs) up to their originally defined and assigned demand level. The logic flow of this sub-model prevents casualties from: receiving too much overall blood, receiving more than a defined volume in any one instance - added to imitate the usual delivery of this emergency resource in a protocol driven manner and finally, from receiving PRBCs when stock has been exhausted. The latter is determined by continuous reference to the type O PRBC resource level, which like all resources, is defined and tallied in the spreadsheet window of Arena. As a casualty passes through this logic tree, the number of units for transfusion (based on demand and their availability) are assigned to the casualty. As this process involves only Decision and Assign modules there are no time-dependent steps until this point.
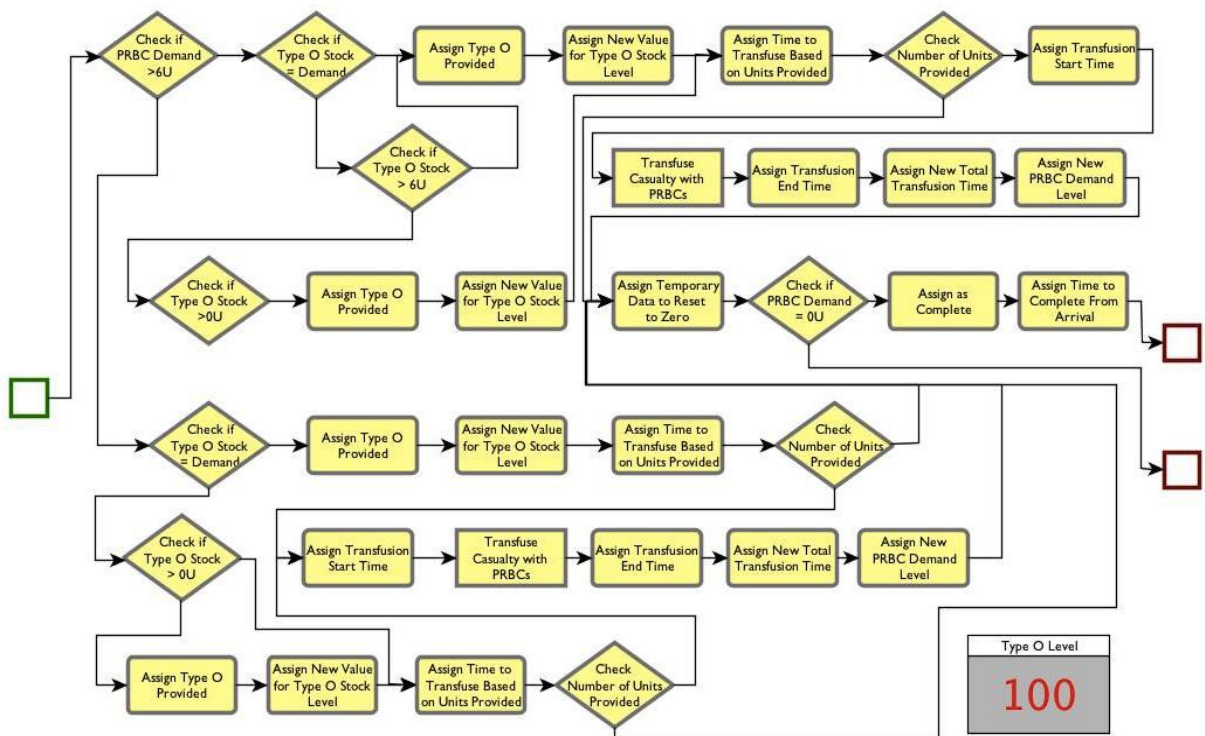
Figure 3.9 The Emergency PRBC Provision sub-model with Entry ☐ and Exit ☐ points linking it with the main model map. A type O PRBC inventory counter is also provided for observation of stock levels (in Units of PRBC) during a simulation run within the sub-model.

At this stage, the casualty is labelled with the current simulation time before entering the transfusion Process module titled – 'Transfuse Casualty with PRBCs'. This Process module samples from a probability distribution to determine the time to infuse a single unit to the respective patient; this is based on their priority and the number of units requiring transfusion, to give an overall event time. This event time is added to a total overall transfusion time which accumulates as the casualty is treated within the model.

A new updated PRBC demand must now be set for the casualty subsequent to this transfusion and this takes place immediately afterwards in an Assign module. Once an appropriate transfusion has taken place, or not, in the case of supply exhaustion, the casualty exits the sub-model back to the main model window (Figure 3.6). Prior to this, all casualties are checked to establish if their original PRBC demand has been met. If their demand has been satisfied, they are assigned as complete and proceed to the Exit and Data Collection sub-model via the main model window. This sub-model is described in more detail at the end of this section.

Casualties who still require a PRBC transfusion having received emergency PRBCs are divided by their assigned, but as yet unestablished blood group (Figure 3.6) and proceed to enter the Wait for Group Confirmation sub-model (Figure 3.10 A-D). These four sub-models have a similar format and therefore are discussed collectively. The casualty enters the respective sub-model and immediately enters a decision module to determine whether or not the blood group has been established yet. If it has, they are further checked for ongoing PRBC requirements. If their demand is met they exit the sub-model ready to terminate via the main model, if not, they exit back to the main model and enter the Type A, B, AB or O PRBC Provision sub-models.

A)

B)

C)

D)
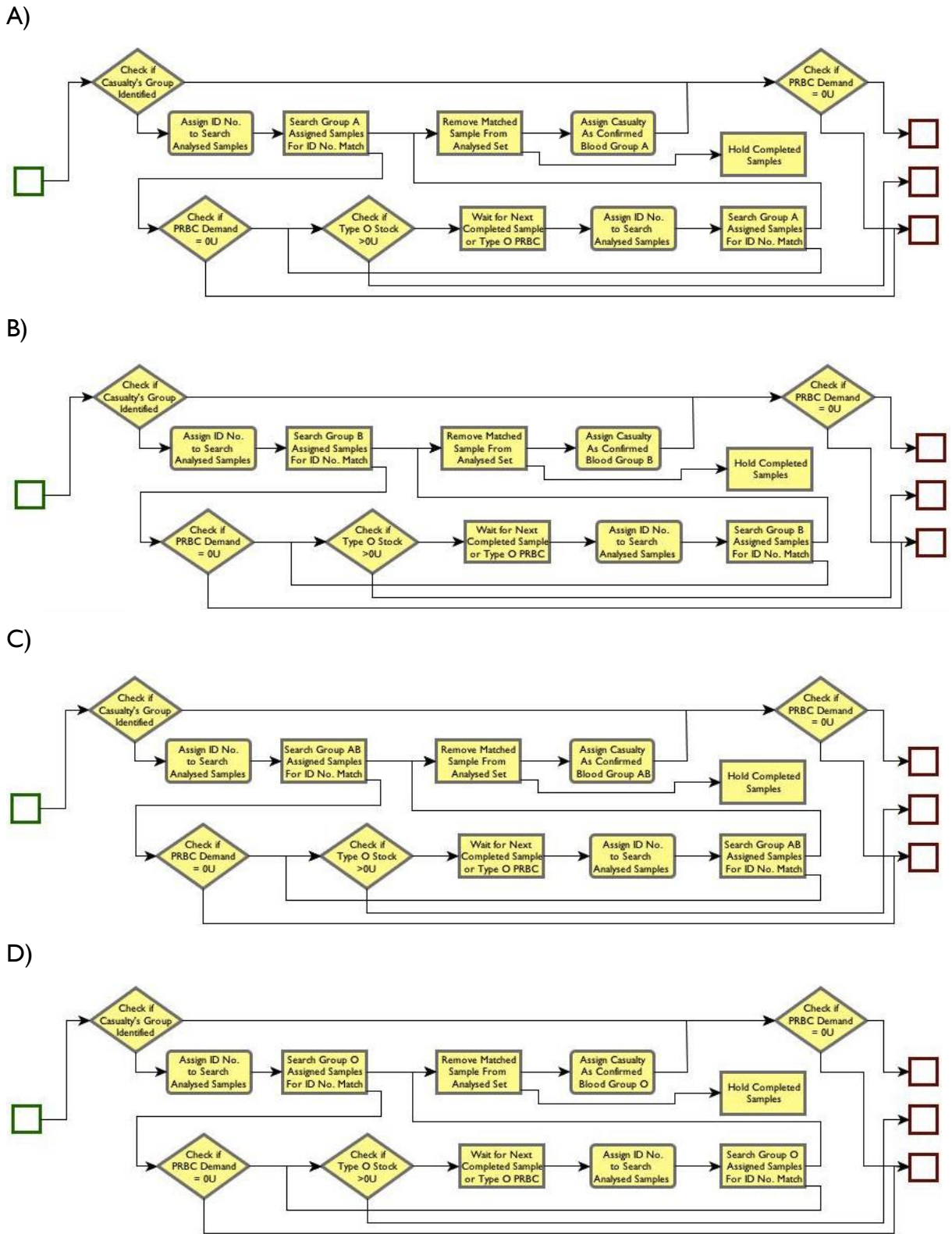
Figure 3.10 The Wait for Grouped PRBCs: A (A), B (B), AB (C) or O (D) Confirmation sub-model with Entry ☐ and Exit ☐ points linking them with the main model map.

Those casualties for whom a blood group is still unknown are assigned a unique identification number (the same as their hospital number). This is used to search the model for a corresponding processed blood sample with the exact same hospital number using a Search module. Should this be found, the sample is removed from the held sample module in the Transfusion Laboratory sub-model (Figure 3.8) using a Remove module and placed in a completed samples hold within this sub-model. Neither of these processes is time-dependent and therefore do not represent discrete events within the simulation.

At this point, the casualty can now be assigned as having a known blood group and is permitted to receive group-specific PRBCs. Should the casualty's blood sample not be ready at this time, they enter a Decision module to establish if they still require a transfusion, if they don't, they exit the model. Those that do still require PRBCs and for whom emergency type O PRBCs are available, exit the sub-model and re-enter the Emergency PRBC Provision sub-model to recycle through the system. When the type O PRBC supplies are exhausted and the casualty group is yet to be established, the entities enter a Queue module – 'Wait for Next Completed Sample or Type O PRBC', where they wait for one of these conditions to be satisfied, following which, they follow the appropriate path as described above.

Casualties requiring a transfusion who have an established blood group, gain access to the respective Type A, B, AB or O PRBC Provision sub-models. As per the preceding section, these are discussed collectively due to the similarities between sub-models (Figure 3.11 A-D). An identical logic tree-based process is followed for group-specific PRBC provision as was the case for emergency type O PRBC provision (Figure 3.9). There are, however, three notable exceptions:

Firstly, before group-specific units can be transfused to a casualty, they need to be released by the transfusion laboratory by way of a Process module. This occupies a resource in the form of a laboratory technician who takes a specified amount of time to release each required unit. Secondly, the released units of PRBC must be collected and delivered to the casualty. This relates to the issue of casualties moving through the hospital as their

treatment progresses, in contrast to emergency type O RBCs, which are generally available locally throughout the critical areas of care via automatic satellite blood fridges. The collection and delivery of PRBC units is a time dependent process which also occupies a resource, in the form of a hospital porter, for a defined period of time. Porters, like laboratory technicians are a finite resource within the model; the number available is determined along with other simulation resources in the spreadsheet window of Arena's user interface. Finally, these sub-models allow the transfusion of group compatible PRBCs when the primary group is unavailable. The casualty passes through each available PRBC group option in order of least expected demand competition to greatest, until either their demand is satisfied or all compatible PRBC supplies are exhausted.

Having passed through their respective group-specific provision sub-model, casualties enter a Hold module. From here they either recycle through the model to complete their transfusion demand, are held pending replenishment of stocks or exit to the main model to terminate in the final sub-model – the Exit and Data Collection sub-model (Figure 3.12). All bleeding casualties exit the model via the main model map followed by the Exit and Data Collection sub-model (Figure 3.6 & Figure 3.12). Those that have been treated to completion in terms of their PRBC demand are divided by Decide modules into priority groups and subsequently by whether their blood group was established prior to their completion. This data is written into Excel by the VBA module which follows immediately prior to entities entering the final sub-model.

A)

Check if PRBC Demand >6U

Check if Type A Stock = Demand

Assign Type A Provided

Assign New Value for Type A Stock Level

Assign Time to Transfuse Based on Units Provided

PRBC Dispensed by Transfusion Lab

Check Number of Units Provided

Assign Type A Provided

Assign New Value for Type A Stock Level

Check if Type A Stock > 6U

Assign Type A Provided

Assign New Value for Type A Stock Level

Check if Type A Stock = Demand

Check if Type A Stock > 0U

Check if PRBC Demand Was > 6U

Check if Type O Stock = Demand

PRBC Delivered to Casualty

Assign Transfusion Start Time

Transfuse Casualty with PRBCs

Assign Transfusion End Time

Assign New Total Transfusion Time

Assign New PRBC Demand Level

Assign Temporary Data to Reset to Zero

Check if PRBC Demand = 0U

Queue For Compatible PRBCs

Assign as Complete

Assign Time to Complete From Arrival

Check if Type O Stock > 6U

Assign Type O Provided (Temp)

Assign Type O Provided

Assign New Value for Type O Stock Level

Check if Type O Stock = Demand

Assign Type O Provided (Temp)

Assign Type O Provided

Assign New Value for Type O Stock Level

Check if Type O Stock > 0U

Assign Type O Provided

Assign New Value for Type O Stock Level

Type A Level	Type O Level
75	100

B)

Check if PRBC Demand >6U

Check if Type B Stock = Demand

Assign Type B Provided

Assign New Value for Type B Stock Level

Assign Time to Transfuse Based on Units Provided

PRBC Dispensed by Transfusion Lab

Check Number of Units Provided

Assign Type B Provided

Assign New Value for Type B Stock Level

Check if Type B Stock > 6U

Assign Type B Provided

Assign New Value for Type B Stock Level

Check if Type B Stock = Demand

Check if Type B Stock > 0U

Check if PRBC Demand Was > 6U

Check if Type O Stock = Demand

PRBC Delivered to Casualty

Assign Transfusion Start Time

Transfuse Casualty with PRBCs

Assign Transfusion End Time

Assign New Total Transfusion Time

Assign New PRBC Demand Level

Assign Temporary Data to Reset to Zero

Check if PRBC Demand = 0U

Queue For Compatible PRBCs

Assign as Complete

Assign Time to Complete From Arrival

Check if Type O Stock > 6U

Assign Type O Provided (Temp)

Assign Type O Provided

Assign New Value for Type O Stock Level

Check if Type O Stock = Demand

Assign Type O Provided (Temp)

Assign Type O Provided

Assign New Value for Type O Stock Level

Check if Type O Stock > 0U

Assign Type O Provided

Assign New Value for Type O Stock Level

Type B Level	Type O Level
25	100

C)

Type AB Level
10

Type A Level
75

Type B Level
25

Type O Level
100

134

D)

Figure 3.11 Type A (A), B (B), AB (C) or O (D) Provision sub-models with Entry □ and Exit □ points linking them with the main model map. All applicable PRBC inventory counters are also provided for observation of stock levels (in Units of PRBC) during a simulation run within each sub-model.

Figure 3.12 The Exit and Data Collection sub-model with the Entry points □ from the main model window.

This final sub-model receives all casualties suffering haemorrhage who enter the model via two entry points. The first receives all bleeding P1 and P2s who have received their full treatment within the model and are assigned as complete. The entities are assigned statistics relating to the current state of the model at their time of exit including resource levels, occupancy of staff and current queue lengths. This allows further information regarding the overall activity during a simulation to be recorded during a run. In addition to this ad-hoc statistics collection, there is a separate data collecting entity created within this sub-model for the sole purpose of monitoring these parameters on a regular basis. The data collecting entity is created every five minutes from the start and is assigned the same information regarding resources, staff occupancy and queue lengths. This entity is separated by a Decide module which also splits the casualty entities into their corresponding blood groups prior to recording all data into Excel through a linked VBA module.

The second entry point receives the duplicated entities of the P1 and P2s identified as bleeding in the Patient Characteristics sub-model. This was required as not all casualties suffering haemorrhage will go on to receive their full PRBC demand and therefore exit the model. The duplicate casualty entities are divided by their assigned blood group and recorded via a VBA module. This allows monitoring of the number of casualties unaccounted for at the end of the simulation and given their blood type, aids in determining the reasons for their failure to receive full treatment by the end of the simulation run. All entities are held in a Hold module within this sub-model, whilst they could be disposed of by Arena at this point, the Hold module allows checking of individual entities when testing and evaluating the model during its development.

3.5 Chapter Three Conclusion

This chapter has established DES as the most suitable modelling approach for the study objective based on the conceptual model plan. The various commercially available simulation software packages were then evaluated for criteria most relevant to this particular study and following a weighted scoring system, the Arena simulation package was selected as the most appropriate program in which to build the model. The theoretical design of the model was described and this was then coded into Arena to form a complete structural map describing all system components and their interconnecting processes.

In order to complete Aim Two and produce a working mathematical model of in-hospital PRBC provision, the simulation model required the population of the various definable fields within each model component with appropriate evidence-based inputs. This included all resource numbers, probability distributions and mean values applied within the various modules discussed in detail during this chapter. This essential process ensures the model provides a realistic representation of the real-world system and forms the focus of the following chapter.

CHAPTER FOUR

Informing the Model

4.1 Introduction to Data Acquisition and Input Modelling

4.1.1 Introduction

In Chapter Three, a modelling methodology was selected using a conceptual model of the system under study. This was subsequently developed to produce a structural description of the model which could be coded and implemented in the Arena environment to create a computerised version. Having established the structure of the simulation model the data inputs which are required to drive the model are now clearly apparent and the input modelling process may be performed. The effects the various individual components, as well as the sum of their combined effects on the outcome of a simulation run are dependent upon the quality and accuracy of the data used to populate their definable fields. Consequentially, the input modelling phase of system modelling is vital in delivering a true representation of the real-world system and satisfying Aim Two of this study (163, 243).

4.1.2 Categories of Data

The data applied to a model can be broadly grouped into three levels of availability: Available, unavailable but collectable and neither available nor collectable (163). Chapter Two illustrated the relative paucity of historical literature based data currently available to mass casualty event (MCE) blood planners. Whilst certain data inputs for this particular model are non-MCE specific and maybe readily available, other inputs required specific data collection exercises or the use of alternative methods to cope with those inputs which

were completely unavailable. Completely unavailable data can be handled in one of two ways, either through estimation of the parameter concerned, possibly through a surrogate data source, or by classing the parameter as an experimental factor within the simulation model (163). Experimental factors are investigated across a variety of values and over multiple simulation runs in order to establish their true or optimal value depending on the purpose of the model.

4.1.3 Data Sampling Options for Input Modelling

Collated data can be applied to the model data fields using several techniques. Data values can either be dealt with in a fixed deterministic or variable stochastic manner, as discussed previously in Chapter Three (174). For example, certain data values may represent known fixed constants and can therefore be assigned to the model component's input field directly and specified as such, ensuring the exact value will recur every time that field is applied during a simulation run. Other input values may vary across a range of fixed known or experimental values which the model can be designed to reference from directly during the simulation. This sampling of an external data set in a specified order is otherwise known as, trace sampling (163, 174).

Although some data input fields require the application of a single or range of known deterministic values, this study is primarily focused around variable inputs and stochastic simulation methods. Many of the model components therefore utilise a variable degree of random sampling with which to populate the data fields during a simulation run. These random sampling methods can range from uncontrolled pure random number generation through to pseudo-random sampling. An example of the latter would be a systematic selection processes combining trace sampling with a random point of initiation within the trace (163).

Determining the suitability and type of random sampling required for a particular stochastic input requires consideration of a number of factors including: the data type, the sufficiency of available data, its reliability and the intentions of the simulation study, as well as whether there is a need to investigate circumstances not represented by the dataset. Sampling from a probability distribution is a commonly applied method employed during simulation input modelling. Any suitable and available reference data can be used to determine the probability distribution of the variable, the input values can then be derived automatically during the simulation run through random sampling from that specific distribution. This technique allows the model to experiment beyond historical datasets and compensate for situations where data availability is minimal or the data spread is based on expert judgment alone (163, 174).

There are a variety of standard probability distributions built into the Arena software, allowing both continuous and discrete sampling (Appendix III). In addition, customised empirical and theoretical probability distributions can also be defined to suit the data concerned (174). The Arena software package is accompanied by an input analyser tool which is able to read and interpret a formatted dataset in order to estimate parameter values and determine the probability distributions which best-fit the provided data. Various statistical analyses can then be performed to determine which distribution should be incorporated into the model and used for random sampling during the simulation (174).

4.1.4 Chapter Four Objective and Aims

The objective of this chapter was to describe the input values, probabilities or sampling distributions applied to each definable model component involved in the simulation. Given the various methodologies required to manage the different types of data inputs and their levels of availability, the data acquired to populate the model are described through four individual sub-study investigations categorised by the type of data required. These were explored through the following four broad aims: 1) To determine packed red blood cell

(PRBC) demand both individually and overall, 2) To define casualty arrival rate and the injury severities received, 3) To establish the timings for processing each casualty type, and 4) To quantify both blood group analysis timings and overall major trauma centre (MTC) resource levels.

4.2   Defining Packed Red Blood Cell Demand

4.2.1   Introduction

The number of casualties suffering haemorrhage and their individual demand for blood are two of the key data inputs required to drive the model. They were considered to be the most important factors in terms of effect on simulation outcomes during the model's design and development stage. Furthermore based on the literature review of Chapter Two, these inputs were thought to be the most challenging in terms of obtaining an accurate estimation for the model from the available information sources. The first aim of this chapter was therefore focused on investigating these two areas of greatest uncertainty.

Chapter Two's review of MCE blood use revealed prediction and planning blood needs for MCEs requires broad casualty descriptors. The review revealed a strong association between the number of Injury Severity Score (ISS) >15 casualties and the PRBC use following terrorist MCEs. Furthermore, the majority of literature discussing casualty resource demands in MCEs, does so using cohorts describing injury burden or acute healthcare service requirements. Examples include ranking casualties generally by severe, moderate or mild injury, the triage priority scoring system or similarly to Chapter Two by using the ISS strata of >15, 9-15 and <9 (111, 119, 294-298).

Current UK and military based planning methods apply the priority system for MCE resource forecasting. The advantage of this is the tool is by definition MCE specific, relates generally to casualty needs on an approximate time defined basis and is available at a relatively early stage in the time course of an event (87). The priority scoring system was applied to the study model in order to reflect this planning approach. However, from the literature review whilst ISS was available for 50% of the events, Triage Sieve/Sort (TS) was reported in just eight percent. In view of this lack of literature based data regarding casualty priority, establishing a model input value for casualty blood demand in terms of TS required an alternative approach to inform the model appropriately.

As discussed, the priority system is designed for MCE situations, the collection of standard civilian trauma data as a surrogate means of defining this input was therefore deemed inappropriate for an accurate reflection of the population concerned. The principal reasons for this being that casualty priority would need to be calculated based solely on admission observations, the injury mechanisms involved are of comparatively much lower energy when compared to those experienced during MCEs, and civilian trauma results in a very low number of casualties being received in any one instance, therefore eliminating the institutional strain characteristic of an MCE.

Establishing a feasible solution to this aspect of the input modelling process therefore required the use of an alternative surrogate dataset involving casualties and scenarios similar to those experienced during an MCE. Outside of civilian MCEs the only environment in which these circumstances are replicated is during military operations, where the TS system is also applied. The high energy mechanisms of injury (MOI) experienced in combat, regularity of traumatic injury involving multiple or mass casualties and subsequent strain placed on responding healthcare units, suggest a military data source offers an appropriate surrogate from which applicable data may be obtained. In addition to establishing demand for PRBC and overall rates of haemorrhage based on the TS system, the military's reporting of both TS and ISS would also facilitate a greater understanding of the relationship between these two measures. This would allow comparison with the results from the civilian MCE

review in terms of blood demands and potentially aid other aspects of the input modelling process.

The first aim of this chapter was therefore investigated through interrogation of a recent joint UK and USA military dataset of operational activity during war. The purpose of this being to assess casualty priority level in terms of ISS, characterise individual priority level PRBC demands and determine the rate of bleeding casualties expected within each priority cohort.

4.2.2 Methods

A retrospective review and interrogation of the Lab Information Management System (LIMS) was performed of all casualties treated at the joint task force combat medical facilities in Afghanistan during the calendar year January to December 2010. The Joint Theatre Trauma Registry (JTTR) was then interrogated for the identified individual casualties' injury descriptors and PRBC requirements. The study population considered included all adult casualty types regardless of nationality or affiliation who survived the initial traumatic insult. Paediatric cases (<16 years) were excluded due to the variations in transfusion protocols applied in their treatment. All casualties were assessed for: MOI, TS at admission, ISS and their PRBC demand during initial emergency department (ED) care and whilst undergoing emergency surgery at the area's principal military hospital termed Role Three (R3).

Where not previously assigned, the systolic blood pressure (SBP), respiratory rate (RR) and Glasgow Coma Score (GCS) at R3 were interrogated for each casualty and applied to the TS system in order to allocate casualty priority from one to three (P1-3). When TS data was unavailable the physiological and anatomical information available from the point of injury to R3 admission was analysed in order to score the casualty appropriately. This process was performed through two independent expert reviewers with a third review

carried out in situations where there was a discrepancy between the reviewers' opinions. Throughout the process of assigning priority, reviewers were blinded to further information regarding casualty outcomes and any additional information deemed inaccessible at the point of triage. The P4 expectant category was not applied during the review process as sufficient information regarding resource availability could not be determined from which to make an informed decision. The ISS scores were independently and prospectively entered by the independent JTTR data entry team using the 2005 revised version of the Association for the Advancement of Automotive Medicine Abbreviated Injury Severity Score (AIS) (19).

Finally, the ratio of bleeding casualties within each priority category was investigated. In order to account for aggressive military transfusion policies and the lack of cautionary blood use in non-MCE scenarios, those casualties receiving two or fewer units of PRBC during their initial resuscitation were deemed to either not be suffering acute haemorrhage or manageable without the receipt of any transfusion they received. All PRBC units registered in the JTTR as provided to casualties in the ED or in theatres were assumed transfused in full. Data analysis was performed in GraphPad Prism (GraphPad Software Inc. San Diego, CA, USA) and distribution fitting undertaken using the Arena Simulation Input Analyzer (Rockwell Automation, Pittsburgh, USA). The input analyser was limited to discrete distribution fitting only so as to ensure individual casualty PRBC demand and therefore also PRBC supply, remained in the appropriate discrete units during simulation runs. Unless stated, a p-value of <0.05 was considered significant in all statistical analysis.

4.2.3 Results

The review of LIMS provided 486 adult casualties treated at the main R3 military medical facility in Afghanistan during the 2010 calendar year who met the inclusion criteria. Ten casualties were excluded due to insufficient data availability preventing their TS status from being determined or due to missing ISS data. 474 casualties were therefore included in the

analysis. The expert review process required a third expert reviewer decision on 31 (6.5%) of the cases, following which, the dataset comprised 323 P1s, 47 P2s and 104 P3s. The various MOI encountered are shown in Table 4.1. The ISS ranged from 1-75 with a median of 13 (inter-quartile range (IQR) 9-20), the distribution of ISS for each priority category is shown in Table 4.2. As the model is designed to include only those casualties likely to require PRBCs and the P3 category describes walking wounded casualties assumed not to require transfusion, the remainder of this sub-investigation concentrates purely on the P1 and P2 cohorts.

Table 4.1 Total number of casualties by MOI included in the JTTR analysis

MOI	Casualties*
Aircraft Incident	2
GSW	177
Explosive	289
Stab	2
MVC	3

MOI for one casualty was not able to be determined from the data available, GSW – Gun Shot Wound, MVC – Motor Vehicle collision.

Table 4.2 ISS distribution for each priority score

	P1	P2	P3
Minimum	1	1	1
25% Percentile	10	10	5
Median	17	13	9
75% Percentile	22	17	10
Maximum	75	50	19
Number of values	323	47	104

The IQR of injury scores for P1 and P2 casualties includes both the >15 and the 9-15 cohorts classically described in the literature as representing severe and moderate injury respectively. The median ISS value for a P2 of 13 lay in the moderately injured range and the P1 median of 17 in the severe injury range as shown in Figure 4.1 (203, 299-301). The PRBC demand for all P1 and P2 casualties totalled 3,692U with a median use of eight units per casualty (IQR 2-14U). The distribution of PRBC demand for P1 and P2 casualties is shown in Figure 4.2. The median PRBC use was nine units (IQR 4-15U) and two units (IQR 2-6U) for P1 and P2 casualties respectively. The P1 and P2 PRBC demand dataset was subsequently evaluated using the Arena Input Analyzer. The analysis identified the Poisson distribution (Appendix III) with a mean of 10.7U - [POIS(10.7)] for P1 casualties and 4.7U - [POIS(4.7)] for P2 casualties as the best-fit discrete distributions for application to the model. There was no statistically significant difference between the sample data and the fitted distributions on Chi-Square testing.
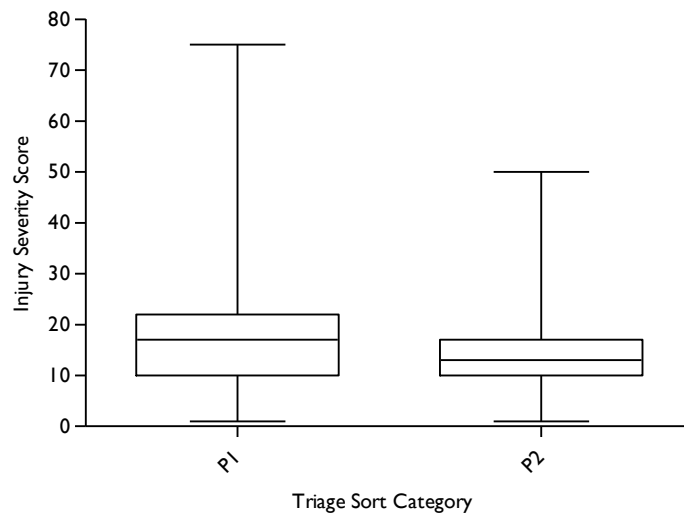
Figure 4.1 The ISS distribution for P1 and P2 casualties over one year of military operations in Afghanistan.

Finally, the ratio of casualties within each cohort requiring a transfusion was investigated (Table 4.3). The dataset revealed approximately 80% of P1 casualties received over two

units of PRBC during initial resuscitation, leaving around 20% deemed as not requiring a transfusion. In contrast, from the 47 P2 casualties included in the study, around half received two or fewer units of PRBC during their resuscitation, giving an approximate 50% transfusion rate in the P2 cohort.
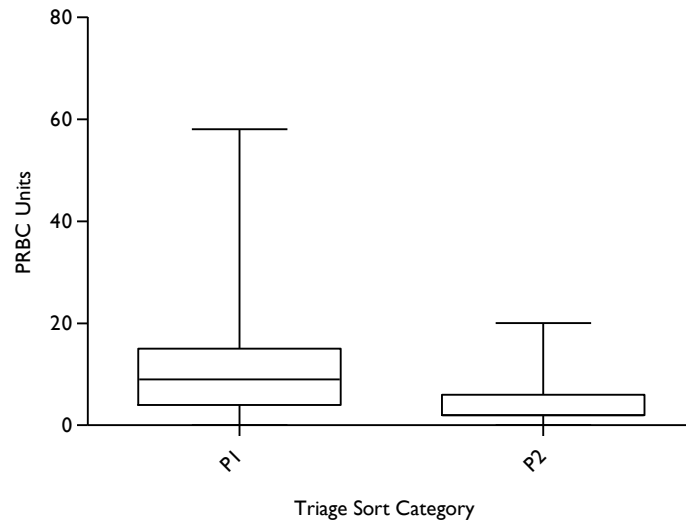
Figure 4.2 The distribution of PRBC demand for P1 and P2 casualties over one year of military operations in Afghanistan.

Table 4.3 The ratio of bleeding to non-bleeding casualties in the P1 and P2 cohorts

	P1	P2
Number of Bleeding*	252	23
Number of Non-bleeding	71	24
%Ratio of Bleeding to Non-bleeding	78:22	49:51

*Bleeding defined by the transfusion of greater than two units of PRBC during initial resuscitation.

4.2.4 Discussion

This study of the military JTTR over one calendar year provided a surrogate dataset for some of the key inputs required to drive the simulation model. The study was able to provide input modelling parameters for: individual P1 and P2 casualty PRBC demands through a best-fit Poisson distribution, identify the approximate ratio of bleeding to non-bleeding casualties within each priority cohort, and provide greater appreciation of the relationship between ISS and TS. Although a surrogate for real data, the results appear to offer appropriate model inputs based on previously published experience.

The study highlighted the relationship between the early TS categorisation and injury severity, indicating P1 casualties best reflect those with severe injuries and an ISS >15, whilst the P2 casualty cohort is similar to those classically described as moderately injured with an ISS ranging from 9-15. Understanding this relationship between TS and ISS allows greater interpretation of historical literature based MCE data where TS is often neglected in favour of reporting overall injury burden using the ISS system.

The consumption of PRBCs during the calendar year was significant, reflecting the high volume of trauma experienced on a daily basis during military operations and indicating the suitability of the dataset as a substitute for primary MCE data. The median PRBC use of eight units when both P1 and P2 casualty cohorts were considered together shows similarities with previous studies. In Israel, an average PRBC use of nearly seven units per moderate and severely injured casualty was identified during a study of 103 MCEs over a five year period from 2000 to 2005 (118). Furthermore, the median P1 PRBC use in this study was nine units, this is compared with the 100 year MCE literature review of Chapter Two in which an upper quartile level of over eight units per casualty of ISS >15 was identified. These slightly higher estimates found in this study may be explained by the changes to transfusion protocols seen over this time and the increased emphasis now placed on major haemorrhage protocols (MHP(s)) and the aggressive treatment of trauma haemorrhage in general.

The different proportions of bleeding casualties in the P1 and P2 cohorts was mirrored by their triage category with significantly more P1s requiring early PRBCs compared with P2s. The observed 80% transfusion rate reflects the high rate of haemorrhage experienced following major trauma as discussed in Chapter One and although not as high, there remains a significant transfusion burden in the P2 cohort as well.

4.2.5 Limitations and Conclusion

There were a number of limitations with the sub-study design, which although unavoidable, should be appreciated when translating the inputs into the model. Firstly, whilst contact with hostile forces through gunfire or the detonation of explosives, often generates multiple casualties, MCEs on the scale of civilian events are rarer and the dataset will therefore reflect this reduced strain on resource availability. Secondly, as discussed during the literature review in Chapter Two, military data largely concerns physiologically fit young men who have the benefit of adjuncts such as body armour to reduce the burden of injury. This may distort the bleeding rate and individual demand for blood amongst the casualties received at the responding hospital.

Thirdly, there is the benefit of a large amount of first responder training with specific haemorrhage control equipment available on scene (including earlier PRBC availability) in the military setting, as well as a well-rehearsed and rapid ability to extricate casualties to an equivalent MTC early in their course of treatment. This is in contrast to a civilian MCE, when communication and infrastructure are disrupted to a greater extent, delaying access to casualties by trained healthcare providers and with events which often occur in unexpected circumstances. Finally, the simulation was designed to model a generic MCE and this dataset consisted almost exclusively of either GSW or explosive injuries. There was an appreciable variation in blood demands seen in events with alternative MOI such as structural collapse observed in the literature review of Chapter Two, which should be accounted for in interpreting the model's outputs.

Despite these limitations, in the absence of an alternative data source which may provide more reliable input data, the high energy trauma and case volume of the JTTR appears to offer a suitable modelling alternative. The surrogate dataset has been able to provide input data for bleeding rates and individual PRBC demand suitable for application in the model, as well as aid in characterising a relationship between priority scoring systems and ISS.

4.3   Determining Casualty Arrivals and Severity Loads

4.3.1   Introduction

The rate of casualty arrivals into the MTC system as well as the proportion of P1 to P2 casualties within the arriving population is definable at the start of the simulation run. Having established the inputs for PRBC demand and the proportion of bleeding casualties within each cohort, these were considered the next most challenging input parameters to satisfy within the model. In addition, although an experimental factor, an overall load of total casualties received following an event also required defining. This was essential for the testing and evaluation of the model in a baseline state prior to performing any experimental analysis. Therefore, along with arrivals and severity distributions, an overall number of arrivals received following a generic MCE was also determined during this sub-study.

The classic arrival surge experienced following MCEs has been described as occurring early in the course of the MCE response, with the peak in arrivals taking place within one hour of the first casualty presenting to hospital (113). In attempting to establish the best evidence-based time pattern for model arrivals, as well as overall volumes casualties and their priority level, the original civilian MCE literature review of Chapter Two was revisited. Although this

review was originally focused on blood use in these events, the search strategy was such that it could be easily modified for this sub-study (Appendix I).

Determining proportions of each priority was also potentially challenging. The investigation of the first aim of this chapter illustrated the lack of adequate priority status reporting in relation to blood use during previous MCEs. However, the number of P1 and P2 casualties received irrespective of their blood use was not initially considered. In addition, the results from the first sub-study describing the relationship between priority status and ISS in the military setting, provided a possible adjunct should insufficient data be available from this repeat review of the literature.

4.3.2 Methods

The comprehensive literature search strategy as described in Appendix I and Chapter Two previously identified available literature regarding both collective reports of MCEs, as well as individual accounts of specific events occurring over the last hundred years (1911-2011). The results of the previous search were therefore re-appraised for this investigation. Reports of events were collated and analysed for descriptive data regarding casualty arrival times, their triage status and the individual event total P1 and P2 casualties received at responding units following incidents.

The previous definitions applied in Chapter Two were maintained to ensure consistency in reported values. This investigation also required the following two additional definitions to be applied. Firstly, the number of casualties within each triage priority cohort was taken as the number reported as P1 or P2 or using equivocal terminology within the article. Following on from the established relationship between TS and ISS described in Aim one, this included ISS groupings of >15 and 9-15 being applied as acceptable substitutes for P1 and P2 category casualties respectively. Secondly, the event time was defined as the time of the initial insult. Where the event involved multiple insults the event time was recorded as

time of the event directly relevant to the reporting unit. All reports of events describing at least the time of incident and the time to the final study-relevant casualty arriving at a single unit were included in the investigation.

Determination of casualty arrivals, triage priorities and total casualty numbers following events required, in certain instances, the collaboration of several reports of individual incidents which were managed as per the methods in Chapter Two. In addition, it was necessary to assume that unless specified, arrivals between reported time points occurred in a linear fashion, this included reports where the only times available were that of the event time and the hospital arrival time of the final P1 or P2 casualty. All arrivals were recorded as a cumulative percentage of all P1 and P2 or equivalent casualties received at the reporting unit over the course of the event. Arrival time periods were recorded at 15 minute intervals across all events with an overall mean cumulative percentage recorded across all events. No adjustment was made for the individual sizes of the events reported. When the triage category was not described in relation to arriving casualties, unless stated, it was assumed reporting was predominantly referring to P1 and P2 type casualties. This was justified by the preponderance to treat P3 type casualties at the incident scene or at lesser equipped units following MCEs.

The mean cumulative arrival percentage per 15 minute interval was represented graphically and analysed using the curve fitting software EasyFit Professional version 5.5 (MathWave Technologies, 2004-2010). The Kolmogorov–Smirnov non-parametric test of equality was used to compare the sample data with a range of reference probability distributions. The highest ranked significant distribution was accepted for application to each casualty load experimented with within the model. The proportion of casualties received of either category P1 or P2 was determined using the overall proportions of each type across all the reported events considered. The total casualty load for application in the baseline model was determined using the upper quartile level for all received P1 and P2 (or equivalent) casualties per individual event. The upper quartile was selected to test the model against a demand burden which would significantly challenge an MTC or equivalent facility. Where

events were discussed collectively, the casualty load was recorded as the mean across events. Unless stated, a p-value of <0.05 was considered significant for all statistical analysis.

4.3.3 Results

The original literature review produced 262 full-text articles discussing specific or collective MCEs. From these 23 (8.8%) articles provided descriptive data regarding casualty type and arrivals following 106 separate MCEs (Figure 4.3). The events involved a total number in excess of 22,000 casualties. The cumulative arrival times for each article are provided in Table 4.4. The mean cumulative percentage casualty arrival times across all events plotted at 15 minute time intervals are shown in Figure 4.4 A.
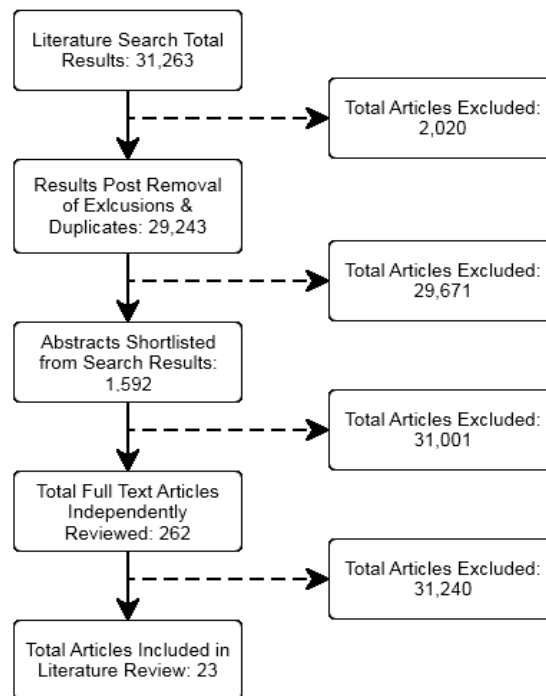
Figure 4.3 The search strategy for the literature review of casualty arrival times.

Table 4.4 Hours from the start of reported MCEs to the arrival of all P1 and P2 casualties received at the reporting units

Year	Location	MOI*	Hours from Start of MCE to Arrival of all P1 & 2 Casualties
			0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 · 10 · 11 · 12 · 13 · 14 · 15
1942	USA	Fire (218)	
1965	Vietnam	Bombing (230)	
1966	Vietnam	Bombing (230)	
1973	UK	Bombing (230)	
1974	UK	Bombing (230)	
1980	Italy	Bombing (230)	
1987	UK	Bombing (230)	
1989	UK	Plane Crash (206)	
1991	UK	Bombing (230)	
1993	India	Bombing (300)	
1993	USA	Bombing (230)	
1994-8	Israel	Bombing (230)	
1994-8	Israel	Bombing (230)	
1996	USA	Bombing (230)	
1998	Germany	Train Crash (301)	
1998-04	Finland	Multiple** (302)	
1999	UK	Bombing (230)	
1999	UK	Bombing (222)	
2001	USA	Plane Crash / SC (231)	
2001	Israel	Bombing (303)	
2001	Serbia	Bombing (211)	
2001	USA	Plane Crash / SC (294)	
2001	USA	Plane Crash / SC (294)	
2002	Pakistan	Bombing (304)	
2003	Turkey	Bombing (305)	
2004	Spain	Bombings (233)	
2004	Spain	Bombings (216)	
2004	Eygpt	Bombing (306)	
2005	Israel	Bombing (307)	
2005	UK	Bombings (119)	
2005	Israel	Bombing (308)	
2006	Israel	Bombing (111)	

*MOI given as the principal MCE causing mechanism, **Multiple MOI inclusive of MVCs, GSWs, fires and stabbings, SC – Structural Collapse, MVC – Motor Vehicle Crash*

All P1 and P2 type casualties were reported as having arrived within 16 hours of the initial insult for all 106 events, with half of all arrivals occurring within two hours and 75% of the total casualty load arriving at reporting units by three and a half hours. Curve fitting analysis of the cumulative data using the Kolmogorov–Smirnov test of distribution equality, ranked the Johnson Special Bounded (SB) distribution (Appendix III) first amongst the significant input distributions compared with the collated data (Test statistic = 0.06). The Johnson SB distribution parameters fitted to the sample data are detailed below and the distribution shown in Figure 4.4 B:

$$Johnson\ SB\colon \gamma = 1.0, \delta = 0.55, \lambda = 15.0, \xi = 0.05$$

The arrival of casualties following an MCE occurs in a discrete manner. As such, in order to apply the fitted sample arrival data to the model, a discrete distribution was required. The Johnson SB distribution was therefore divided into 16 one hour time bins. The model applies the overall defined casualty load to the probability distribution and randomly samples arrivals during each hour of the simulation run. Arrivals for any pre-defined casualty load could therefore occur from the first to the last second of this timeframe during a simulation.

A)

156
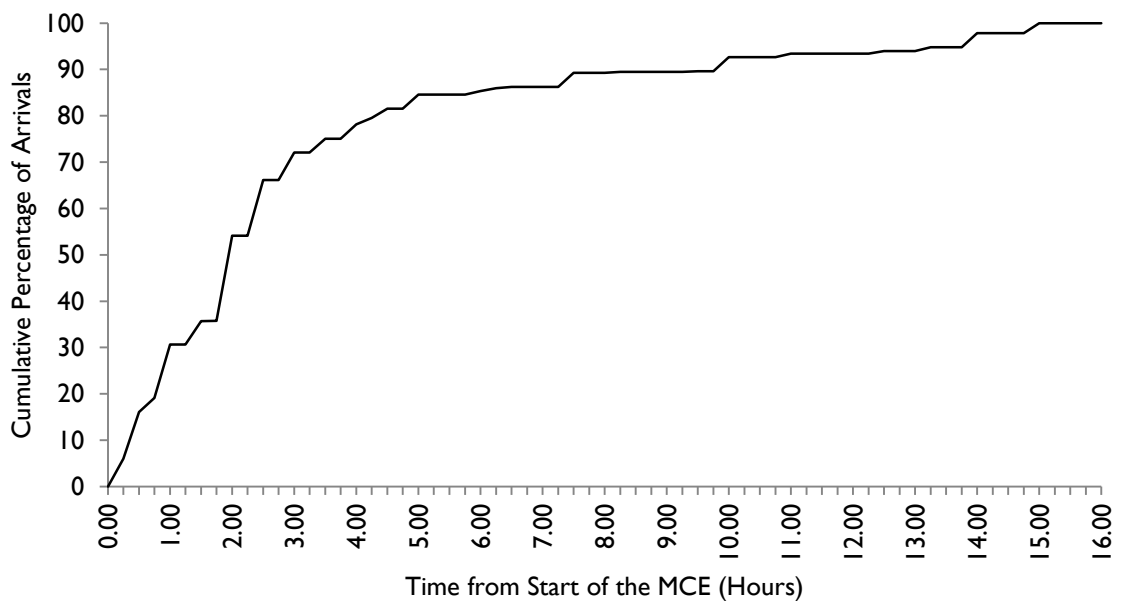
B)
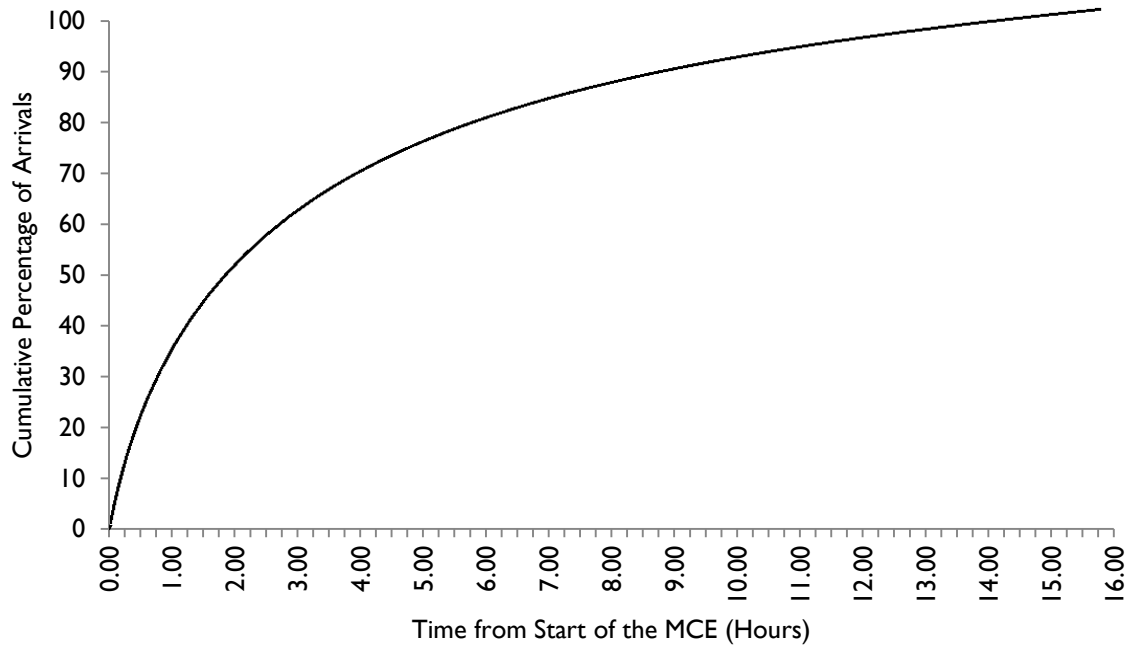
Figure 4.4 (A) Cumulative mean percentage of P1 and P2 arrivals across all MCEs reviewed and (B) Curve fitting analysis of the mean sample data to provide a best-fit cumulative distribution (Johnson Special Bounded (SB) distribution) of P1 and P2 casualty arrivals.

The proportion of P1 and P2 casualties entering the model was also derivable from the literature base. From the 262 full-text articles discussing specific or collective MCEs, 24 (9.2%) provided quantitative data regarding the ratio of category P1 to P2 casualties received at reporting units following an event (Figure 4.5). These 24 articles reported on approximately 9,000 injured patients resulting from MCEs, including over 1,500 P1 and P2 or equivalent casualties. The overall ratio of P1s to P2s received across all MCEs for which applicable data was available, was approximately 60:40, however, there was a notable intrinsic variability to this (Table 4.5).
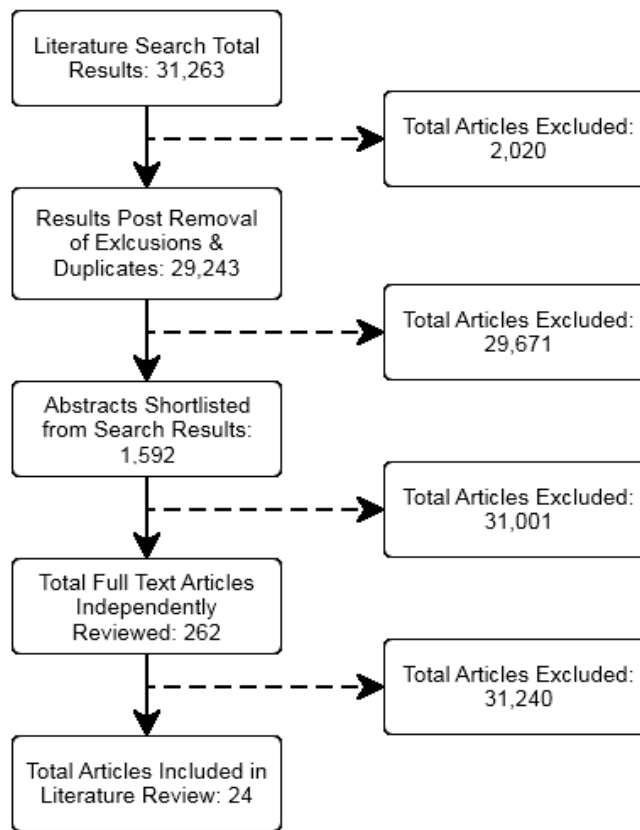
Figure 4.5 The search strategy for the literature review of proportions of P1 and P2 casualties received.

Interestingly, in all event reports where the number of P1 casualties exceeded P2s, the events involved a terror precipitated attack and all 'accidental' MCEs involving MOI such as transport failures, there was an exclusive tendency towards greater numbers of P2 casualties. In addition to the proportion of P1 and P2 casualties, the total casualty load of these casualties received at the responding hospitals following the events was also calculated. Across all individual events reported the median casualty load was found to be 25 with an upper quartile of approximately 40 P1 and P2s received per event.

Table 4.5 Proportion of P1 and P2 casualties received at reporting units following various MCEs

Year	Location	MOI	P1s	P2s
1980	Italy	Bombing (205)	25	39
1985	USA	SC (309)	4	12
1994	Argentina	Bombing (208)	18	16
1994-1998	Israel	Bombings (123)	96	44
1994-1998	Israel	Bombings (185)	15	7
1997-2005	Israel	Bomb & Shootings (124)	50	44
1999	India	Train Crash (221)	12	31
2000-2002	Israel	Bombings (298)	77	49
2000-2003	Israel	Bombings	178	90
2000-2003	Israel	Bombings (108)	111	56
2000-2003	Israel	Multiple (293)	287	158
2001	USA	Plane Crash / SC (294)	8	4
2001	USA	Plane Crash / SC (294)	12	3
2001	Israel	Bombing (303)	3	1
2001	Serbia	Bombing (211)	4	4
2003	Israel	Bombings (299)	11	5
2004	Egypt	Bombing (306)	3	12
2004	Pakistan	Bomb & Shooting (296)	13	10
2005	Israel	Bombing (308)	2	4
2005	UK	Bombings (119)	8	19
2006	Israel	Bombing (111)	12	14
2008	USA	Train Crash (295)	25	34
2009	Netherlands	Plane Crash (310)	13	22
Total			**987**	**678**

Multiple MOI inclusive of bombings, shootings, MVCs and stabbings

SC - Structural Collapse, MVC – Motor Vehicle Collision

4.3.4 Discussion

This study has provided model input data for casualty arrival rate and the proportion of P1 and P2 casualties expected within an overall casualty population received. The established arrival rate consisted of half of the total casualty load arriving at hospital within two hours, which is similar to the arrival pattern suggested by the CDC in it's MCE casualty predictor tool (113). This is further supported by the opinion that beyond this time casualties begin to succumb to their injuries due to delay in treatment, therefore producing this left skewed distribution of arrivals amongst the P1 and P2 cohort (313). This presentation pattern adds to the pressure on hospital resources beyond purely coping with an excess volume of casualties. The early arrival of casualties is also dominated by casualties with the greatest needs and resource demands, emphasised by the acute consumption of three quarters of PRBCs during this timeframe which was observed in the literature review of Chapter Two.

The proportion of P1 and P2s within the overall casualty loads experienced during the various events was observed to show an overall preference towards the P1 cohort. However, this ratio was noted to vary considerably between events and may suggest the impact of event type on the resulting casualty severities. This was highlighted by the apparent distinction between intentional terror based events and unintentional accident focused MCEs with contrasting dominances in numbers of P1s and P2s respectively. For the purposes of the baseline model the overall ratio of 60:40, P1:P2 casualties was applied, however, this may be a factor to consider when interpreting the model outputs.

The final input value to be identified in this sub-study was the total P1 and P2 casualty load to which the arrival pattern and proportions above would be applied. As discussed, this was primarily used to satisfy a baseline model for testing, as MCE casualty load was one factor of interest from the overall list of the thesis' aims and hypothesis. The median total P1 and P2 casualty load for all individual events was 25. However, in order to plan for the large scale events which are likely to allow for the greatest impact in terms of improving casualty outcomes, as well as challenge larger institutions such as MTCs, the upper quartile of 40

combined P1 and P2 casualties was chosen to apply to the baseline model as per the study methods.

4.3.5 Limitations and Conclusion

The derivation of input values using historical MCE literature avoided the requirement for use of a surrogate dataset, however, despite this; there were several recognised limitations to the study design. For example, there was no weight adjustment performed between events of differing sizes. This was unfortunately not possible due to the nature of the reporting of the events in the articles reviewed and allowed some smaller events to have an equal impact on input values compared with the more substantial MCEs. Furthermore, due to the nature of arrival time reporting in the MCE articles, the casualty arrivals during the periods between those described had to be assumed as linear. This meant that in cases where only the first and last casualty arrival times were provided, a linear arrival pattern was recorded for the event. Despite this restriction, the cumulative arrival pattern appeared to accurately reflect that suggested in previous MCE casualty arrival rate discussions.

In addition to these issues and specifically relating to the arrival pattern, a further assumption was required when translating the data into the model. As whilst the simulation was designed to commence with the arrival of the first casualty, the rate of arrivals described here, relates predominantly to times of arrival from the time of the actual incident occurring. Unfortunately, the description of arrival data in the reviewed articles did not allow for this difference to be corrected. Regardless of this, the time from an event to evacuation of casualties to hospital is itself known to be highly variable between MCEs, depending on the mechanisms involved and the proximity to healthcare facilities. As a result, the pattern of arrivals and timings between arrivals were expected to be of a similar nature and therefore accepted as a reasonable estimation for application within the model.

Finally, although reporting of priority level was found to be better when not restricted to it's relationship to blood use in MCEs, there remained a need to extrapolate some data based on certain assumptions. These included applying the relationships between priority status and ISS established in the first aim of this chapter to broaden the evidence base. These assumptions may have had a consequential impact on the validity of this particular input in the model, although a superior alternative was not found to be available at the time. In spite of these necessary assumptions and the limitations listed above, the inputs were nevertheless directly derived from historical MCE literature and this sub-study remains a strongly evidence based assessment of the model inputs considered, providing greater confidence in the model prior to any formal evaluation exercise.

4.4   Establishing Casualty Processing Times

4.4.1   Introduction

Provision of PRBC to casualties in the model structure involved two main casualty centric processes which consume both time and available resources. Casualties are immediately assigned a priority state upon entering the model and therefore the first simulation event is the initial assessment or 'primary survey' of the casualty, during which their bleeding status is ascertained and concomitantly, intravenous (IV) access is established. In the case of bleeding casualties, this also provides a route for transfusion of PRBCs later on, as well as the acquisition of a blood sample for laboratory processing and determination of the individual's blood group. The second casualty specific event occurs with the transfusion of the casualties recognised as suffering haemorrhage with their demand volume of PRBCs. The third aim of this chapter was therefore to determine the data input values for these key time dependent processes.

The input modelling of these two events required both the occupation of a resource in the form of a healthcare provider to assess the casualty, gain access or initiate a transfusion and a defined time distribution, during which the process would take place. The former was considered in the fourth aim of this chapter along with all model resource availability, whereas this sub-study, aimed to determine the time distributions for these events. Timings of casualty assessment, securing IV access and PRBC unit transfusions were not reported in any of the MCE literature reviewed for this study. Neither was the information available from the JTTR military database used for determining casualty haemorrhage rates and PRBC demand. A separate surrogate dataset was therefore required in order to model these inputs and provide the time distributions for these events. This sub-study describes the collection, analysis and application of a further surrogate dataset from a UK based MTC trauma service with which the model was informed.

4.4.2 Methods

The study consisted of a retrospective review of civilian trauma data collected between October 2008 and October 2012 as a part of the Activation of Coagulation and Inflammation in Trauma 2 (ACIT II) investigation (314). This was a prospective observational study performed at the Royal London Hospital (RLH), one of the four MTCs in London, UK. The inclusion criteria for the study were all traumatically injured patients of 16 years of age or older who at admission exhibited an abnormal primary survey, were likely to require admission for at least 24 hours and were received at hospital within the study recruiting hours of 08:00-22:00 (when an investigator was on-site).

The exclusion criteria for the ACIT II study consisted of: arrival at the MTC greater than two hours following injury, transfer from another healthcare facility, those patients who had received over two litres of IV fluids prior to MTC admission or those patients who refused informed consent to take part in the study. The ACIT II study was granted ethical approval

through the East London and The City Research Ethics Committee and complied fully with the Declaration of Helsinki (314).

The data collected was exclusively from civilian non-MCE trauma and as such no priority level was established. For the purposes of the surrogate dataset and in keeping with the PRBC demand data established in aim one of this chapter, all casualties receiving a massive transfusion (MT) of 10U of PRBCs or more, were therefore considered to represent P1 casualties and those receiving a transfusion of less than 10U were considered P2s. The assessment of haemorrhage time, inclusive of the time to gain IV access was taken as the time from casualty admission to the time initial physiological observations were obtained, combined with the time to then initiate the first unit of PRBCs. This therefore included both an assessment component and IV access component. Both timings were recorded as standard protocol in the ACIT II study (314). Only those casualties with acute blood demands, taken as requiring a unit of PRBCs within one hour of admission were included in the study.

The individual timings of each PRBC unit transfused were also documented prospectively as part of the ACIT II study. The minimum time between consecutive blood units was recorded as the least amount of time over which blood could be administered in an emergency. The timings for all included casualties were collated to provide a range of assessment and transfusion times for the P1 and P2 cohorts. These could then be analysed using the Arena Input Analyzer software to provide inputs for these two distinct model events. Unless stated a p-value of <0.05 was considered significant in all statistical analysis.

4.4.3 Results

During the four year period 675 casualties met the criteria for inclusion into the ACIT II study. 464 (68.7%) of these received no initial PRBC transfusion and were excluded from this study along with one casualty who received just half a unit of PRBCs before the

transfusion was ceased. 117 (55.7%) of the remaining 210 individual trauma cases had documented timings for their arrival, primary survey and receipt of the first unit of PRBCs they received. These casualties were therefore included in the analysis of time to assess for bleeding status and gain IV access. In addition, 107 (51.0%) of the 210 cases were reported as receiving uninterrupted consecutive PRBC units transfused following their ED admission and were therefore included in the time to transfuse analysis.

Data regarding time to assess casualties included 30 P1s and 87 P2s based on the definition of volume of PRBCs initially transfused. The distribution of the timings for each triage cohort is described in Table 4.6. The time distribution data was analysed in Arena Input Analyzer to determine the best-fit continuous distribution for application in the model for both casualty types (Figure 4.6 A & B). The Gamma distribution (Appendix III) ranked highest under Kolmogorov Smirnov continuous distribution equality testing for the two casualty groups, the distribution parameters for which are shown below:

$$P1\ Time\ for\ Assesment\ and\ IV\ Access - Gamma\ Distribution: \alpha = 2.1, \beta = 5.0$$

$$P2\ Time\ for\ Assesment\ and\ IV\ Access - Gamma\ Distribution: \alpha = 1.7, \beta = 11.0$$

Table 4.6 Time distribution for the assessment and establishment of IV access for P1 and P2 casualties based on data from the ACIT II study 2008-2012 (314)

	Minimum	2nd Quartile	Median	3rd Quartile	Maximum
P1	0.00	4.25	10.00	14.00	33.00
P2	0.00	8.50	14.00	27.00	65.00
All	0.00	7.00	13.00	22.00	65.00

A)
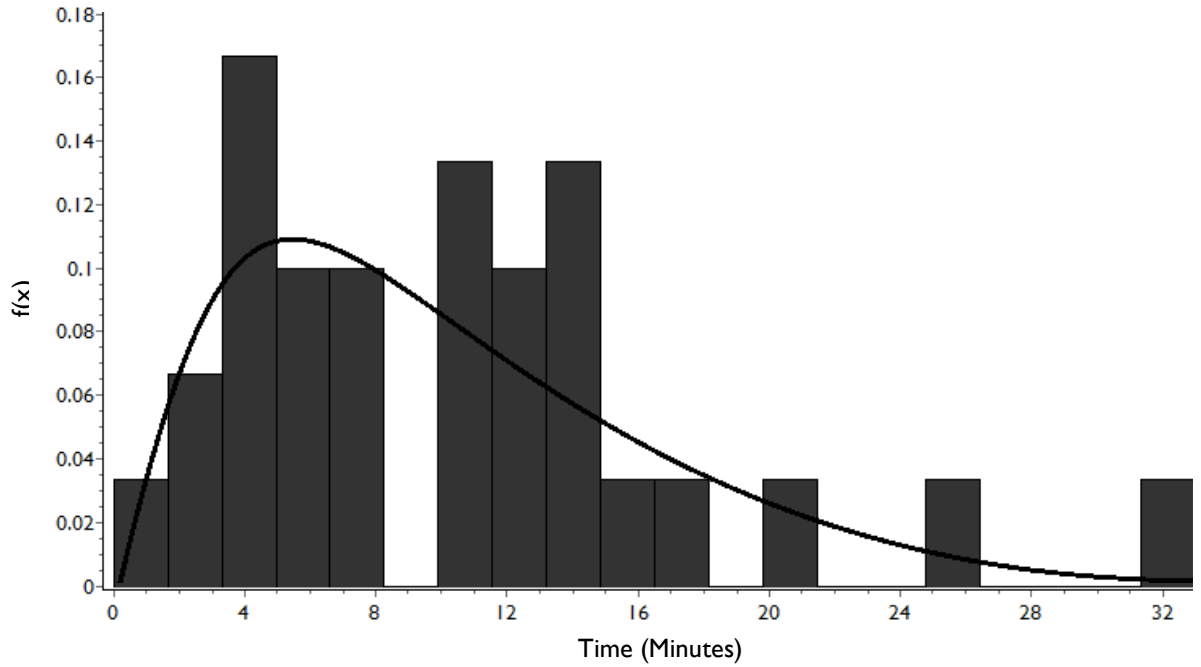
B)
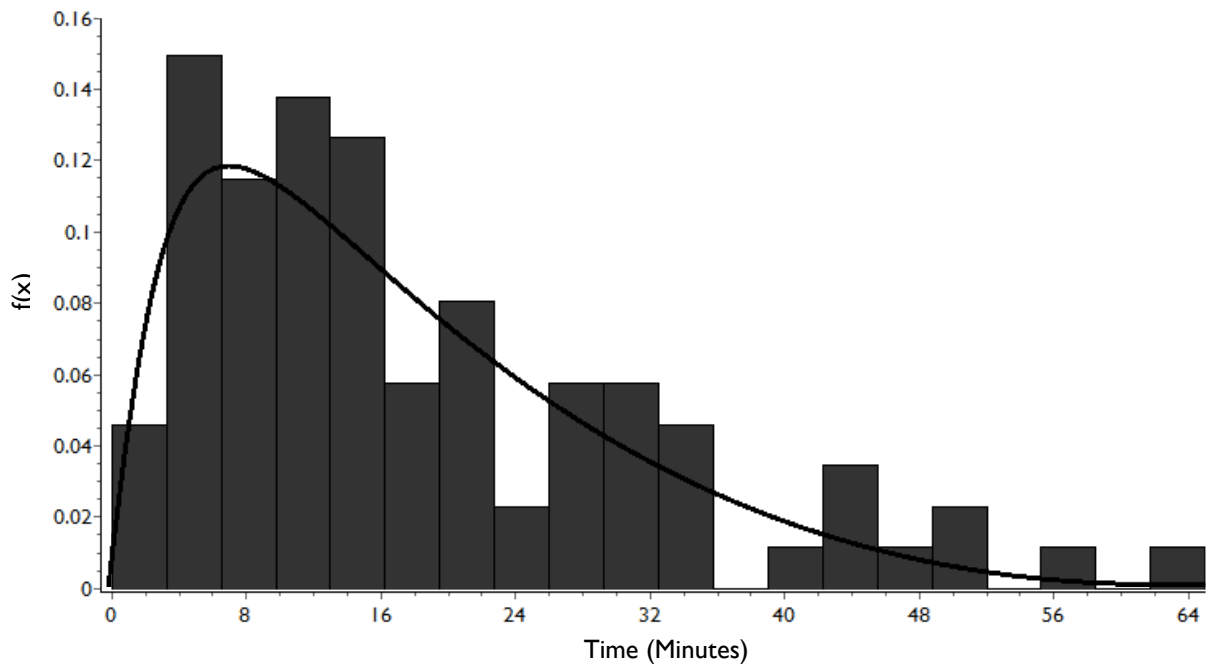
Figure 4.6 Probability density function of time to assess and achieve IV access in A) P1 casualties and B) P2 casualties.

————— = Best-fit Gamma distribution, Arena Input Analyzer (Rockwell Automation, Pittsburgh, USA)

The analysis of the 107 casualties with applicable documented transfusion times included 31 P1s and 76 P2s based on the definition of volume of PRBCs initially transfused. The distribution of the timings for each group is described in Table 4.7. The time distribution data was also analysed using the Arena Input Analyzer in order to determine the best-fit continuous distribution for application to the model for both casualty types (Figure 4.7 A & B). The Kolmogorov–Smirnov test of distribution equality ranked the Johnson Special Bounded (SB) distribution (Appendix III) highest for the two casualty groups, the distribution parameters for which are shown below:

$$P1 \; Time \; to \; Transfuse \; 1U \; PRBC - Johnson \; SB: \gamma = 2.1, \delta = 0.75, \lambda = 29.0, \xi = 0.56$$

$$P2 \; Time \; to \; Transfuse \; 1U \; PRBC - Johnson \; SB: \gamma = 1.2, \delta = 0.62, \lambda = 29.0, \xi = 0.84$$

Table 4.7 Time distribution for the transfusion of individual units of PRBCs for P1 and P2 casualties based on data from the ACIT II study 2008-2012 (314)

	Minimum	2nd Quartile	Median	3rd Quartile	Maximum
P1	1.00	1.00	2.00	5.00	17.00
P2	1.00	2.00	4.00	10.00	25.00
ALL	1.00	2.00	4.00	7.00	25.00

A)

B)
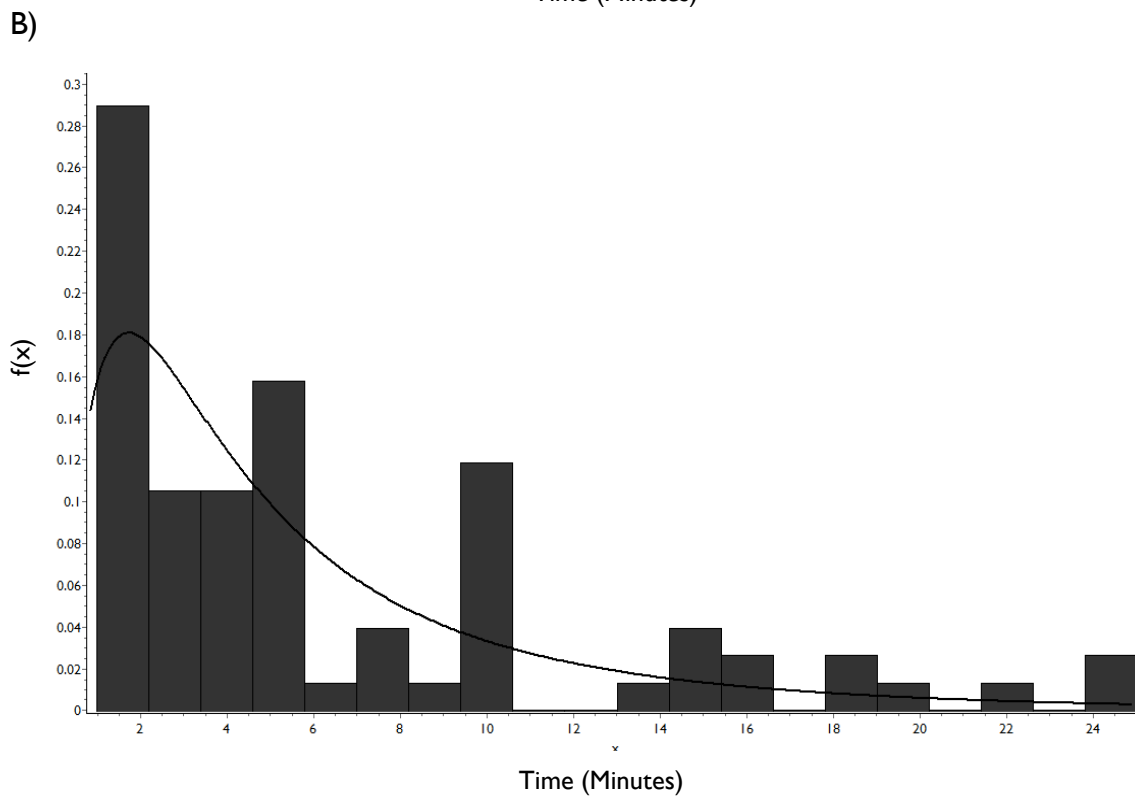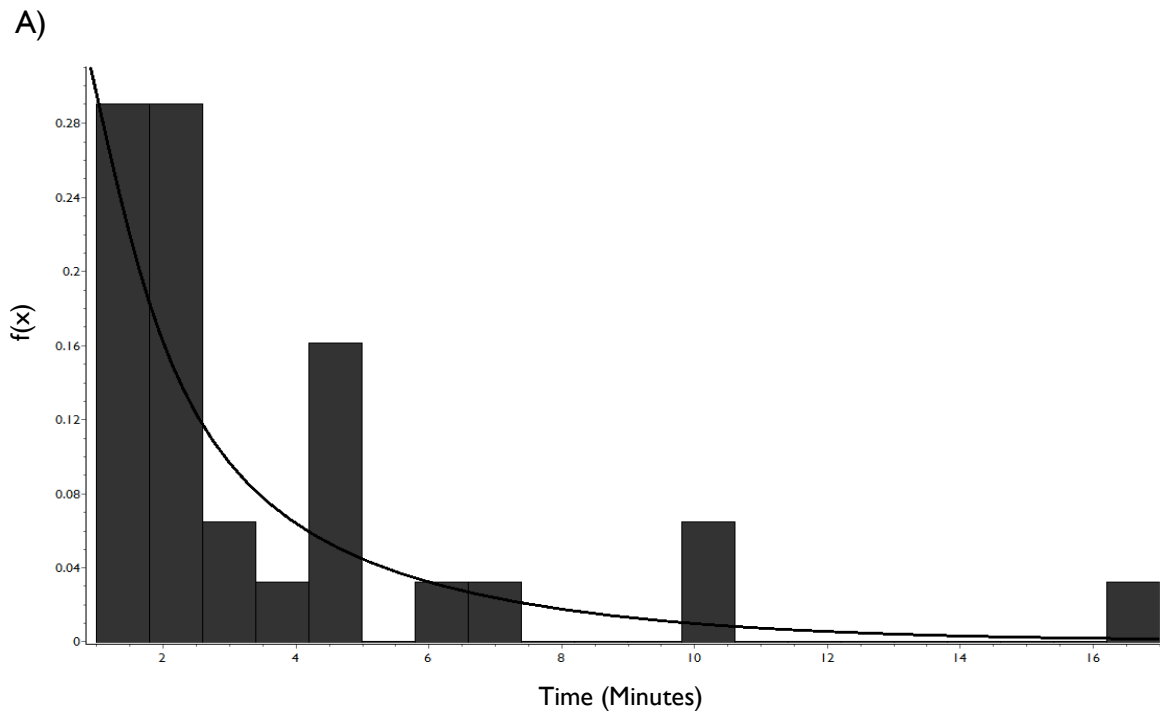
Figure 4.7 Probability density function of time to transfuse a single PRBC unit in A) P1 casualties and B) P2 casualties.

———— = Best-fit Johnson SB distribution, Arena Input Analyzer (Rockwell Automation, Pittsburgh, USA)

4.4.4 Discussion

This study provided timing distributions for the two principal casualty centred events within the model. There is clearly considerable variation in the time to assess casualties and determine whether or not they are suffering active haemorrhage and require a transfusion. As discussed in Chapter One, certain casualties demonstrate substantial physiological reserves following trauma with the ability to compensate for significant blood loss before the presence of active haemorrhage becomes apparent. Conversely, other casualties may rapidly display the signs and symptoms associated with shock and MH and this is reflected in the dataset.

Time to transfuse individual PRBC units was also observed to consist of wide variation between casualties. Several factors are involved in rate of transfusion, including the calibre and quantity of IV access as well as the ability to provide positive pressure to the infusion, both these factors may be rationed during an MCE with priority given to those more critically injured. Aside from the physical resources, the influence of human resources in the timing of both assessment and suitable IV access will also have an effect. Higher grade clinicians and greater numbers of personnel would likely be managing the sicker P1 casualties. We would therefore expect infusion times to be significantly shorter in the P1 cohort compared with the P2 as depicted in this dataset.

4.4.5 Limitations and Conclusion

The principal limitation in defining these input values lay in the requirement to source a second surrogate dataset. The specific nature of individual casualty assessment and transfusion timings inevitably precluded the data from being mined directly from the literature base or the previously investigated JTTR database. The use of a civilian trauma database also meant there was a need to establish a separate method for determining

casualty priority levels to account for variation in timings between the two severities. PRBC use was applied over injuries sustained or physiological parameters as it related directly to the issue the timings were being applied to, however, this approach creates further margin for error which should be appreciated when interpreting these values for inputting into the model. Furthermore, the civilian setting involves mostly individual trauma cases. This resulted in timings which were not recorded under the surge and resource constrained conditions of an MCE and despite best efforts to account for this, the results will remain limited by this fact.

Despite the requirement to use a further surrogate dataset and the inherent issues associated with extrapolating data from a more standard civilian trauma environment into that of an MCE, the prospective collection of data and the significantly injured population involved in the ACIT II investigation appears to offer the best alternative for the circumstances. The values presented therefore are believed to offer a reasonable estimate for application in the model with input timing distributions seemingly realistic for the simulation setting.

4.5 Transfusion Laboratory Processing and Major Trauma Centre Resources

4.5.1 Introduction

The fourth and final aim of this chapter was to define the inputs involved in the processing of blood from the point of blood sampling (assumed to occur during the establishment of IV access), through to the delivery of group-specific PRBCs to the patient. The time to convert

casualties from use of emergency type O PRBCs to group-specific units may impact heavily on the capacity to manage casualties and the subsequent mortality from MCEs. Adequately modelling the inputs involved was therefore critical in gaining confidence in the outputs of the model. In addition to processing times, several physical and human resources are consumed or occupied during these and other model processes which required quantifying. This study therefore also established the standard availability of these resources for the baseline model settings.

As was the case for aim three, neither the literature review nor the JTTR military dataset provided adequate information regarding timing of blood processing or resource availability to satisfy these model inputs. Therefore, in order to establish typical timings and resource levels for the model, the transfusion laboratory managers of all four London based MTCs were contacted and requested to participate in a transfusion service survey. The following study details their responses from which standard reference or reference ranges were derived for each process and resource input. In relation to this, the distribution of blood groups in the population was also defined for allocation to the casualties arriving into the model.

4.5.2 Methods

The four hospitals providing London's MTC network were approached for data, these included: The Royal London Hospital (RLH), King's College Hospital (KCH), St George's Hospital (SGH) and St Mary's Hospital (SMH). All four transfusion laboratory managers and lead biomedical scientists (BMS) were contacted to participate in the study. They were asked to complete a survey detailing the processing steps along with timings, required to provide a trauma patient with group-specific PRBCs following admission to the ED. In addition, they were also asked to provide quantitative data for a specific list of available resources at their MTC. The ten question survey is available in full in Appendix IV. The

survey was supplemented by email and telephone correspondence, as well as face-to-face meetings to develop a clear understanding of the variations in practice between the units.

All survey responses were collated and evaluated to determine an average baseline for the model. In addition to the survey, recent National Health Service Blood and Transplant (NHSBT) literature was also reviewed to determine the national prevalence of each blood group in the UK population. The approximate ratio of groups could then be allocated to casualties arriving into the model in order to reflect the demand for each blood group amongst bleeding casualties. Unless stated a p-value of <0.05 was considered significant in all statistical analysis.

4.5.3 Results

All four of the MTC transfusion units contacted responded to the survey and all follow-up enquiries in full. The mean value for all responses for each component of the blood sample processing procedure is provided in Table 4.8. All MTCs were confirmed to use an automated pneumatic air tube system for transporting samples as per the assumption during the model's design. Furthermore, the basic steps in processing samples were found to be universal across the transfusion laboratories sampled, therefore, no adjustment to the structural design of the model (originally based on the RLH) was required. The time to receive the samples and perform manual tasks such as sample booking and verification were relatively constant in the survey response and therefore were treated as such in the model.

The time to centrifuge a sample although variable between machines and protocols is a fixed process and was therefore also maintained as a constant input for the model. The time described for respective analysers to provide a group for a sample was between 10 and 12 minutes across all four sites, therefore a constant 11 minutes was applied to this model input. The full antibody screen for provision of cross-matched blood was included as an

optional decision in the model design and therefore is included in the data Table 4.8. As the sample size was small, only a basic Triangular distribution (Appendix III) could be applied to this input using the mean and ranges provided by the survey responses.

Table 4.8 Mean time and resource occupation for blood sample processing across four MTC transfusion units

	Resource Required	Time (Minutes)
Sample Delivery	None*	3
Book Sample on Lab System	1 Technician	1
Centrifuge Sample	1 Centrifuge Slot	5
Verify Sample & Load to Analyser	1 Technician	1
Sample Analysis	1 Analyser	11
Unload & Verify Sample	1 Technician	1
Full Ab Screen if Required	1 Analyser	TRIA (25,35,90)**
Dispense Group-specific PRBCs	1 Technician	0.5 per PRBC Unit
Deliver Group-specific PRBCs to Patient	1 Porter	5

*All times are constants unless stated, *Samples were delivered automatically through the pneumatic air tube system, **Triangular distribution minimum value 25 minutes, mean value 35 minutes and maximum 90 minutes*

The various resources required for the model included consumables such as PRBCs, human resources such as staff members and physical resources such as centrifuges and antibody analysing machines. The mean quantity of each resource available at the MTCs surveyed is described in Table 4.9. The generic healthcare personnel required for assessing casualties, establishing IV access and initiating transfusions were considered to be an unlimited resource in the model. The various MHPs of the four MTCs surveyed described provision of PRBCs for bleeding casualties in six unit packs and therefore this was assigned as the maximum volume received by casualties during any single request.

Table 4.9 The mean total quantity of resources involved in processing blood samples and the provision of group-specific PRBCs across the four MTCs surveyed

Resource	Mean Value
Technicians	6 (7-1)*
Porters	4
Centrifuge Capacity	15**
Analyser Capacity	180***
Type O PRBC Units	100
Type A PRBC Units	75
Type B PRBC Units	25
Type AB PRBC Units	10

*Due to the relocation of one technician to the ED to check and manage casualty blood samples
**MTCs reported an average of 2 available centrifuges each with an average sample capacity of 15 samples,
***Analysers were described as continuous loading and therefore the sum total capacity may include multiple analysers.

Discussion with the survey participants regarding modifications to procedures during an MCE revealed two MCE specific protocols relevant to the model setup. The first was the consensus that the majority of emergency type O PRBCs would be relocated to the satellite storage fridges based in the ED and theatres for immediate availability upon transfusion laboratory notification of an MCE. This aspect of the simulation was already part of the model's architecture, having been established through expert discussions during the model design phase. Secondly, in order to avoid sample rejection due to mislabelling and to aid stock management, the majority of units would deploy a transfusion technician to the ED to oversee blood management during the event. This was similarly the case at the RLH during the London bombings of 2005 as described in Chapter One. In terms of the model, this would mean a reduction of one staff member able to contribute to processing samples in the transfusion laboratory Table 4.9.

The NHSBT literature regarding the national distribution of blood groups amongst the UK population revealed the following statistics: Type O 44%, Type A 42%, Type B 10% and Type AB 4% (315). The quantities of overall PRBC stock held at the four MTCs surveyed,

along with the reported transfusion laboratory staffing levels, showed encouraging similarities to those reported in the literature review of Chapter Two. There were however variations in the quantities of the specific individual groups held between the surveyed MTCs, on discussion, this was revealed to be primarily related to the variation in blood groups observed in the different ethnic communities they serve. Despite this, the greatest emphasis in PRBC stock holding remained on levels of type O PRBCs due to their critical importance in the early management of traumatic haemorrhage.

4.5.4 Discussion

Processing of blood samples is not routinely discussed in the literature and no report reviewed as a part of this study discussed sample timing or the associated processing resources required. The transfusion practices identified in this study were found to be similar between the four centres surveyed. The principal differences were seen to occur in relation to the manufacturer of the equipment used at each site and the stock hold of each PRBC group for the populations the hospitals serve. Much of the sample processing follows a relatively uniform and predictable course, with all MTC managers highlighting full PRBC antibody screening as the process with most variation in timing. This process was included in the model structure as an option but not in the baseline simulation as all four experts agreed the priority in MCE management would be primarily establishing the blood groups of the casualties received.

The two other principal policy modifications declared in the event of an MCE were the stockpiling of type O PRBCs in acute care areas using the standard satellite fridges available and the assignment of a laboratory technician to the ED. The former was already translated into the model design by making all type O PRBCs available for immediate transfusion as and when required, whereas type specific PRBCs entailed an additional collection and delivery process prior to transfusion. The latter was modelled through reducing the baseline number of laboratory technicians available in the model by one at the start of the simulation

run. This procedure will reduce the number of personnel available to process and group blood samples arriving in the laboratory and therefore potentially prolongs a casualty's time to treatment.

The benefit from a real-world and modelling aspect in this staff allocation is the policy is designed to reduce errors in sampling and expedite sample transport. As this model does not incorporate equipment or human errors, any real-world reduction in these will increase the model's accuracy. The only resource not quantified following the survey was the number of healthcare staff available. The decision to assign this model input as an unlimited resource was made following discussion with the experts consulted during the model design. The unanimous view was that staff numbers vary in response to the volume of casualties received and should this fail to be the case, the ability to provide PRBCs would be of little consequence in casualty outcomes.

4.5.5 Limitations and Conclusion

This sub-study provided a clear set of baseline values with which to inform the model using a primary source of data directly related to MCE transfusion practices. There were however some limitations in this study's design. Firstly, there is always a risk of bias when surveys are unblinded and include a direct reflection of an individual's practice. As a result, the values provided are more likely to represent an ideal best-practice standard rather than average practice. Secondly, the timings provided in the literature survey were mostly provided through the experience of the expert providing the response rather than being directly audited. Due to this, it could not be verified whether or not any best-guess approximations were employed when replying to the questionnaire.

Finally, the survey responses could not account for the inevitably chaotic nature of an MCE and the impact this would have on the business as usual operations. This is difficult to establish outside of an event and as such was considered acceptable for the study aims.

Despite these issues, the four MTC transfusion laboratories provided a detailed account of blood processing procedures and timings, as well as resource availability across the system during an MCE. The timings and practices across all sites were remarkably similar and the independent expert responses meant no further alternation to the model code was required to meet MCE specific policies. From the perspective of the model's design this was reassuring, providing a greater degree of confidence in the simulation as a whole.

4.6 Summary of Model Inputs, Baseline Run Setup and Chapter Four Conclusion

A summary of the input data which has been determined during each of the sub-studies in this chapter is collated below (Table 4.10). Along with the resource levels for the baseline model described above in Table 4.9, these tables provide all required inputs to drive the model. Prior to performing a simulation, the final step in completing the baseline model was to define the simulation run setup (Figure 3.5). Certain settings needed to be formally defined and are discussed in full in the following chapter. However, in order to evaluate the model and allow testing during its construction, best-guess predictions of these parameters were required, a summary of these is also provided in Table 4.10.

Although a previous review of simulation projects has shown three to five replications to be adequate, here the number was estimated based on similar models to this one (316). These models involved the application of simulation to triage and surge capacity during MCEs, performing 100 replications during their experiments to ensure result accuracy (188, 280). This was therefore selected for baseline use prior to the full model evaluation. Run statistic collection was set in Arena to occur at the end of each run in addition to the continuous in-run recording of data into Microsoft Excel (Microsoft Corp. Redmond, WA, USA).

As discussed in the conceptualisation of the model and its design during Chapter Three, the length of the simulation was defined as 72 hours to encompass the time of maximum PRBC demand and likely reduced restocking capability. This time represented the terminating event with only an internal modelling error causing a simulation run to stop prior to this. The base time units used by the model were minutes in keeping with the defined inputs determined during this chapter. The warm-up period was initially set to zero for model evaluation. This was in anticipation that this would be applied for the experimentation phase based on a time window available in most MCEs to prepare the system for casualty arrival.

Table 4.10 A summary of the data sources and input values for each simulation parameter

Input Parameter	Data Source	Input Description
Casualty Arrival Rate	Literature Review	Johnson SB Distribution (γ 1, δ 0.55, λ 15, Υ 0.05)
Casualty Load	Literature Review	Constant 40 Casualties
Casualty Blood Type	NHSBT	A = 42%, B = 10%, AB = 4%, O = 44%
Proportion of P1:P2s	Literature Review	P1 = 60%, P2 = 40%
Assessment and Access Time	RLH ACIT II Dataset	Gamma Distribution P1 = (α 2.1, β 5.0), P2 = (α 1.7, β 11.0)
Proportion of P1 & P2s Bleeding	Military Surrogate Dataset	P1 = 80%, P2 = 50%
P1 & P2 PRBC Demand	Military Surrogate Dataset	Poisson Distribution: P1 = (10.7), P2 = (4.7)
Blood Sample Transport	MTC Survey	Constant (3)
Book & Verify Sample	MTC Survey	Constant (1)
Centrifuge Sample	MTC Survey	Constant (5)
Verify Sample & Load Analyser	MTC Survey	Constant (1)
Analyse Sample	MTC Survey	Constant (11)
Unload Sample & Verify	MTC Survey	Constant (1)
Full Antibody Screen on Analyser	MTC Survey	Default Group Only, Full Screen Uses TRAI(25,35,90)
Dispense Grouped PRBC	MTC Survey	Constant 30 Seconds per Unit of RBC
Delivery of PRBC	MTC Survey	Constant 5 Min
Transfusion Time	RLH ACIT II Dataset	Johnson SB Distribution: P1 = (γ 2.1, δ 0.75, λ 29.0, Υ0.56), P2 = (γ 1.2, δ 0.62, λ 29.0, Υ 0.84)

Table 4.11 Simulation run-setup parameters applied to the baseline model

Run – Setup Field	Parameter Decision
Replications	100
Statistics Collection	End of Run (As well as continuous data collection via VBA)
Date and Time Stamp	Present Day
Warm-up Period	0 Minutes
Replication Length	72 Hours
Hours per Day	24
Base Time Units	Minutes
Terminating Condition	N/A

The preceding four sub-studies provided all data values required for informing the model and representing the MCE transfusion system during simulation of the model. Inputs were drawn from a variety of resources with the best-evidence available sourced to inform the model's components. The lack of primary data for certain aspects of this process required the use of surrogate datasets and application of certain assumptions which inevitably introduced a number of limitations to the study. Interpretation of the model's results will need to take these into account.

Having produced the structural design of the model, coded the elements within the simulation program and populated the required component data fields with evidence based inputs, all the requirements of Aim Two were satisfied. The model was now deemed suitable for evaluation in accordance with Aim Three of the thesis. This process would include the first experimental procedures to be performed using the model through a sensitivity analysis, after which, the formal experimentation phase of the study could commence and the final three aims of the study investigated. The following chapter therefore describes the full evaluation of the model and the methods applied in ensuring its suitability for this experimentation.

CHAPTER FIVE

Evaluating the Model

5.1 Introduction

Chapter Three established the model's design and its implementation in the Arena (Rockwell Automation, Pittsburgh, USA) software environment. The model construction was then completed through the population of the model's input parameters using the various input modelling techniques described in Chapter Four. This satisfied Aim Two and resulted in the production of an operational baseline computer simulation model representing the provision of Packed Red Blood Cells (PRBCs) to Priority 1 (P1) and Priority 2 (P2) casualties at a Major Trauma Centre (MTC) during a Mass Casualty Event (MCE). Prior to the experimentation phase of the simulation study, the model must first be assessed to ensure it is fit for purpose and the results generated relatable to the real-world system. Evaluation of the model forms Aim Three of this study and consists of three interconnected processes: verification, testing and validation (317).

These three processes are discussed here as an important stage in a simulation study before model experimentation, however, it should be noted that they were continuously practiced throughout the model building and coding process to improve and refine the model in-line with the study objectives (317). There is some discrepancy in the literature regarding the constituents these three processes entail, a description of those applied to this study is therefore provided under each process heading. Included in this overall model evaluation a sensitivity analysis was also performed as an extension of model validation. This allowed an assessment of the effects Chapter Four's data inputs had on the model outputs. The analysis consequently involved the first informal information yielding experimentation to be performed using the model. Following this, the experimental hypotheses directly relating to the overall study objective could be investigated (163).

The objective of this chapter was therefore to evaluate the model and determine whether the baseline state was an adequate representation of the system it was designed to imitate.

This was achieved through the following three aims: The first aim was to verify and test the model as an accurate representation of the real system. The second aim was to validate the model to ensure the representation of the system produced results accurate for the model's original purpose. The third and final aim was to perform a sensitivity analysis study to determine the effect of varying the model's inputs on it's output performance.

5.2 Model Verification

The process of model verification aims to ensure the model has been truly and accurately translated from the original specification as described in the conceptual modelling and design phase, into the coded computerised environment of Arena (317). Verifying the model can be performed solely by the creator of the computerised version of the model as no expert knowledge of the system under study is required, only a clear paper-based description from which the model was coded (163).

Verification involves meticulously checking the entirety of the simulation code to determine whether the computerised model's actions are functioning as specified in the system design. This requires inspecting model inputs, outputs and the intermediate logic which relates them, i.e. the white-box model components, both individually and as a whole during the model's construction. Reviewing the model code can be done either through the straight forward reading and confirmation of each line of simulation script or visually, by running the simulation and observing the animated system interactions which occur. The latter is one of the principal advantages of visual interactive modelling systems (VIMS) type software and hence its inclusion in the selection of simulation software as discussed in Chapter Three.

Visual assessment is particularly useful in checking that the inputs and white-box model components are performing as intended. For instance, a complete model walkthrough can

be performed, whereby the simulation is run at a very slow speed, intermittently paused, the system state analysed and the run then resumed (163, 317). Repeating this process for each section of the simulation allows the verification of these particular aspects of the model, checking various system features including the following:

- The entry and exit of entities into and out of the model is appropriate for the defined run parameters.
- The channelling of entities through the model based on their individual characteristics is correct.
- The data values based on those directly programmed or those derived from sampling distributions are appropriately assigned during the simulation.
- The entities act or are acted on by other system elements in an expected manner.
- The state of the overall system evolves fittingly during or following a simulation event, including the use and consumption of resources.
- The event times and advancing simulation clock are directly related to the events within the model and the model termination occurs solely in relation to the time limit prescribed.

The outputs from the simulation are verified through inspection of the resulting data propagating from a simulation run to confirm it relates accurately to the observations within the model. This can be determined through a visual assessment approach as described above or alternatively, by assigning certain parameters with constant values over either an entire run or section of the simulation. The results are subsequently checked to ensure they deliver the expected values – a form of black-box verification (163).

Both the script of the simulation code and the visual assessments described were carried out throughout the model building process and upon completion of the baseline model. All anomalies in the translation of the system into Arena were corrected and the process repeated in its entirety following any necessary modifications. The verification process and testing described in the following section required 53 model revisions from version 1.0 through to version 5.3, involving approximately 80,000 simulation runs and over 600 hours of computer processing before a final satisfactory baseline model was reached.

5.3 Model Testing

Testing the simulation model identifies errors within the model coding which may cause the failure of a simulation run either at its initiation or at some stage during a run. In addition, testing identifies events within the model which represent impossibilities or are incorrect based on the intended logic of the system being modelled. For example, in relation to this particular model, if following a completed run of the model the PRBC stock level of group A blood is found to be of a negative value, this would imply the incorrect delivery of PRBCs to casualties, when in fact supplies were exhausted. The error must therefore be found and identified within the simulation script and corrected appropriately. This can be a lengthy process if performed as a single exercise once the model is completely built. As such, a significant amount of model testing occurs throughout model construction, with components and processes checked as they are added into the model architecture (317).

Although the process of model testing also occurs during both the verification and validation of the model it remains distinct from these two processes, in that it does not involve determining whether the model is performing as per the real-world system, only that it functions correctly (317). The Arena software offers a debugging tool to inspect the full simulation script prior to running the model; this allows error in the code to be identified early and therefore reduces the possibility of the run failing after several hours of wasted simulation time. Despite this, some errors may only occur during certain configurations within the model, when a number of random events coincide causing an error. This type of failure requires detailed investigation by the modeller and inspection of all the elements involved in generating that error. This is performed either through direct review of the script or visually monitoring the simulation over the time prior to the failure.

As well as ensuring the model is functioning correctly, testing also requires ensuring it is interacting appropriately and correctly with any external resources involved in either

providing inputs or collecting output data during a simulation run. All input data in this model are held within the Arena program, however, the output data was also directly written into a Microsoft Excel (Microsoft Corp. Redmond, WA, USA) spreadsheet during a run. This was also tested to ensure accurate translation of data between the two programs. As per the verification procedures discussed above and hence the interlinked relationship between the testing, verification and validation processes, the model may be run under fixed inputs and constraints. This ensures expected values are appropriately occurring in the output reports generated within Excel.

Finally, an important aspect of the testing process is to ensure extreme values which remain within the realms of possible outcomes are not interpreted as errors in the model. Care was taken at each stage of model testing to ensure this bias did not occur and only impossible or functional errors within the code were corrected. The validation of the model which follows this section aids in further testing the model and determining its ability to replicate the real life system.

5.4 Model Validation - Part One: Design, Inputs and White-box Components

5.4.1 Introduction

Validation of the model as defined by Balci is; "substantiating that the model, within its domain of applicability, behaves with satisfactory accuracy consistent with the study objectives" (317). A model is therefore validated as suitable for the desired purpose or found unsuitable following this process and if found to be valid is only valid for the

objectives for which it was designed, i.e. a model cannot be generally validated for all purposes (163). The types of validation performed on a model can be categorised into six domains assessing: the initial model design, the inputs that drive the model, the white-box components, the input-output relationships (black-box validity), the experimental results and finally the accuracy of the model solutions (163). The first three of these validation processes will be dealt with in this section and the remaining processes in the sections which follow.

5.4.2 Model Design Validation

Validation of the model design was performed during the conceptualisation phase of the study through discussions with a panel of experts in the field of blood provision in MCEs. The panel was formed of 12 specialists including: biomedical scientists, blood bank managers, pre-hospital care physicians, trauma surgeons, haematologists and emergency department physicians and nurses. Panel members had either had first-hand experience of such an event themselves or were actively involved in planning future MCE transfusion strategies. The model objective is provided below for reference:

'Design a mathematical model for developing strategies to improve packed red blood cell (PRBC) provision to casualties across a range of mass casualty event (MCE) sizes and applied conditions.'

The components required to achieve this objective were agreed upon by the panel with the inclusion of a number of simplifications, such as the development of a PRBC only model, limiting the study to a single centre and investigation of solely P1 and P2 casualties. Following which, the retained components of the system and the interactions between them as laid out in the model design were deemed appropriate in order to provide a valid representation of the system for the defined objective.

5.4.3 Data and White-box Model Validation

The input modelling process established all non-experimental input values for the model. The reasons for the data sources used, their justification for application to the model and analysis of the respective datasets as valid primary or surrogate inputs are provided in detail in Chapter Four and therefore, not discussed further here. Similarly, the white-box validation, whereby the components in the computerised model and their interactions are assessed for accuracy were, in part, assessed during the verification phase. In addition the computerised model was also explained to, and inspected by, the expert panel to ensure continuity between the validated paper-based model and the working Arena model. This process was performed at several stages during the model building phase and again in full upon its completion.

5.5 Model Validation - Part Two: A Comparison Study

5.5.1 Black-box Model Validation

This second part of the model validation description discusses the methods used for black-box validation procedures. Black-box validation of the model assesses the input and output relationships of the model and is often regarded as the most important aspect of the validation process (163). This validation procedure is usually performed using one of two methods. Firstly, the model can be compared directly with the real-world system using identical inputs and observing the outputs produced. Secondly, the model can be run to the same specifications as another previously developed and validated model of the same

system and the two results compared (163). As no other suitable model exists with which to make an evaluation, the former method of real-world system comparison was selected for this aspect of the validation process.

5.5.2 Introduction

Chapter Two highlighted the paucity of detailed information regarding PRBC use in MCEs. Identifying a suitable case-study with which to compare the model accurately was therefore challenging. The London bombings of July 7th 2005 was the most recent large-scale MCE experienced in the UK for which casualty documentation and blood use were recorded and potentially accessible to the investigator. This event was therefore selected to validate the model with using data from casualties received at a single centre - The Royal London Hospital (RLH) following the event. The RLH was selected as the study centre as this unit received the majority of P1 and P2 casualties on the day of the bombings.

5.5.3 Methods

All P1 and P2 casualties treated at the RLH on the day of the bombings were included in the comparison study. Information relating to these casualties was obtained through a number of separate avenues which included: analysis of the RLH transfusion laboratory data registry, examination of individual computerised health records relating to the event and discussion with both RLH biomedical scientists (BMS) and transfusion laboratory managers, who were either involved or had in-depth knowledge regarding the event and the response at the RLH. These sources were examined for all available data relating to casualty arrival and processing times, the individual use of group-specific and emergency type O PRBCs and the transfusion related timings of all units requested. The assimilated data was then collated for analysis. Where contradictions in the obtained data occurred between separate sources a

third independent source was used to confirm the correct value, such as discussion with those involved or if this was not possible, the source regarded as the more primary of the two was selected.

The model was designed to provide PRBCs to casualties on a continuous basis until such time as their initial PRBC demand is met and they are therefore deemed as treated to survival in terms of haemorrhage. In order to account for this when interpreting and comparing the real data from the event, the time to meet an individual casualty's PRBC demand was calculated as: The sum of the time from casualty arrival to commencement of their first unit of PRBCs, in addition to the time interval from each request for PRBCs to the time of their transfusion to the corresponding casualty. In order to maintain the anonymity of casualties treated at the RLH, the bleeding casualties who were directly compared with the model outputs were assigned an alphabetic identifier based on their PRBC demand as opposed to their order of arrival. Furthermore, the casualties' specific injuries, demographics and individual outcomes following the event are not commented on further during this study.

The application of black-box validation dictates that the model should, as far as possible, be run under the same input conditions as the real system with which it is being compared (163). Following collation of all available data, the Arena based simulation model was therefore set to replicate the initial state and response of the RLH on the 7th of July 2005; this included programming the model with the following inputs:

1. The resources including number of transfusion staff available and shelf-stock levels of each group of PRBCs were set to the actual RLH values of the day.
2. The individual P1 and P2 casualties were programmed to arrive at the exact time that they did on the day of the bombings.
3. The P1 and P2 casualties who did not require a transfusion in the initial 72 hours of the event were assigned also not to require a transfusion in the model.

4. Those P1 and P2 casualties who did require a transfusion in the initial 72 hours were set to require the same exact volume they received during this timescale in the model as they did in real life.

5. All P1 and P2 casualties entering the model were assigned their real blood type during the simulation to replicate the demand on type specific PRBC stock levels.

6. The restocking of emergency type O PRBCs was included in the model to replicate the volume and time of arrival of these requests at the RLH on the day of the bombings. This process required the addition of the sub-model as shown in Figure 5.1. These additional model components exerted no further effect on any other aspect of the model aside from increasing the level of type O PRBC held at the designated time of activation, precisely mimicking the real life events.
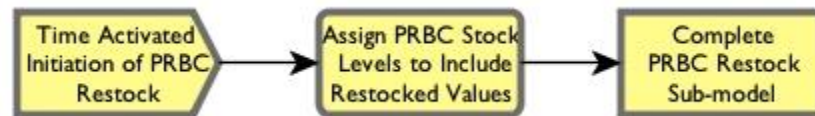
Figure 5.1 The Inventory Restock sub-model activated at the identical time points and providing the same restock volume of PRBC as occurred at the RLH on the day of the London bombings.

All other data inputs and model parameters as described in the data input modelling description of Chapter Four remained unchanged. The simulation was setup to run for a total of 100 replications, each of 72 hours in duration and the summary results compared directly with the actual event data to determine the validity of the model. As discussed at the beginning of this section on validation, the model is validated only for the objectives it was designed to meet and therefore, the outcome measures which satisfy the study objectives are the principal concern in this exercise. All data from both the real event and the model outputs were collated in Microsoft Excel and all subsequent data analysis was performed in GraphPad Prism (GraphPad Software Inc. San Diego, CA, USA). The formula

applied to calculate the confidence interval (CI) for the difference in means between the simulation model and the actual event data is shown below (163):

$$\overline{X}_M - \overline{X}_A \pm t_{2n-2,\frac{\alpha}{2}} \sqrt{\frac{SD_M^2 + SD_A^2}{n}}$$

$\overline{X}_M$ = Mean time in model for a bleeding casualty

$\overline{X}_A$ = Mean time for a bleeding casualty of actual event values

SD_M^2 = Standard deviation of the model output

SD_A^2 = Standard deviation of the actual event

n = number of observations

$t_{2n-2,\frac{\alpha}{2}}$ = Derived value from the Student's t-distribution ($\alpha/2$ = level of significance, 2n-2 degrees of freedom)

Adapted from Simulation: The practice of Model Development and Use, Robinson. John Wiley and Sons, West Sussex, UK 2004.

5.5.4 Results of The Comparison Study

The examination of casualty hospital and transfusion records as well as the material yielded through dialogue with the RLH transfusion personnel provided the following information. On the day of the attacks the RLH received 27 P1 and P2 casualties over approximately three and a half hours, with the first arriving at 10:05am and the last at 1:20pm. From the 27 casualties 19 were triaged as P2s, none of which received a transfusion during the initial 72 hours following the event. In contrast, from the eight P1s treated, seven (87.5%) required a PRBC transfusion over this time. The individual PRBC demand and processing times for the P1 casualties is shown in Table 5.1, accompanied by the changes in stock levels which occurred over the first 72 hours.

Table 5.1 P1 casualty timings, PRBC use and effect on PRBC inventory levels at the RLH following the London bombings of 7th July 2005

Casualty	A	B	C	D	E	F	G	H
Priority	P1	P1	P1	P1	P1	P1	P1	P1
Transfused <72 Hrs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
PRBC Demand (Units)	49.00	40.00	28.00	18.00	14.00	9.00	6.00	0.00
Time to Meet Demand (Minutes)	167.00	126.00	102.00	61.00	59.00	39.00	30.00	N/A
PRBC Grouping	O		A		B		AB	
Initial PRBC Stock Level	168U		102U		18U		18U	
PRBC Stock Consumption	117U		36U		11U		0U	
72 Hour PRBC Stock Level*	281U*		66U		7U		18U	

*A total of three type O PRBC deliveries were received on the 7th of July 2005 totalling 230 Units.

In total, 164U of PRBC were used during the first 72 hours of the event, with over 70% being type O units. The median PRBC demand by the seven transfused casualties was 18U (inter-quartile range (IQR) 11.5-34U) which was met in a median time of 61.0 minutes (IQR 49.0-114.0 minutes). The 100 replications of the model simulating the first 72 hours of the event produced a total PRBC use in all replications of 164U. This was expected, as the individual PRBC demand for the bleeding P1 casualties was set to exactly replicate that of the real casualties and serves principally to demonstrate the model acts correctly. However, the group-mix of emergency PRBC to type specific PRBC provided to individual casualties was not pre-set within the simulation setup. The 72 hour median, IQR and range of each group of PRBCs across 100 replications of the simulation model is shown in Table 5.2 along with the actual values from the real event.

Table 5.2 The median, IQR and range of PRBC levels for each blood group across 100 replications of the simulation model compared with the final values from the real event including the PRBC restocks which occurred

PRBC Group	Minimum	1st Quartile	Median	3rd Quartile	Maximum	Real Values
O	243.0	265.0	**272.0**	277.3	289.0	**277.0**
A	65.0	74.0	**80.0**	89.0	102.0	**76.0**
B	18.0	18.0	**18.0**	18.0	18.0	**18.0**
AB	0.0	0.0	**0.0**	2.0	18.0	**1.0**

One of the principal outcome measures for the study was time to exhaustion of PRBC stocks and specifically, emergency type O stocks. Although the PRBC stocks did not reach exhaustion point during the event, it was possible to compare their final level at 72 hours with that produced by the model. The real 72 hour PRBC level values all fell within the IQR of the results produced by the model and upon paired t-test analysis there was found to be no significant difference between the real event 72 hour PRBC levels and the model output values (p-value = 0.80).

The other principal outcome measures required in realising the model objectives were the number of transfusion requiring P1 and P2 casualties treated within their defined time window of one and four hours respectively. As none of the P2 casualties received at the RLH required a transfusion within the first 72 hours, only the P1 cohort could be investigated. A comparison between the median and IQRs of the model outputs and the real event data is shown in Figure 5.2, this displays the number of transfusion requiring P1 casualties treated within increasing periods of time from their hospital arrival.
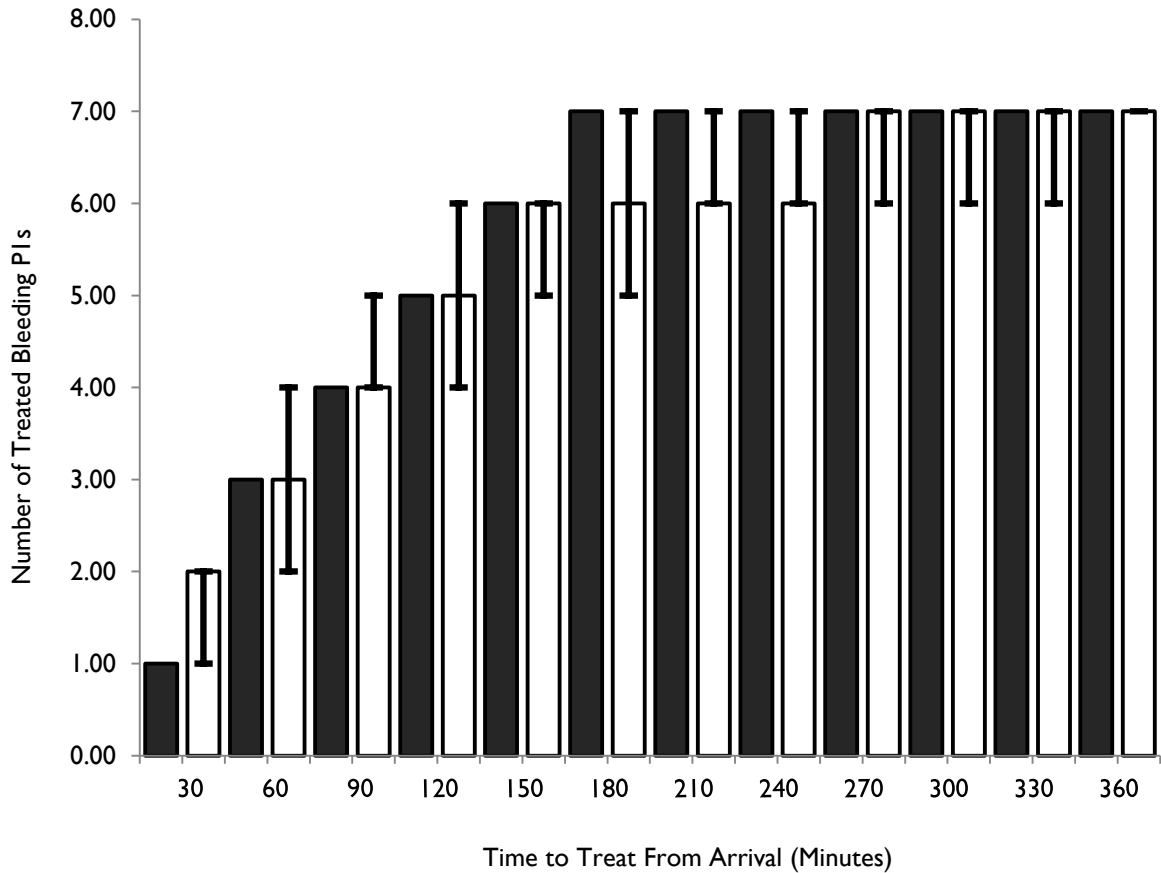
Figure 5.2 A comparison between the median and IQRs (whiskers) of the model outputs (□) and the real event data (■) showing the number of transfusion requiring P1 casualties treated within increasing periods of time from their hospital arrival.

Nearly half of all the transfused P1s on the day of the bombings received their transfusion requirement within one hour based on their time from arrival to initiation of transfusion, combined with the interval from subsequent PRBC requests to them being transfused. Similarly, the model showed a median of three P1s (IQR 2-4) treated within one hour of arrival and no significant difference between the real values and the model output across all time levels on paired t-test analysis (p-value = 0.35).

Due to the inability to evaluate the treatment of bleeding P2 casualties, a further validity assessment of the model was undertaken investigating the overall time for each individual

casualty's PRBC demand to be met, as well as the overall mean time across all casualties. The median time to meet this demand in the model for the seven bleeding P1s was 67.5 minutes (32.4-130.4 minutes) across all replications. The individual timings for these seven casualties are shown in Figure 5.3 along with their corresponding values from the real event. A paired t-test of the median model outputs and real event data showed no significant difference between reality and the model (p-value = 0.28). The confidence interval for the difference in mean time to be treated between the model and the real event across all bleeding casualties was established using the formula as described in the methods and adapted from Robinson et al (163). The 95% confidence interval spanned zero and there was therefore no significant difference between the model and real-world distributions.
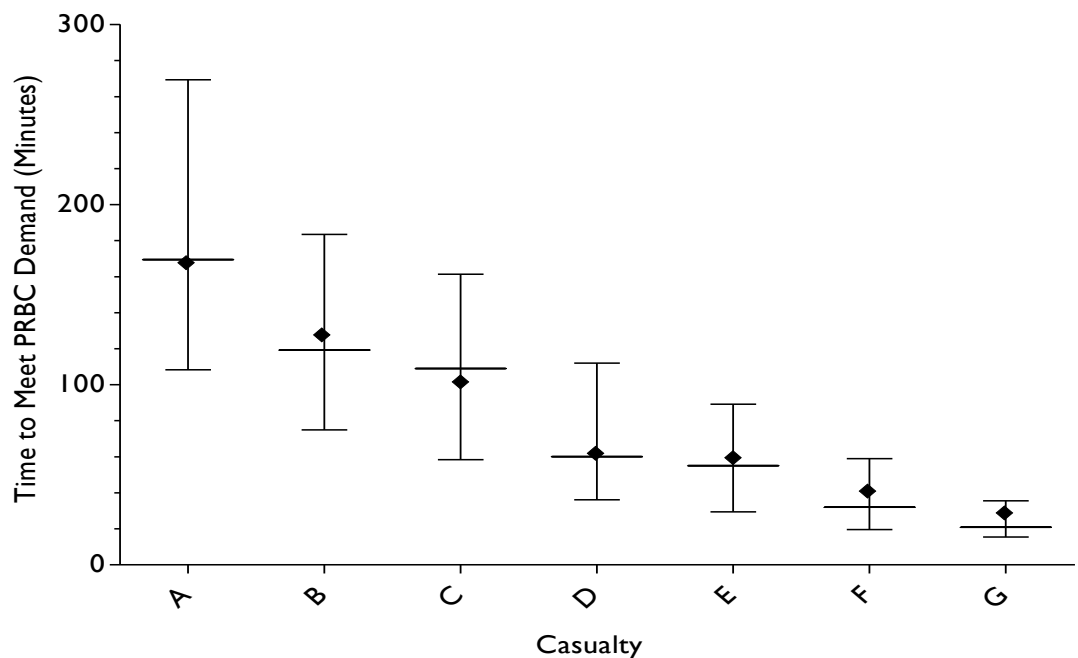
Figure 5.3 The median and IQR of times to meet the PRBC demand of the individual bleeding P1 casualties following 100 replications of the simulation model, accompanied by the actual real life times (♦) for each corresponding casualty's PRBC demand in 2005.

5.5.5 Discussion and Limitations

A model is not designed to be 100% accurate, as any model by definition is a simplification of reality and constructed as a means of understanding a system better using a more intuitive format (163). The time constraints associated with conducting most simulation studies dictates that not every aspect of the model can be evaluated and therefore complete verification and validation is rarely possible. The objective of the evaluation procedures performed above was therefore to gain confidence in the model as a whole and allow the user to draw appropriate conclusions from the model performance and output (163).

This validation study was limited by the relatively small sample of bleeding casualties experienced by the RLH on the day of the attacks. In addition, this population was itself limited due to its consisting solely of P1 casualties, with none of the P2s received at the RLH requiring a transfusion within the first 72 hours. Although every effort was made to gather as much data as possible, the length of time which has passed since the event added to the challenge of acquiring and checking the reliability of all the information collected. As such there was potential for error during the validation process.

Despite these limitations the simulation model appears to perform well in respect of the performance measures required to meet the study objective. Both the investigator and the expert panel involved in the model design and verification processes concurred that the model was found to perform to an acceptable level for the purpose for which it was designed.

5.6 Model Validation Part Three: Experimental Validation, Sensitivity Analysis and Solution Testing

5.6.1 Introduction

The process of experimental validation is necessary to confirm the simulation model is correct so as to ensure accurate results from the experiments performed on it. Several factors in the simulation setup needed to be considered at this stage including: the simulation end-point, the stability and nature of the model output, the length of the simulation run, the state of the model at initialisation and the number of replications required, all of which may affect the accuracy of a model's outputs (163). A number of these factors were predetermined by the design of the model and the study objectives, whilst others had only been loosely applied up to this point in Chapter Four to allow model testing and other aspects of the validation process. There was therefore a requirement to formally determine these model settings through additional system analysis prior to commencing the experimental phase of the project.

5.6.2 Model End-points, Output Stability, Run Length and Initialisation

As discussed previously, simulation of a system may involve replicating the entirety of a system from start to finish, part of a system for a defined period of time or its investigation over a number of repetitive cycles of the same events. Determining the end-point of the model may therefore already be clearly defined as in the first of these examples or as in the latter two instances, left for the investigator to determine. These two types of simulation end-point are referred to as terminating and non-terminating simulations (163). The latter of these requires the investigator to establish the point when the model output reaches a

steady state from which inferences can be made during the experimental phase of the study. This requires further analysis of the model to determine when this point is reached during a simulation and therefore the length of the simulation run required for each experiment.

In contrast, a terminating simulation is more likely to produce a transient output, fluctuating throughout the simulation until the point at which all processes are complete. These simulations may be investigated by analysing certain time points during the simulation run or by looking at overall output parameters depending on the model objectives (163). This model was designed to cover the initial burden on available PRBC stocks following an MCE and to cover the first 72 hours involving the crisis, surge, consolidation and start of recovery phases of the event. The simulation was therefore considered a terminating one, as although the real system continues to operate, the objectives focused on PRBC provision during the time of greatest blood demand and when restocking supplies may be at best challenging or at worst impossible.

The output from the model was therefore also of a transient nature, as not only was the model terminating, but it was also designed to include an initial surge in casualty arrivals, which then reduces as the model progresses through time and therefore consequentially alters the output. Furthermore, the output from the model in relation to the study objectives included both types of transient system analysis with overall parameter values recorded at the end of the simulation such as PRBC stock levels, as well as time point analyses, for example the number of bleeding PIs treated within one hour.

The initial state of the model must also be considered prior to any experimentation. Many systems investigated through simulation are assumed to be active when the simulation commences, such as a factory production line or air traffic control tower for example. The model needs to reflect these conditions during the simulation by initiating at a set appropriate level of work already in progress or by allowing time for the model to reach this level of normal activity, prior to the interpretation of its output – a phase referred to as the warm-up period (163). As suggested during the estimation of these parameters in Chapter Four, this model was designed to replicate the procedures in a generic MTC

following an MCE. When these events occur there is classically a window of preparation time prior to the arrival of the first casualty. During this time the system occupancy and work in progress can be reset to an idle state in preparation for the surge in casualty arrivals (87, 103, 108-110). The simulation model therefore did not require a warm-up period or pre-set workload and replicates the state of readiness which would be expected in the real system following an event.

5.6.3 Determining the Replication Number

Each simulation run performed on the model utilises a new set of random numbers during the sampling of data inputs used to drive the model (163). Therefore, every run of the simulation is different from the others and thus produces variation in its output. Should a small number of replications be performed there may be wide variation in the output from the model, as outliers applied during the random number sampling process will exert a significant effect on the overall summary values produced across all runs of the model. This in turn may significantly affect the conclusions drawn from any experimental data the model produces. In order to account for this, the investigator must determine the number of replications required to reach a mean output value from the simulation which lies within an acceptable confidence interval between replications. The required number of replications can then be set for each experiment performed on the model confident in the accuracy of the subsequent results.

Another important consideration in determining the number of replications to apply during a study is the timescale required to carry them out. This in part, is related to the number of experiments the investigator wishes to perform as well as the timescale available for the study as a whole. The capability of the software in which the model is constructed is also important, as many, including Arena, have automatic settings allowing replications to be run in batches which can dramatically reduce the computational burden of the experimentation phase.

The actual number of replications required for accurate results has been discussed widely in the literature, with some authors suggesting as few as three and others as many as 1000 in order to establish the mean performance of the model (163, 164, 174, 318). One method for determining this aspect of the model setup is to use the graphical method described by Robinson in his text on the practice of model development and use, in which he describes plotting the mean model output and confidence interval over increasing replications, until such point as the graph plateaus to an acceptable level (163).

Applying this method to the baseline model from this study, the model was set to run over 500 replications as an initial assessment of the model's performance. The mean output relating to the principal study objectives were then considered in terms of the overall cumulative mean along with the variation in confidence interval across all runs. A confidence interval of 5% was applied based on the best practice recommendations set out by the International Society for Phamacoeconomics and Outcomes Research and the Institute of Operational Research and the Management Sciences (ISPOR-SMDM) joint task force (283). The results were plotted individually and inspected to determine an appropriate number of replications required during the model experimentation phase. The confidence interval from the mean output for each objective parameter was calculated using the formula described below (163). The principal study outcomes of: the number of bleeding P1 and P2s treated within one and four hours of arrival and time to reach the minimum type O PRBC level are plotted as cumulative means across 500 replications in Figure 5.4 A-C.

$$CI = \overline{X} \pm t_{n-1,\alpha/2}\frac{SD}{\sqrt{n}}$$

$\overline{X}$ = Mean model output

SD = Standard deviation of the model output

n = number of replications of the model

$t_{n-1,\alpha/2}$ = derived value from the Student's t-distribution ($\alpha/2$ = level of significance)

Adapted from Simulation: The practice of Model Development and Use, Robinson. John Wiley and Sons, West Sussex, UK 2004.

A)
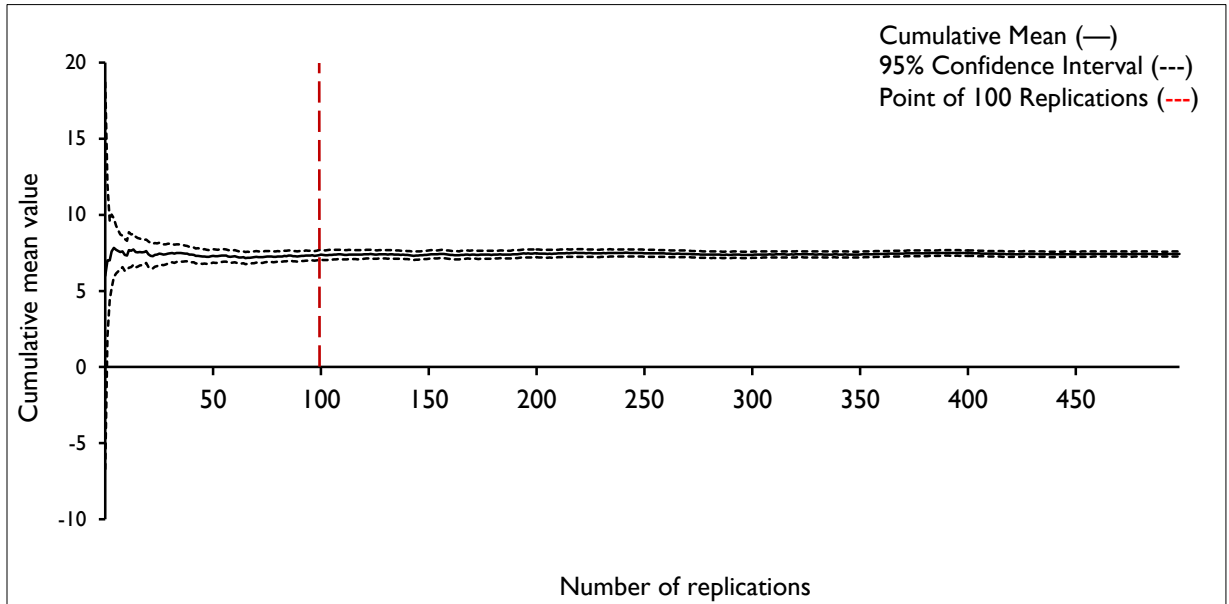
B)
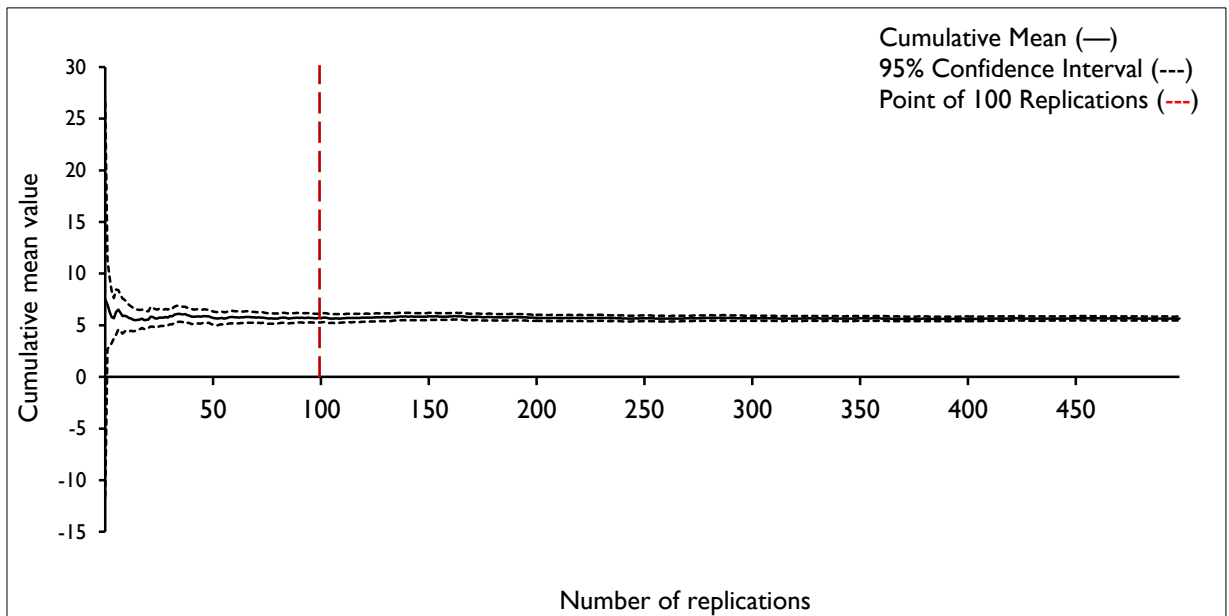
C)
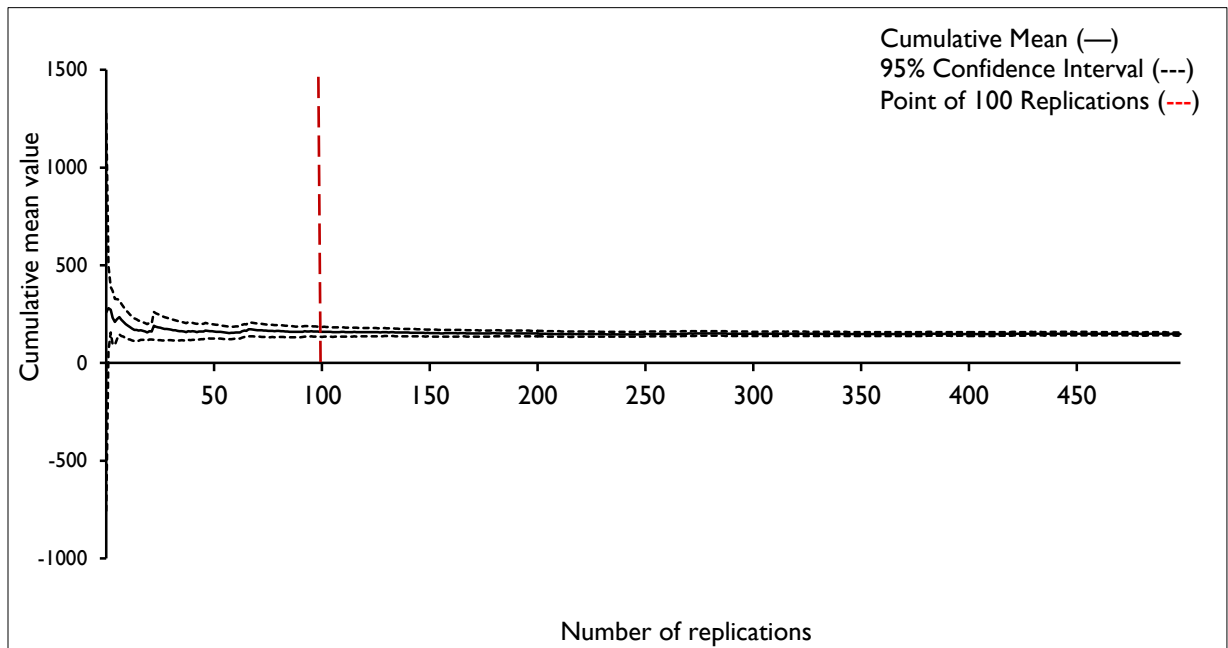
Figure 5.4 The cumulative mean (—) and 95% confidence interval (---) over 500 replications for: A) The number of bleeding P1s treated within one hour or arrival, B) The number of bleeding P2s treated within four hours of arrival and C) The time to reach the minimum type O emergency PRBC level. Dashed red line indicates point of 100 replications.

Following assessment of the graphical data across all 500 replications for each outcome measure it was decided that 100 replications would provide a sufficient balance between experimentation time and the model's performance accuracy. All experiments were therefore, unless stated, set to a 100 replication level and the cumulative mean used as the value reported in the experimentation results. As a result, the simulation settings originally estimated at the end of Chapter Four (Table 4.11) were maintained unaltered in the final baseline model.

5.6.4 Sensitivity Analysis

Sensitivity analysis is a type of experimental analysis applied to a model to establish the effect size each individual input parameter used to drive the model has on outputs during a set of simulation runs. The process serves three key purposes in validating the model and the manner in which its results are interpreted. Firstly it allows the investigator to determine the importance of the model inputs derived from uncertain data sources or a best-guess approach. Secondly, it allows the robustness of the model to be determined and therefore, the investigator to establish how resistant the model is to changes in inputs. The third and final purpose of sensitivity analysis provides the initial yield of experimental information as it demonstrates the effect changes in the model's experimental components have on outcomes. This therefore gives an early indication of the level of change required for a simulation run to produce an appreciable change in output (163).

Sensitivity analysis can be performed using various methods depending on the complexity of the model and study objectives. This study employed a one-way sensitivity analysis. This involves increasing or decreasing individual input parameters by a constant 20% of their baseline value and recording changes in outputs. This percentage change was chosen based on the literature discussion of performing sensitivity analysis within a study of healthcare economics (319). During each batch of 100 runs of the simulation only a single parameter was changed at a time, hence a one-way analysis. When the increase or decrease was in relation to a sampling distribution, the scale parameter of the distribution (Appendix III) was scaled up or down by 20% of its baseline value. Table 5.3 A 20% Increase and reduction in baseline input parameters Table 5.3 describes the 20% changes to the inputs and the effect on the distributions where relevant. The sensitivity of the mean output results relating to bleeding P1 and P2 treatment percentages are shown below in the tornado diagram of response effect (Figure 5.5). The times to exhaustion of type O PRBCs are also shown below as separate line plots for each input variable (Figure 5.6). Line plots were used to illustrate the overall effect of altering the variable on consumption of PRBCs over the course of the run, allowing greater understanding of their impact within the model.

Table 5.3 A 20% Increase and reduction in baseline input parameters

Input Factor	Baseline Parameters	20% Decrease	20% Increase	Effect of Distribution Change
Casualty Arrival Rate	Johnson SB CDF (γ 1, δ 0.55, λ 15, Υ 0.05)	λ = 18	λ = 12	Casualties arrive earlier with a lower value of λ
Overall Number of Casualties	40	32	48	N/A
Proportion of Casualties with Blood Group O*	44%	24%	64%	N/A
P1:P2 Casualty Ratio	60:40	40:60	80:20	N/A
Time to Assess and Gain IV Access	P1s = Gamma Distribution (α 2.1, β 5.0, 0.0), P2s = Gamma Distribution(α 1.7, β 11.0, 0.0)	P1s (β 4), P2s (β 8.8)	P1s (β 6), P2s (β 13.2)	Mean task time reduces with lower value of β
Proportion of Casualties Bleeding within P1 & P2 Cohorts	P1 = 80%, P2 = 50%	P1 = 74%, P2 = 40%	P1 = 96%, P2 = 60%	N/A
Bleeding Casualty PRBC Demand	P1s = Poisson Distribution (10.7), P2s = Poisson Distribution POIS(4.7)	P1 = POIS(8.6), P2 = POIS(3.8)	P1 = POIS(12.84), P2 = POIS(5.64)	Mean demand volume reduces with reducing POIS (mean)
Total Cumulative Time to Group Casualty**	27.5 minutes	22 minutes	33 minutes	N/A
Time to Transfuse 1 Unit of PRBCs to Single Casualty	P1s = Johnson SB Distribution (γ 2.1, δ 0.75, λ 29.0, Υ0.56), P2s = Johnson SB Distribution (γ 1.2, δ 0.62, λ 29.0, Υ 0.84)	P1 = λ 23.2, P2 = λ 23.2	P1 = λ 34.8, P2 = λ 34.8	Task time reduces with a lower value of λ
Initial PRBC Stock Level	O = 100, A = 75, B = 25, AB = 10	O = 80, A = 60, B = 20, AB = 8	O = 120, A = 90, B = 30, AB = 12	N/A
Number of Laboratory Technicians Available	6	5	7	N/A
Number of Porters Available	4	3	5	N/A

*Remaining percentages of alternative blood groups maintained at normal population proportions. **Inclusive of all processes from the transport of acquired casualty blood sample to the transfusion laboratory through to delivery of grouped PRBCs back to casualty.

A)

Demand Vol
Bleeding
Stock Level
P1:P2 Ratio
Arrival Number
Process Time
Time to Transfuse
Access Time
Bld Type
Arrival Rate
Lab Techs
Porters

20% Increase (■)
20% Decrease (□)

-20   -10   0   10   20   30

Percentage of P1s Treated (<1hour) in Relation to Baseline Model

B)

Bleeding
Stock Level
P1:P2 Ratio
Demand Vol
Bld Type
Arrival Number
Access Time
Arrival Rate
Time to Transfuse
Process Time
Porters
Lab Techs

20% Increase (■)
20% Decrease (□)

-30   -20   -10   0   10   20   30

Percentage of P2s Treated (<4 hours) in Relation to Baseline Model

C)

Percentage of P1s & P2s Treated (<6 hours) in Relation to Baseline Model

D)

Percentage of P1s & P2s Treated (<12 hours) in Relation to Baseline Model

Figure 5.5 Percentage effect on A) P1s treated in full within 1 hour, B) P2s treated in full within 4 hours, C) P1s and P2s treated in full within 6 hours, D) P1s & P2s treated in full within 12 hours, following a 20% increase (■) or decrease (□) in input parameter values.

The magnitude of the response following a 20% increase or decrease in an input parameter's value can be described as having a large effect on the outcome measure when the change is approximately 10% or greater, a medium effect when the change is between 5-10% and a small effect when less than 5%. In terms of the percentage of P1s treated within one hour of arrival, a large effect is observed with a change in the percentage of bleeding casualties and the individual PRBC demand of all bleeding casualties. The latter exhibits the greatest effect on the outcome measure with almost a 14% increase in P1s treated with a 20% reduction in the population's PRBC demands (Figure 5.5).

Changes in stock level, overall casualty number and proportion of P1s generated a medium effect on the percentage of P1s treated within an hour, with a small or unappreciable effect occurring with changes to the remaining factors. The predominant effect across all inputs was to produce a greater reduction in this outcome measure when the factor value was increased than occurred in the reverse scenario. Stock level was the only input factor to produce a positive effect on treatment rate when increased. The only exception to this was in instance where the time to assess and gain IV access was considered, which showed a positive effect on P1s treated when both increased and decreased form the baseline value, indicating either the factor to be an unstable input or have a less uniform distribution compared with the other input factors.

In terms of P2s treated within four hours of arrival, an overall similar pattern of effects was observed. Notable exceptions were that the percentage of bleeding casualties, the initial PRBC stock level and the proportion of P1s which had the greatest influence with a large effect on the outcome measure. In comparison, overall demand volume, casualty number and prevalence of the type O blood group in the casualty population were seen to have a medium effect on the outcome.

The overall percentages of bleeding casualties treated within six and twelve hours were also investigated as additional outcome measures for the study (Figure 5.5 C & D). This allowed further insight into the system performance and whether given more time, casualty PRBC

demands could eventually be met if they had not already. The treatment percentages followed the same pattern for each input factor at both time points. As was the case for the treatment of P2s, the rate of bleeding and the initial PRBC stock level generated the greatest effect when varied and the prevalence of the type O blood group in the casualty population continued to have a medium effect on treatment percentages. Furthermore, the overall PRBC demand volume also produced a large effect on both outcome measures as was the case for P1s treated within the hour.

The other principal outcome measure used to assess model performance was the time to exhaustion of type O PRBC stocks. This was applied to indicate the point at which the ability of the responding unit to treat newly received casualties from the event would reach saturation. For the purposes of the sensitivity analysis this was assessed through the change in the level of type O PRBC during the time course of the event. The effect of a 20% increase or decrease in each of the individual input factors on the level of type O PRBC during the first 12 hours of the event is shown in Figure 5.6 A-X, accompanied by the baseline values for comparison.

A) 20% Increase in Time to Assess and Gain IV Access

Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)

Type O PRBC Level

Time from 1st CasualtyArrival (Minutes)
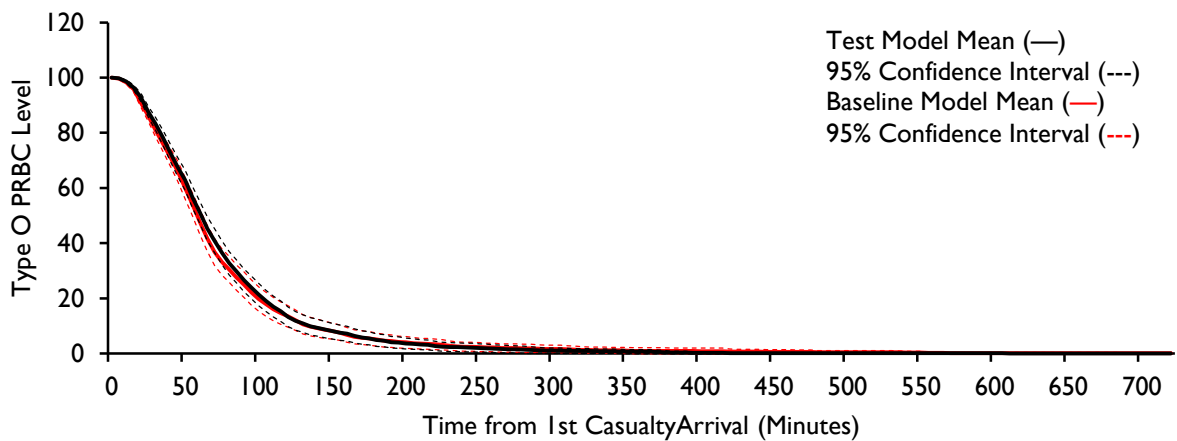
B) 20% Decrease in Time to Assess and Gain IV Access
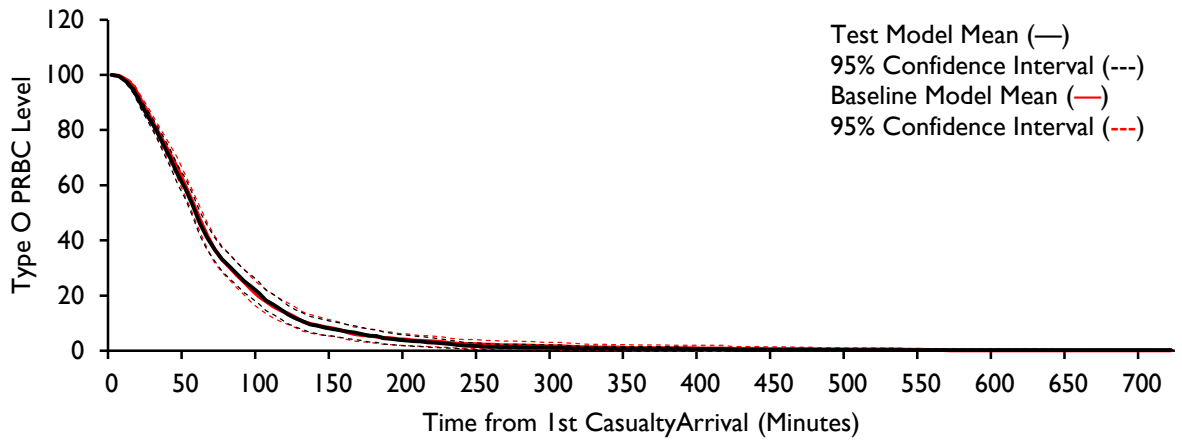
C) 20% Increase in Proportion of Casualties with Blood Group O*
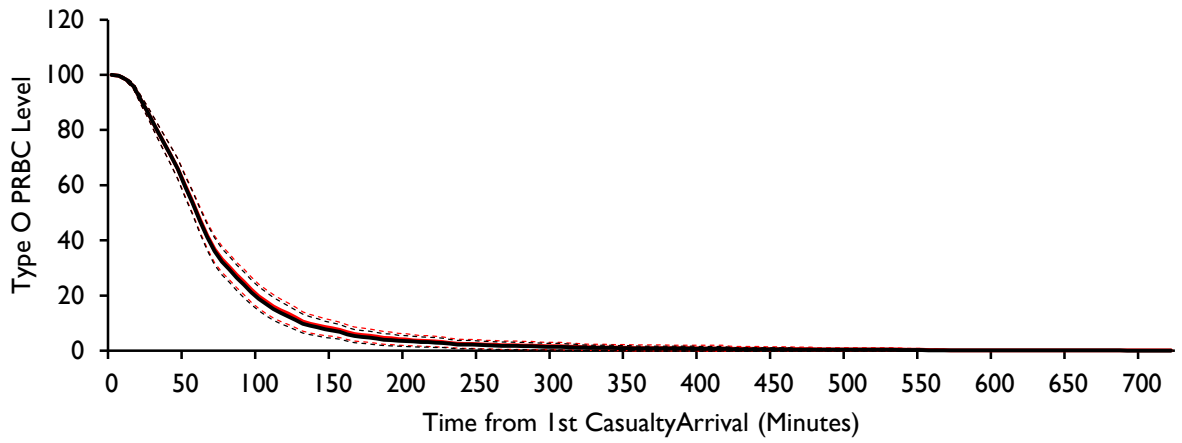
D) 20% Decrease in Proportion of Casualties with Blood Group O*

E) 20% Increase in Proportion of Casualties Bleeding within P1 & P2 Cohorts

Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)
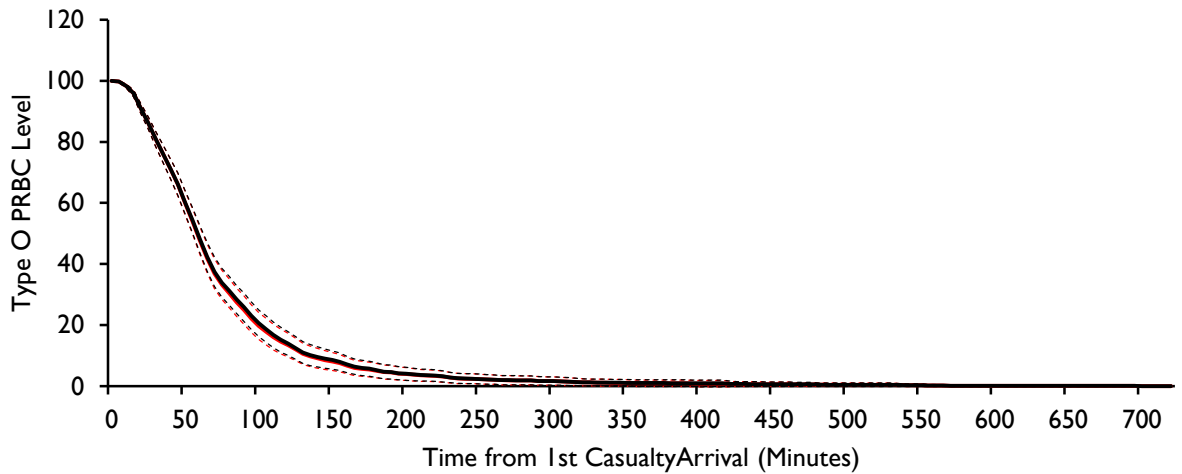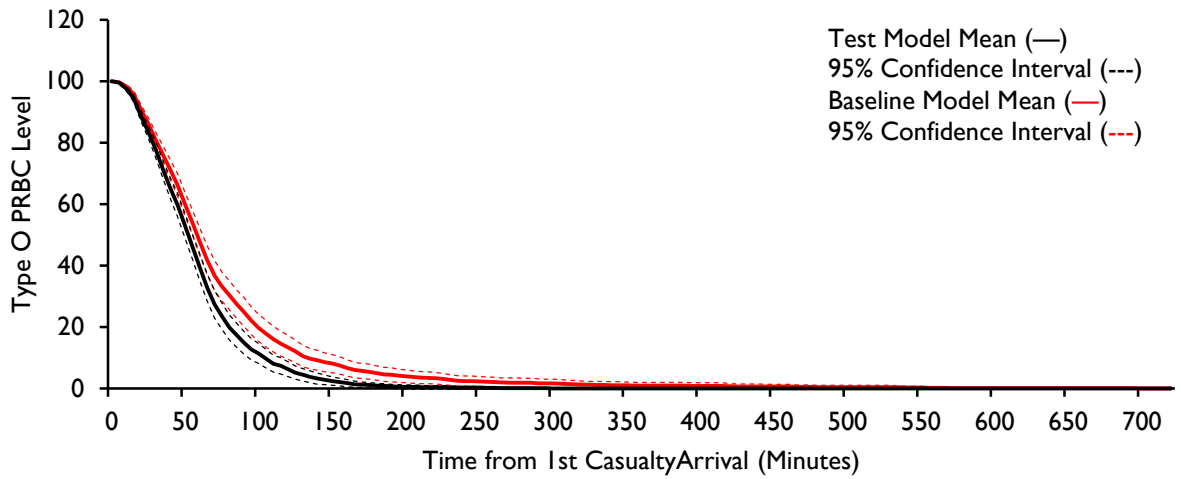
F) 20% Decrease in Proportion of Casualties Bleeding within P1 & P2 Cohorts
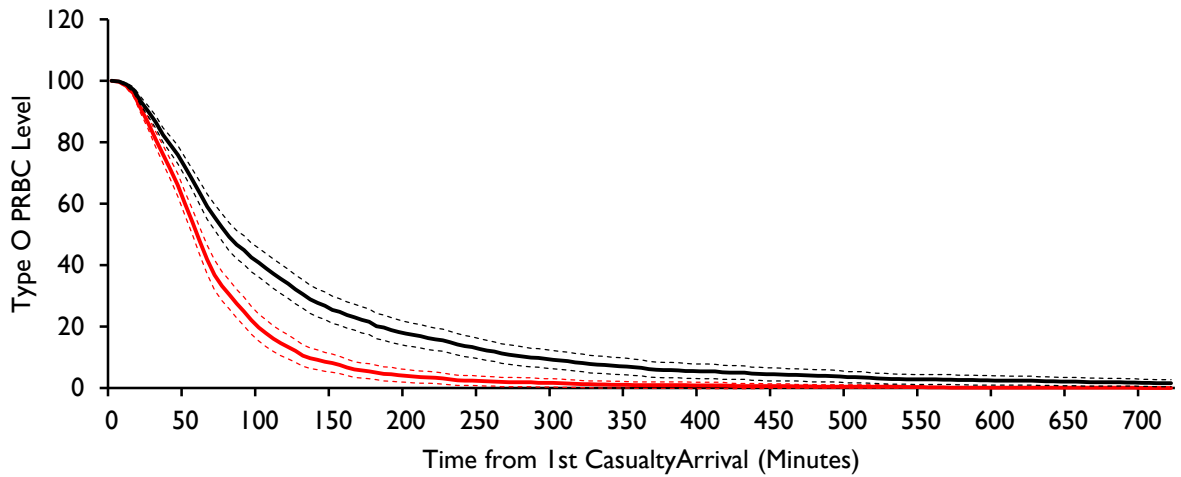
G) 20% Increase in Bleeding Casualty PRBC Demand

H) 20% Decrease in Bleeding Casualty PRBC Demand

Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)
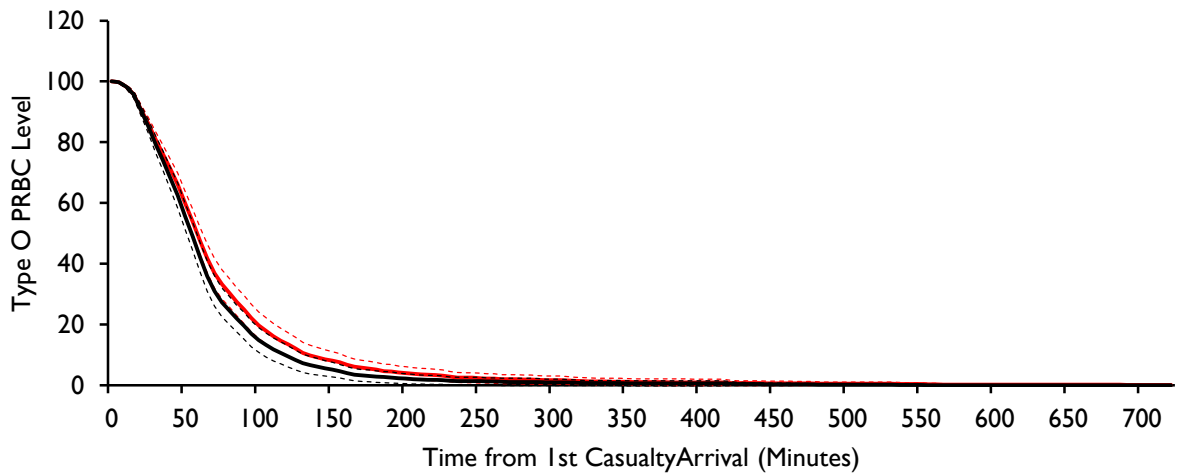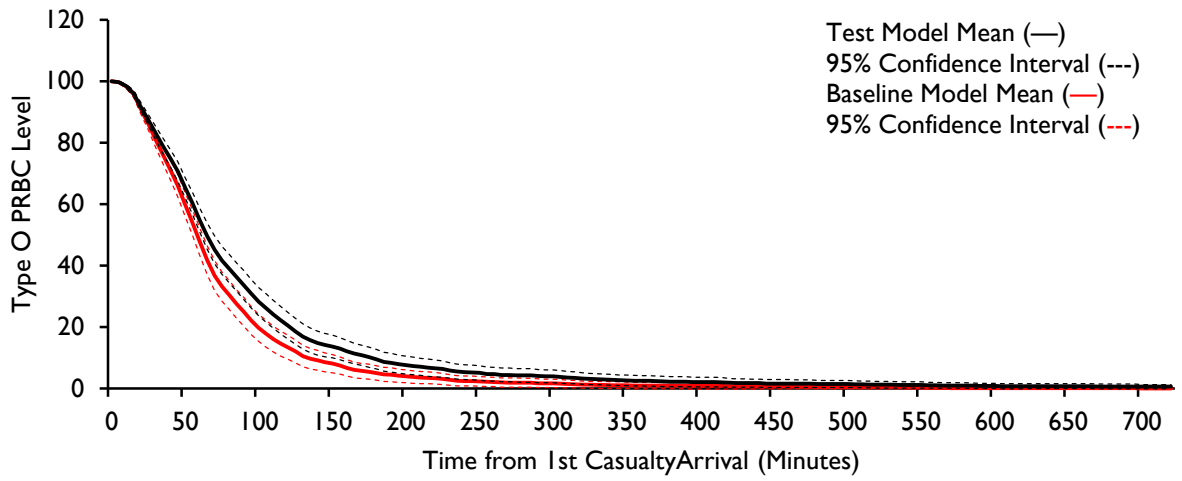
I) 20% Increase in Number of Laboratory Technicians Available
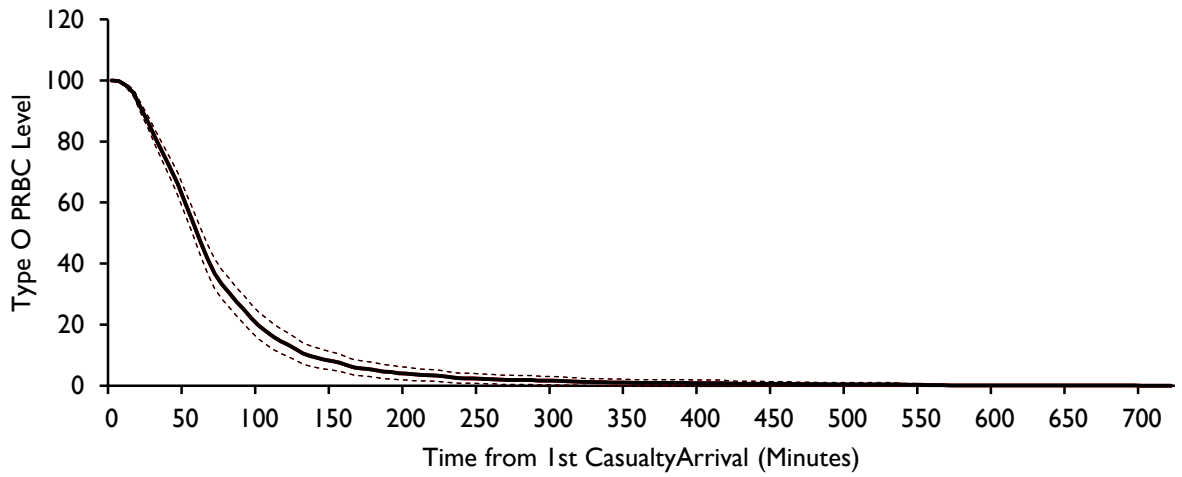
J) 20% Decrease in Number of Laboratory Technicians Available

K) 20% Increase in P1:P2 Casualty Ratio

Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)
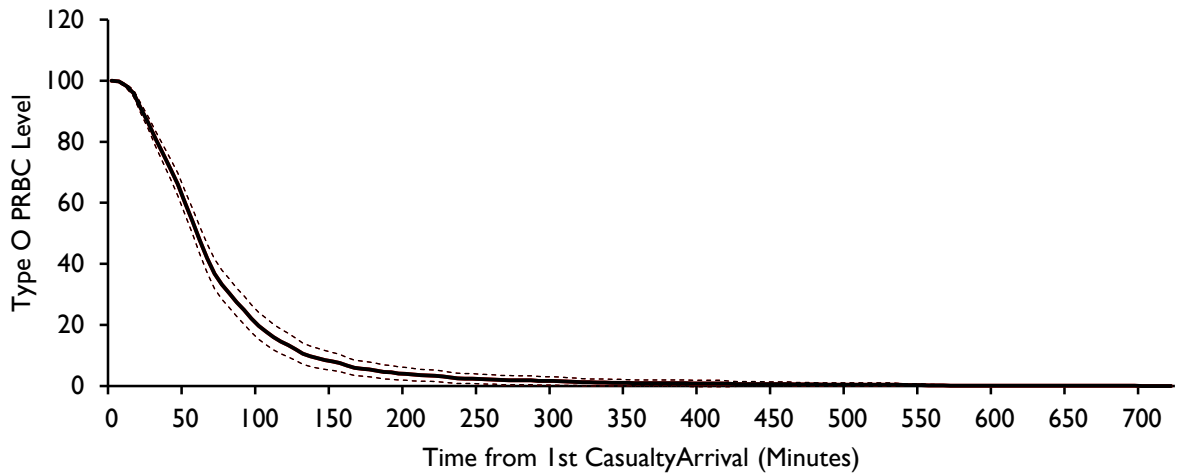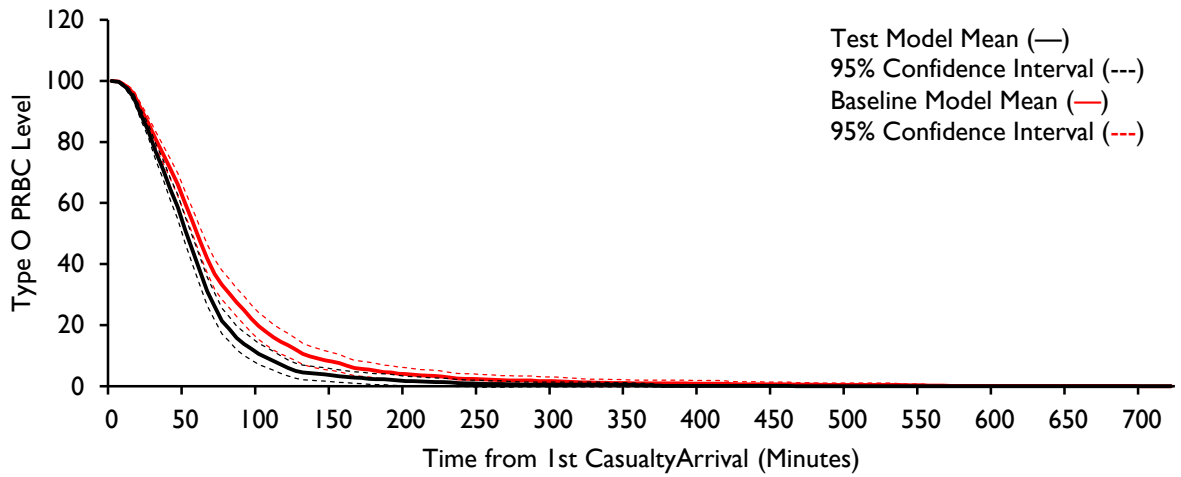
L) 20% Decrease in P1:P2 Casualty Ratio
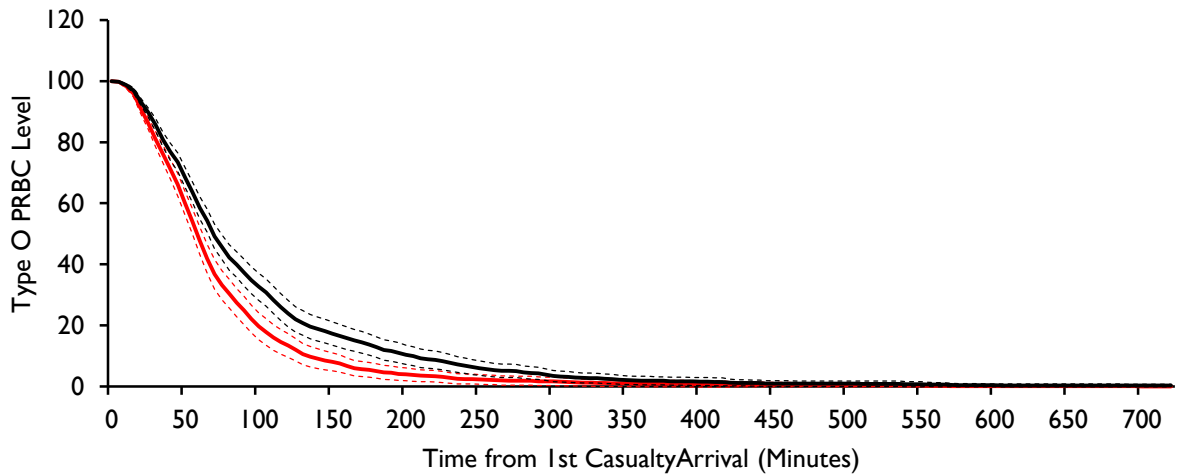
M) 20% Increase in Number of Porters Available
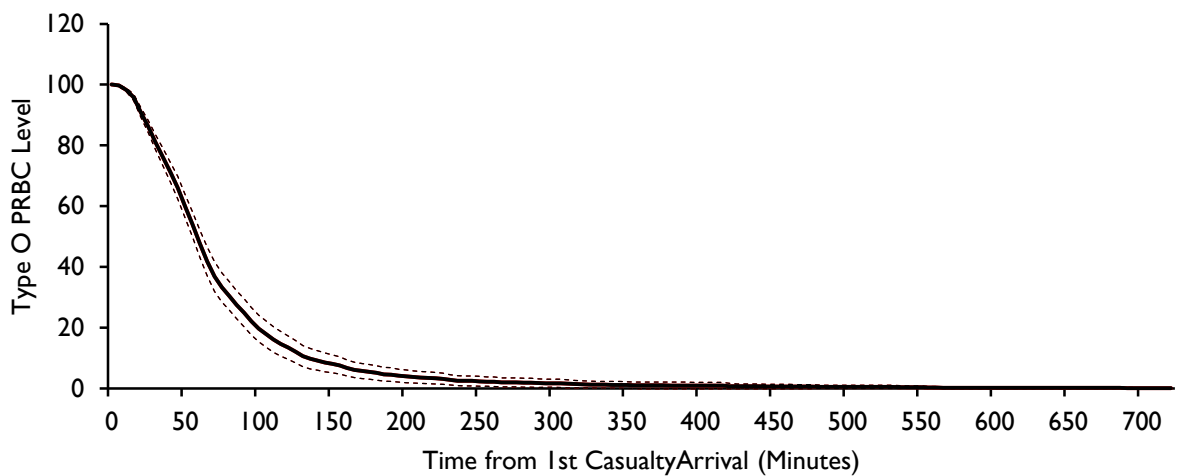
N) 20% Decrease in Number of Porters Available
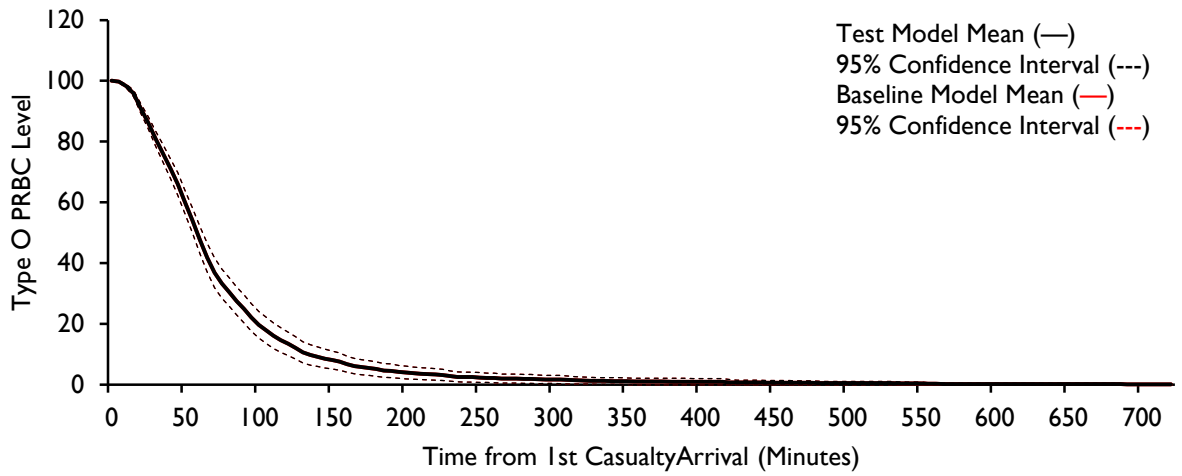
Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)

Type O PRBC Level

Time from 1st CasualtyArrival (Minutes)

O) 20% Increase in Total Cumulative Time to Group Casualty**

Type O PRBC Level

Time from 1st CasualtyArrival (Minutes)

P) 20% Decrease in Total Cumulative Time to Group Casualty**

Type O PRBC Level

Time from 1st CasualtyArrival (Minutes)

Q) 20% Increase in Initial PRBC Stock Level

Legend:
Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)

Y-axis: Type O PRBC Level
X-axis: Time from 1st CasualtyArrival (Minutes)

R) 20% Decrease in Initial PRBC Stock Level

Y-axis: Type O PRBC Level
X-axis: Time from 1st CasualtyArrival (Minutes)

S) 20% Increase in Time to Transfuse 1 Unit of PRBCs to Single Casualty

Y-axis: Type O PRBC Level
X-axis: Time from 1st CasualtyArrival (Minutes)

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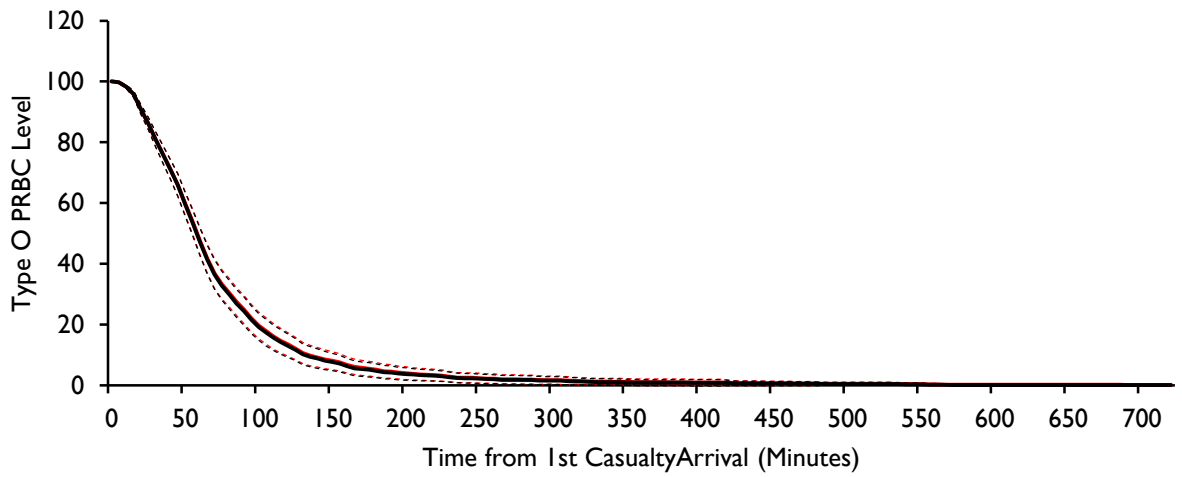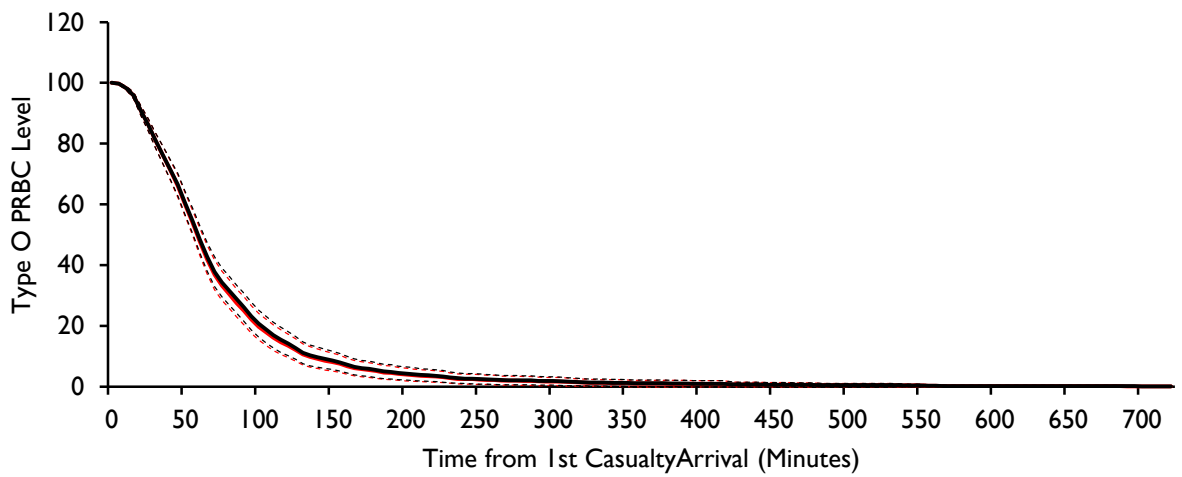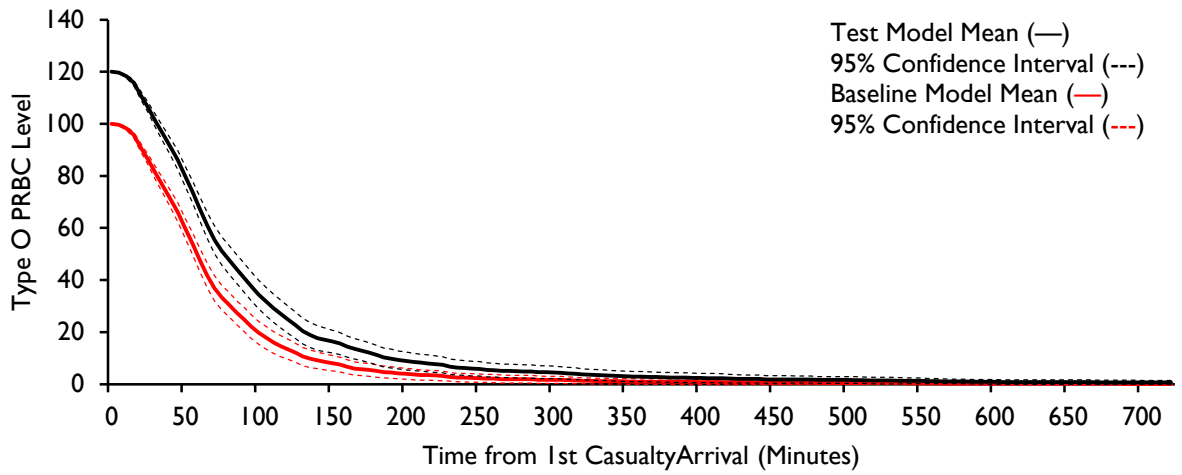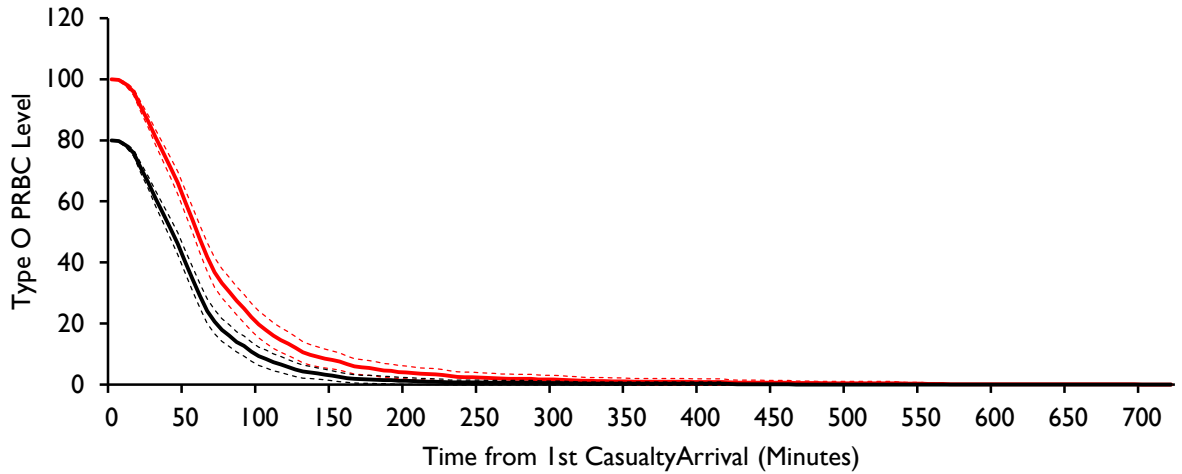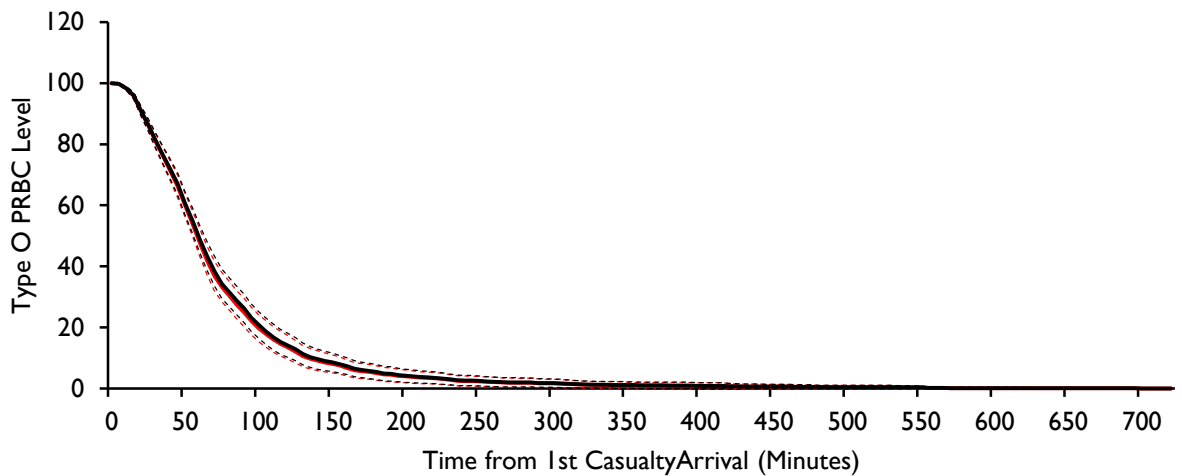
T) 20% Decrease in Time to Transfuse 1 Unit of PRBCs to Single Casualty
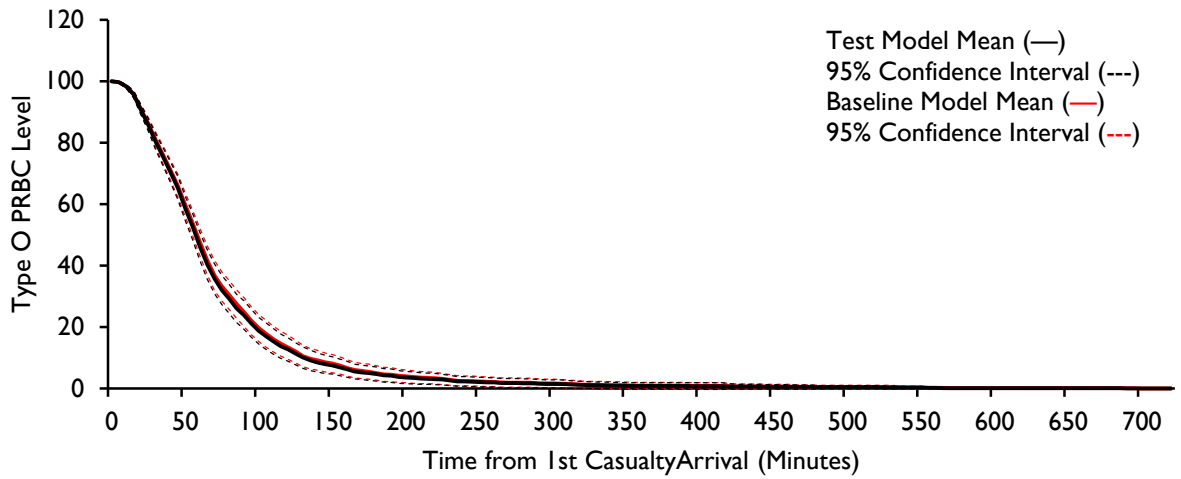
U) 20% Increase in Overall Number of Casualties
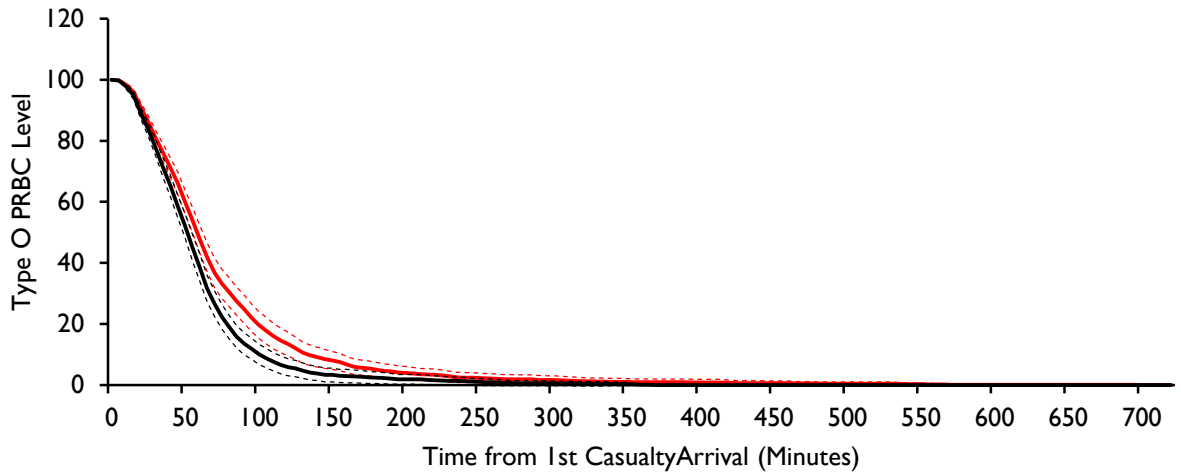
V) 20% Decrease in Overall Number of Casualties

W) 20% Increase in Casualty Arrival Rate

Test Model Mean (—)
95% Confidence Interval (---)
Baseline Model Mean (—)
95% Confidence Interval (---)
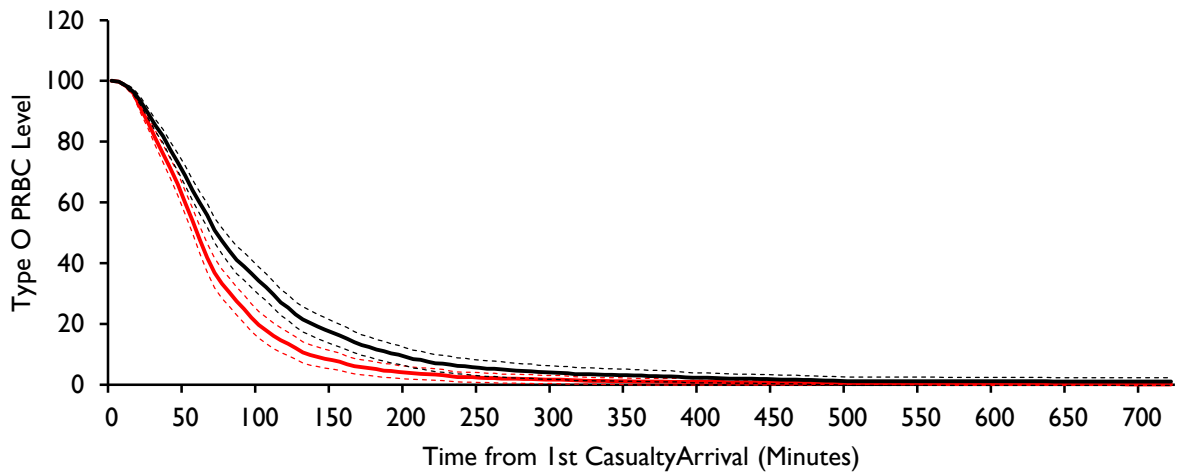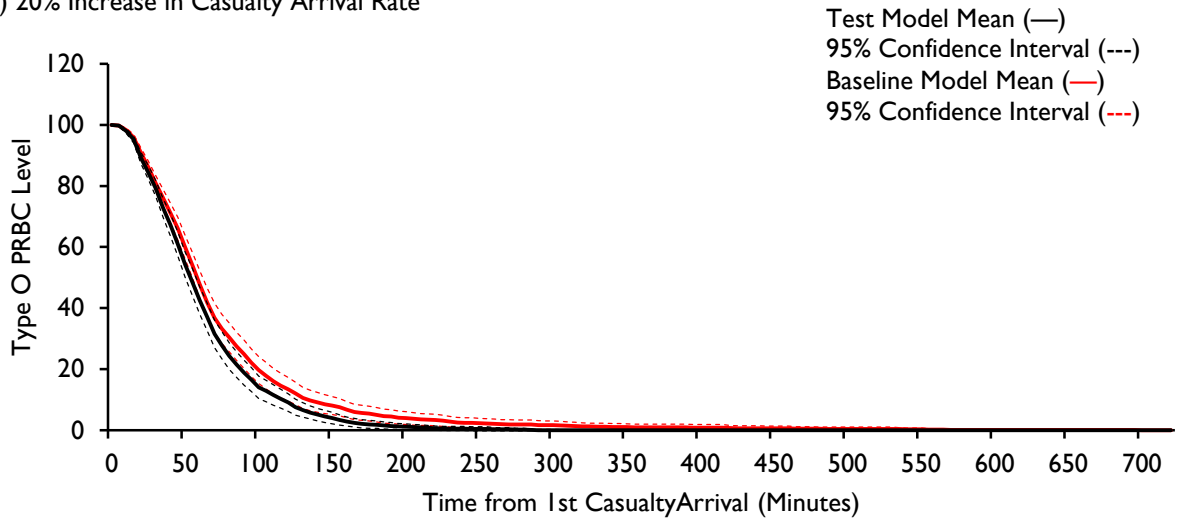
X) 20% Decrease in Casualty Arrival Rate
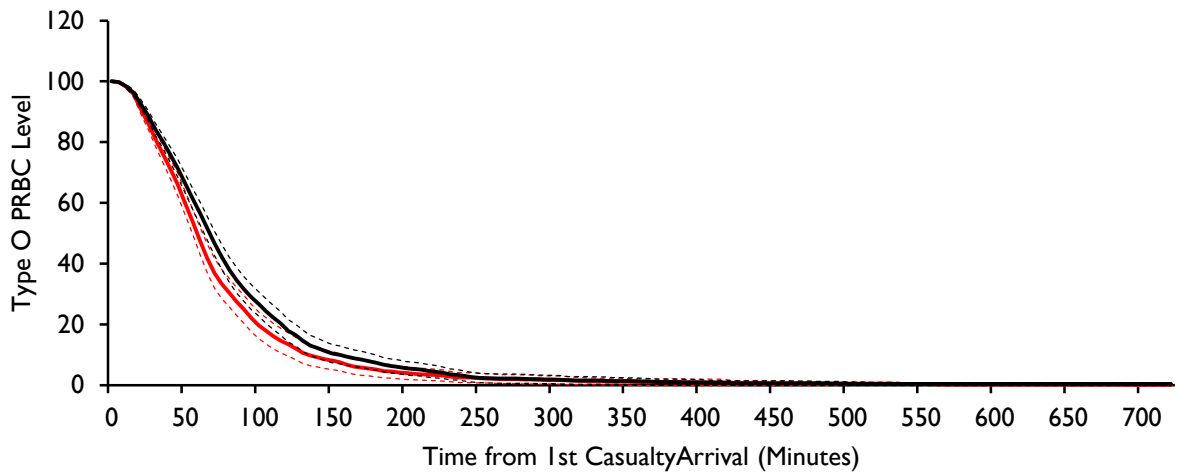
Figure 5.6 Effect on rate of consumption of Type O PRBCs from the available stock following a 20% increase or decrease in input parameter values (Mean [—] and 95% CI [---]) compared with the baseline distribution (Mean [—] and 95% CI [---]).

*Remaining percentages of alternative blood groups maintained at normal population proportions. **Inclusive of all processes from the transport of acquired casualty blood sample to the transfusion laboratory through to delivery of grouped PRBCs back to casualty.

No significant change was seen in the pattern of type O PRBC consumption compared with the baseline model in relation to changes in: the proportion of casualties with blood group

O, the number of available laboratory technicians, the time to determine individual casualty blood groups and dispense type specific PRBCs, the number of available porters, the time to transfuse individual units of PRBCs or the time to assess and gain IV access in arriving casualties. Some shift in type O usage was seen with changes to the PRBC demand of casualties and their arrival rate. A 20% reduction in both factors reduced the rate of type O consumption; although an overlap in confidence intervals between the experimental factor and the baseline state was present in both instances.

The most significant effect on type O PRBC level occurred with changes to the proportion of bleeding casualties in the population, the overall number of casualties received, the initial stock PRBC stock level held and the ratio of P1:P2 casualties. The first of these, the proportion of bleeding casualties, had the most significant effect on type O levels with more than twice as much type O PRBC units remaining at two hours compared with the baseline model when the percentage of bleeding casualties was reduced by 20%. In contrast, an increase in the proportion of bleeding casualties resulted in the type O level reaching a critical volume of 10U (the equivalent volume required to meet the demands of a MT) half an hour earlier than was observed in the baseline model. Finally, although stock level showed a difference between the distributions compared with the baseline parameters, there was no change in the rate of PRBC use observed, only a displacement of the baseline distribution either positively or negatively due to the addition or reduction in the volume of PRBCs initially available within the system.

The sensitivity analysis provided additional understanding of both the model and the provision of PRBCs during an MCE, allowing greater confidence to be gained in the experimentation process which follows in Chapter Six. All principal outcome measures were most affected following variations to: the P1:P2 ratio, the overall casualty load, the percentage of bleeding casualties, the individual PRBC demand volume and the initial PRBC stock holding. In addition, the proportion of casualties of blood type O and the casualty arrival rate also showed an appreciable effect on outcomes. Transfusion planners can exert little or no influence over these factors as the majority relate either to the demographics of the casualties involved or to the nature of the event which generates them. The exception

is stock holding which heavily influences outcomes, however, outside of times of heightened tension with an increased risk of an event occurring, the option of maintaining the required exceptional levels of stock would be limited.

5.6.5 Solution Testing

Solution testing is the final step in the evaluation of the model and involves evaluating the simulation in a prospective manner against real data following implementation of the simulation findings in the real world. In effect this closes the modelling loop by putting into practice what has been understood and learnt throughout the model experimentation process. In the case of this study this would require a repeat of the black-box validation, comparing a solution in a real-world MCE with that predicted by the model under identical conditions. As such, this aspect of validation goes beyond the remit of this thesis and offers a potential follow-up study for the future.

5.7 Chapter Five Conclusion

Aim One of the study sought to investigate the challenges and controversies surrounding PRBC provision in historical MCEs as described during Chapter Two of this thesis. A working model was subsequently designed, developed and fully informed in Chapter Three and Chapter Four in accordance with Aim Two. This chapter has now satisfied Aim Three through the description of the complete model evaluation process in readiness for the experimentation phase of the study. The model was verified and tested through rigorous interrogation before being validated using a real event comparison study. Although validation of the model was challenging with a lack of bleeding P2 casualty data with which

to compare results, the remaining principal outcome measures as well as additional analysis provided confidence in the model's performance. The simulation was therefore deemed to be fit for the purpose for which it was designed.

CHAPTER SIX

Experimentation

6.1 Introduction

6.1.1 Model Experimentation - A Review of the Aims and Hypotheses

Having developed a working simulation model of packed red blood cell provision (PRBC) at a generic major trauma centre (MTC) during a mass casualty event (MCE), the model was evaluated and determined fit for its purpose. The experimentation phase of the simulation study could then commence. This stage of the modelling process was intended to address the final three study aims through the following series of experimental hypotheses:

Aim Four – Investigating PRBC Stock Management: Determine the effect variations in the management of in-hospital PRBC stock has on outcomes across event sizes in terms of the following experimental hypotheses:

- Hypothesis 4A (H_{4A}) – There exists a critical ratio of MTC held PRBC stock levels to the casualty load received, below which, the ability to treat bleeding casualties effectively, becomes overwhelmed.

- Hypothesis 4B (H_{4B}) – Outcomes following an MCE are greatest when a restock of an MTC's held PRBC volume occurs at the earliest opportunity in the timeline of an event.

Aim Five – Varying Laboratory Processing: Through the following hypotheses, investigate the influence on outcomes across event sizes following modifications to the transfusion service's protocols for processing and providing group-specific PRBCs:

- Hypothesis 5A (H_{5A}) – Outcomes from an event can be improved by prioritising the laboratory processing of priority two (P2) casualties to provide group-specific treatment whilst preserving emergency type O PRBCs solely for priority one (P1) casualties.

- Hypothesis 5B (H_{5B}) – In addition to prioritising the blood group analysis of P2s, overall outcomes from an event can be further improved through restricting the processing of bleeding P1 casualties altogether, providing their treatment exclusively through the use of type O emergency PRBCs.

Aim Six – Limiting PRBC Provision: Identify by means of the following hypotheses effective strategies for improving outcomes when restocking of PRBC supplies at an MTC is not possible for MCEs of increasing magnitude:

- Hypothesis 6A (H_{6A}) – Limiting individual casualty overall PRBC provision can improve overall outcomes following an event.

- Hypothesis 6B (H_{6B}) – Overall outcomes can be further improved through additionally limiting all P1s to one 6U pack of emergency type O PRBCs, whilst also denying P2s treatment with this particular resource altogether.

6.1.2 Experimental Techniques in Discrete Event Simulation

Experimentation with simulation models can be executed through interactive or end-point analysis both of which can incorporate either comparison studies or solution space based searches of the model (163). The interactive approach is similar to that described during model evaluation in Chapter Five, whereby the investigator monitors the animated display of the simulation to observe activity patterns and the changes in these patterns following

modifications to the system's configuration or input parameters. In contrast, end-point analysis, which will be utilised in this section, involves studying the numerical output of the model at the end of a run or batch of runs of the model, in order to determine the effect various system changes have on model performance through specific outcome measures.

Comparison or solution space search studies are methods of evaluating the magnitude of the effect that variations within the model setup or input parameters have on the outcome measures considered. Comparison studies assess model performance through directly measuring outcomes between different system scenarios, whereas solution space searches look at all possible combinations of system setups and variations in inputs to determine an optimal design or strategy (163). The latter can be highly complex and requires extensive experimentation time with no guarantee of a solution which remains applicable or practical in the real-world system. For example, with reference to this study, increasing the PRBC inventory level to one hundred times its baseline level would, based on the sensitivity analysis, allow many more casualties to be treated in the required timescale, it is however entirely impractical both financially and resource wise for this strategy to be adopted into healthcare policy and therefore of little experimental value.

The solution search based approach is therefore more appropriate for investigations that centre on generalised system optimisation as opposed to answering specific key questions regarding system modification. This study was designed to investigate a number of experimental hypotheses concerning different aspects of an MTCs blood provision response during an MCE and as such, is best suited to an experimental comparison study approach.

6.1.3 Review of Model Performance

The developmental processes involved in producing the final experimental model themselves involved a degree of experimentation. This allowed a general improvement in our understanding of the relationships which exist within the model and the effects on

outcomes when the baseline system is altered. For example, the sensitivity analysis performed in Chapter Five was in essence, a limited search of the solution space with general variations made across all inputs to determine the overall level of influence each factor has on the model's outcome measures. This allowed greater understanding as to which of the inputs, be it a 'supply level' such as the number of available resources or a 'system lever', which alters the operational characteristics of the system which are most important in manipulating the model's outcomes and therefore, most relevant to future planning.

From this limited search of the solution space it was observed that of the five factors displaying the greatest influence on outcomes, the only element which was completely available to planners to influence was the PRBC stock level held at the MTC, whereas other factors, such as the percentage of bleeding casualties currently remain beyond the control of any emergency planning group. The relatively small response in terms of outcomes seen when varying the other potentially modifiable inputs such as staffing levels, time to transfuse and assessment time, indicate changes in transfusion system policy as opposed to physical resources other than blood offer the greatest potential in managing future events. The experimental aims and associated hypotheses the model was developed to answer focus specifically on such policy changes, targeting the 'system levers' and 'supply levels' within the model which represent feasible solutions for the real-world system.

6.1.4 General Methods of Experimentation

This section describes the universal methods common to the investigation of all of the experimental hypotheses considered throughout this chapter. The alterations to the baseline model and modifications made to the model configuration specific to the individual experiments performed are addressed separately within each respective hypothesis. None of the individual alterations made to the model in order to investigate the various hypotheses involved any alterations to the original timing of casualty processing within the

model and therefore, did not require repeat evaluation of the model. Despite this, full and complete testing of each alteration was performed to ensure any additional model components were performing as intended and no new errors were generated during a simulation run.

The overall study objective was such, that the effect on outcomes for each experimental design was required to be appreciated across a range of MCE magnitudes. In order to achieve this, the model was expanded to run from casualty loads starting at 20 casualties through to a maximum of 300 in increments of 20 casualties per batch of 100 simulation runs. Therefore, for every single set of experimental conditions 1,500 individual runs were performed with the results collated in an Excel spreadsheet (Microsoft Excel, Microsoft Corp. Redmond, WA, USA) via the in-built Visual Basic for Applications (VBA) commands. The arrival rate for each variation in casualty load was sampled from the same distribution as was applied to the baseline model and throughout the model evaluation process.

The baseline model with the addition of the expanded casualty loads was termed the experimental baseline model. The configurations of the definable parameters within the simulation run setup remained unchanged across all experimental designs and are described in Table 6.1. The input values for definable data fields within the model unless stated within the individual methods of each hypothesis were also maintained as per the experimental baseline model as summarised in Table 6.2. Whilst each individual aim involved a specific experimental design, they were all investigated through the same set of principal study outcome measures described previously and provided again here for reference:

1) The percentage of bleeding P1 and P2 casualties receiving their required level of transfusion within the time allocated by their triage category (within one hour for P1s and four hours for P2s).

2) The median time point at which emergency type O PRBC inventory levels were exhausted (a surrogate for the inability to treat and therefore receive further bleeding casualties).

In addition the treatment levels within 6 and 12 hours of admission for combined P1 and P2 bleeding casualties were also considered where appropriate as a further outcome measure.

Statistical analysis was performed in GraphPad Prism (GraphPad Software Inc. San Diego, CA, USA) and Microsoft Excel (Microsoft Corp. Redmond, WA, USA). Confidence intervals for each set of 100 replications within the various experiments performed were calculated as per the methods previously described in Chapter Five. The simulation software's use of common random numbers in the model allowed for comparison between scenarios, such as the difference in outcomes between the baseline model and an experimentation model through a paired t-test approach (163). Statistical significance was measured at a p-value of <0.05 unless otherwise stated. Confidence intervals (CI) for paired-t analysis were calculated using the following formula:

$$CI = \overline{X} \pm t_{n-1,\alpha/2} \frac{SD}{\sqrt{n}}$$

$\overline{X}$ = Mean difference between scenarios

SD = Standard deviation of the differences between scenarios

n = number of replications of the model performed (must be equal between scenarios)

$t_{n-1,\alpha/2}$ = derived value from the Student's t-distribution ($\alpha/2$ = level of significance)

Adapted from Simulation: The practice of Model Development and Use, Robinson. John Wiley and Sons, West Sussex, UK 2004.

Table 6.1 Configuration of simulation run settings across all experimental studies

Simulation Parameter	Setting
Terminating or Non-terminating	Terminating
Individual Run Length	72 Hours
Batched Runs or Single Runs	Batched Runs
Replications per Batch	100 Replications per Batch
Animated or Non-animated Runs	Non-animated
Real-time or End Point Analysis	End-point Analysis

Table 6.2 Experimental baseline model data input values and distributions

Model Parameter	Input Data
Casualty Arrival Rate	Johnson SB Distribution (γ 1, δ 0.55, λ 15, Υ 0.05)
Casualty Load	20 - 300 (in 20 casualty increments per batch run)
Casualty Blood Type	Probability: A = 42%, B = 10%, AB = 4%, O = 44% (of casualty load)
Proportion of P1:P2s	Probability: P1 = 60%, P2 = 40% (of casualty load)
Assessment and Access Time	Gamma Distribution P1 = (α 2.1, β 5.0), P2 = (α 1.7, β 11.0)
Proportion of P1 & P2s Bleeding	Probability: P1 = 80%, P2 = 50% (of P1 and P2 loads)
P1 & P2 PRBC Demand	Poisson Distribution: P1 = (10.7), P2 = (4.7)
Blood Sample Transport	Constant (3min)
Book & Verify Sample	Constant (1min)
Centrifuge Sample	Constant (5min)
Verify Sample & Load Analyser	Constant (1min)
Analyse Sample	Constant (11min)
Unload Sample & Verify	Constant (1min)
Full Antibody Screen on Analyser	Default Group Only, Full Screen Uses TRIA(25,35,90)
Dispense Grouped PRBC	Constant 30 Seconds per Unit of RBC
Delivery of PRBC	Constant (5min)
Transfusion Time	Johnson SB Distribution: P1 = (γ 2.1, δ 0.75, λ 29.0, Υ0.56), P2 = (γ 1.2, δ 0.62, λ 29.0, Υ 0.84)
Technicians	7 Staff
Porters	4 Staff
Centrifuge Capacity	30 Samples
Analyser Capacity	180 Samples
Type O PRBC Stock	100 U
Type A PRBC Stock	75 U
Type B PRBC Stock	25 U
Type AB PRBC Stock	10 U

6.2   Aim Four – Stock Management

6.2.1   Introduction

The sensitivity analysis illustrated the significant effect stock level has on all the study outcome measures. Holding ever increasing volumes of on-shelf PRBC inventory continuously at an MTC in preparation for an event is however, not a practical or financially viable solution. Although increasing held stock levels either locally of nationally during times of heightened risk such as during the Olympics is already part of practiced procedure, the effect on outcomes of either maintaining additional stock or restocking MTCs from local supplies is not completely understood. The aim of this set of experiments was to determine the effect variations in the management of MTC PRBC stock levels has on outcomes across increasing magnitudes of MCE.

6.2.2   Experiment 4A – Stock Hold (H_{4A})

'There exists a critical ratio of MTC held PRBC stock levels to the casualty load received, below which, the ability to treat bleeding casualties effectively, becomes overwhelmed.'

6.2.2.i Methods

The experimental baseline model was configured to examine changes in total casualty loads in relation to variations in the level of held on-shelf PRBC stock. The increase in casualty

loads were pre-set in the experimental baseline as described in the general methods section above, therefore, the only additional experiment specific alteration required was an increase in the held PRBC inventory level. For each casualty load the entire total on-shelf PRBC stock inventory was increased up to 10 times the standard volume by the addition of one complete PRBC inventory level each time (Table 6.3). The ratio between individual blood groups was therefore maintained with increasing overall stock levels.

Table 6.3 Variations in the experimental baseline model data input values for Experiment H_{4A} (shown as Units of PRBC)

Experimental Model Inputs										
Blood Group	Multiples of Baseline Stock Level									
	1	2	3	4	5	6	7	8	9	10
Type O PRBC	100	200	300	400	500	600	700	800	900	1000
Type A PRBC	75	150	225	300	375	450	525	600	675	750
Type B PRBC	25	50	75	100	125	150	175	200	225	250
Type AB PRBC	10	20	30	40	50	60	70	80	90	100
Total PRBC Stock	210	320	630	840	1050	1260	1470	1680	1890	2100

6.2.2.ii Results

Prior to the investigation of increasing levels of stock hold, the baseline experimental model state was examined to appreciate the effect of increasing casualty loads on system performance under standard operating conditions. A single batch run of the baseline experimental model for all casualty loads considered up to the maximum of 300 casualties, involved 1,500 individual simulation runs and over eight hours of computer processing time. The baseline model results in terms of the study's principal outcomes measures of bleeding

P1 and P2s treated within one and four hours respectively, as well as the median time to exhaustion of type O PRBC supplies are provided below in Figure 6.1 A-C.

A)
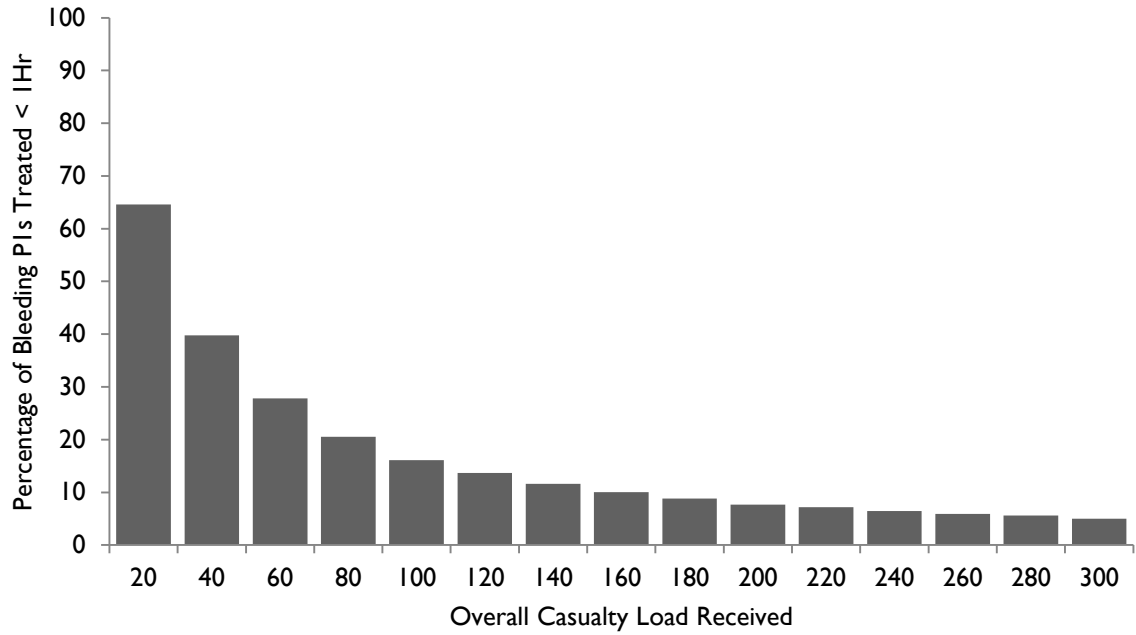
B)
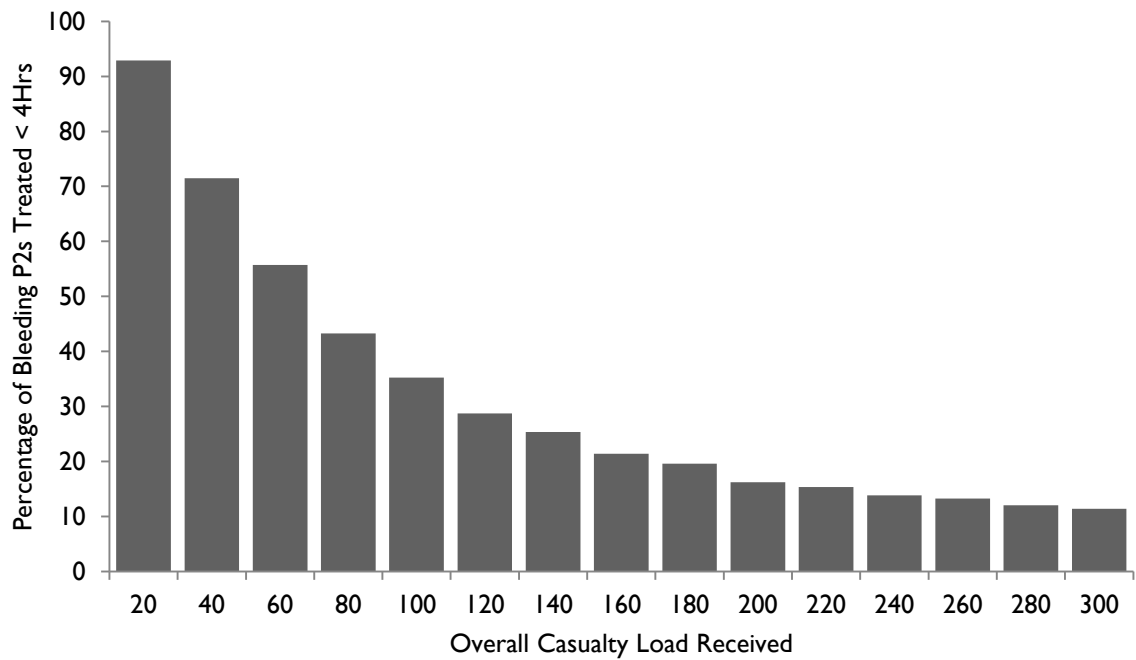
C)
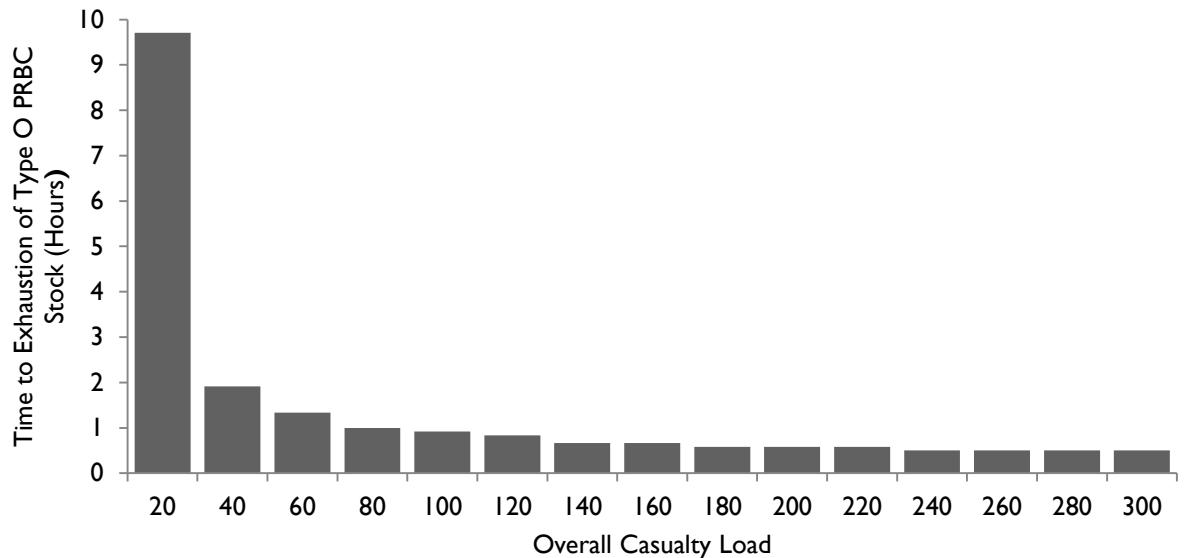
Figure 6.1 The study's primary outcome measures of: A) The percentage of bleeding P1 casualties receiving full treatment within one hour, B) The percentage of bleeding P2 casualties receiving full treatment within four hours and C) The median time to exhaustion of emergency type O PRBC supplies (A surrogate for the inability of the MTC to accept further P1 casualties), investigated using the baseline experimental model and run across all casualty loads considered.

All of the primary outcome measures displayed a non-linear inverse relationship with casualty loads of increasing magnitude, the greatest change occurring for all outcomes between the 20 and 40 casualty levels. There is an approximate 20-25% fall in the percentage of treated casualties between these casualty volumes and more specifically, the proportion of bleeding P1s treated within one hour of their arrival falls below half with this doubling of casualty load. Similarly to treatment rates, the most marked reduction in the median time to type O PRBC exhaustion also occurs between these two casualty levels, with an 80% decrease from just under ten hours of available supply to less than two.

In terms of the percentage of bleeding P1 and P2 casualties receiving their full PRBC demand within their defined timescales, the outputs ranged from 65% to 93% respectively with the smallest casualty load of 20 (approximately 13 bleeding casualties), through to just 5% and 11% respectively when the largest load of 300 (approximately 200 bleeding casualties) casualties was considered. Similarly, the median time to exhaust type O supplies ranged from almost 10 hours to just half an hour between these two total casualty levels.

The time constraints within which treatment must be provided were defined by the casualties' P1 or P2 status and could be seen as the reason for failure to treat in the model. This was addressed by considering the percentages of all bleeding casualties treated within 6 and 12 hours of their arrival (Figure 6.2 A & B). Despite these longer treatment times even a casualty load of just 20, leaves a mean eight percent of bleeding casualties still requiring a further supply of PRBC to meet their demand beyond these time thresholds. When the highest casualty loads of 300 are considered, this statistic climbs to around 93%, with no appreciable improvement occurring in the percentage treated within 12 hours, compared with that at 6 hours for any of the casualty loads considered. Furthermore, whilst type O PRBCs are observed to last much longer with the smallest casualty load considered, exhaustion of the supply still occurs within 12 hours of the simulation start.

A)

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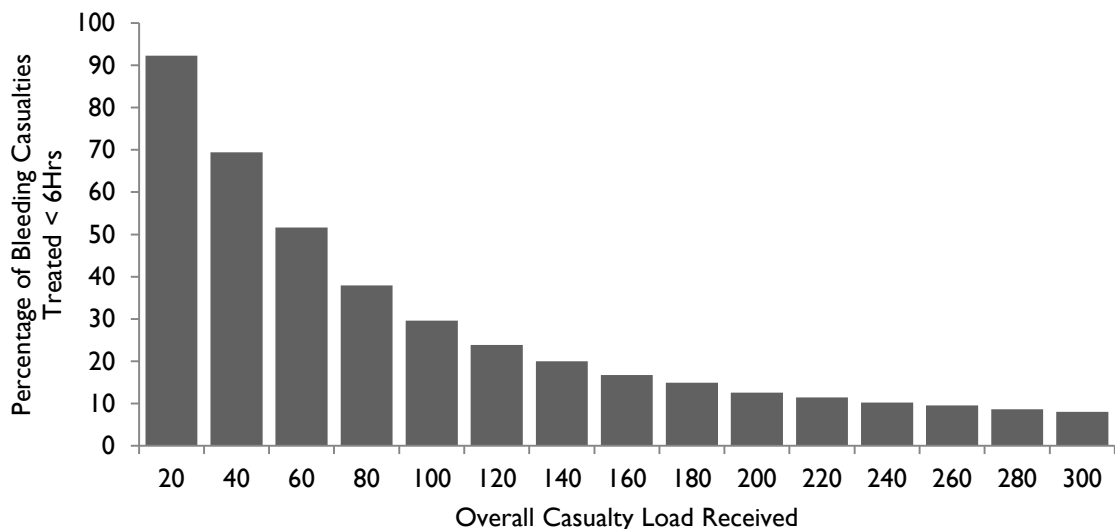
B)
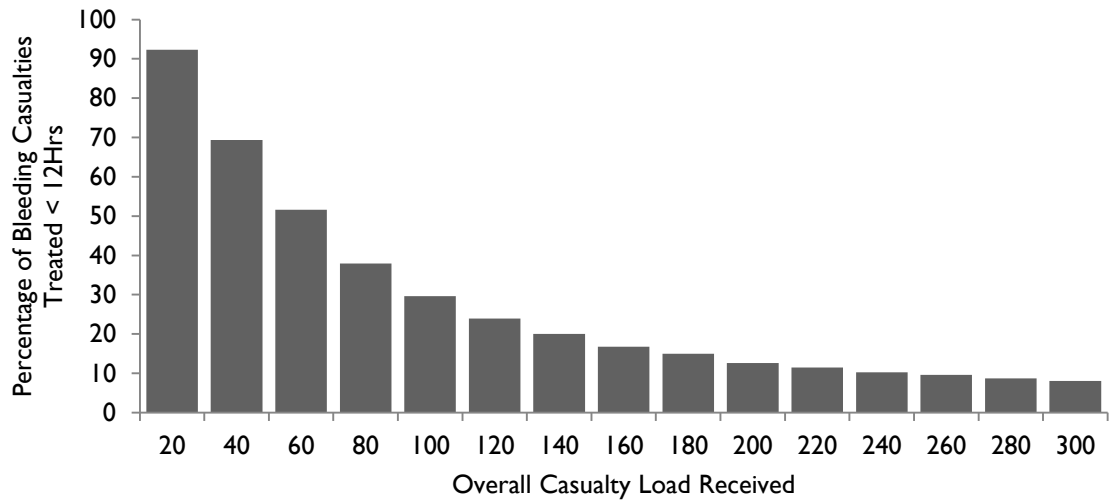
Figure 6.2 Investigated through the baseline experimental model and run across all casualty loads considered: A) The percentage of bleeding casualties receiving full treatment within six hours and B) wihtin twelve hours, of their arrival.

This analysis of the baseline system across increasing casualty loads indicates the standard configuration rapidly proves inadequate for even relatively small demand states, and has already begun to fail in terms of delivering the required level of care during MCEs of just 20 casualties. The first experimental hypothesis of aim four was that a critical ratio exists between PRBC stock levels and casualty load, below which, the adequate care of casualties rapidly deteriorates. The investigation of this relationship between stock hold, casualty load and the outcome measures, involved 15,000 simulation runs and over 80 hours of computer processing to complete, the results of this are shown in Figure 6.3 A-C and Figure 6.4 A & B.

A)

Multiples of Held PRBC Stock

Percentage of Bleeding P1s Treated in Under 1 Hour

Total Number of Casualties Received

B)

Multiples of Held PRBC Stock

Percentage of Bleeding P2s Treated in Under 4 Hours

Total Number of Casualties Received
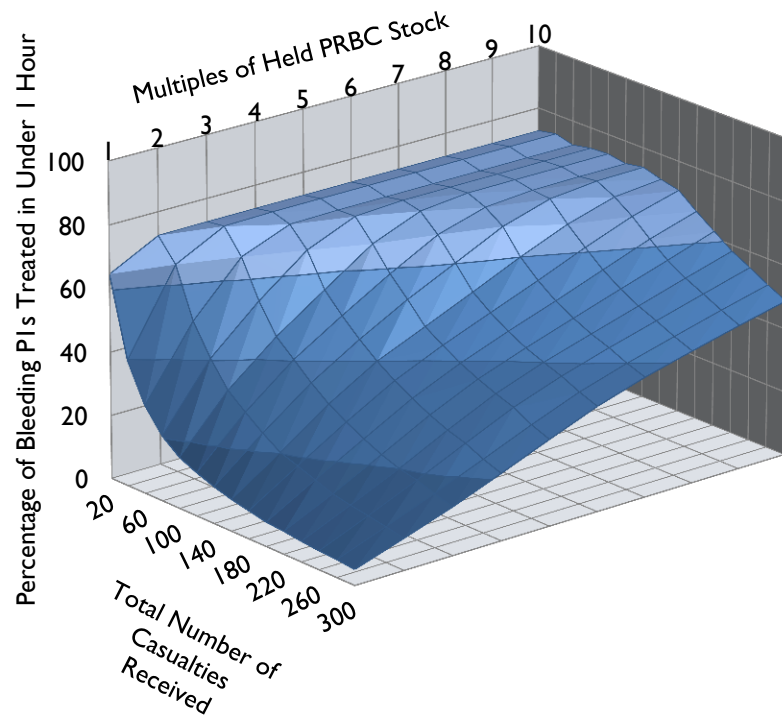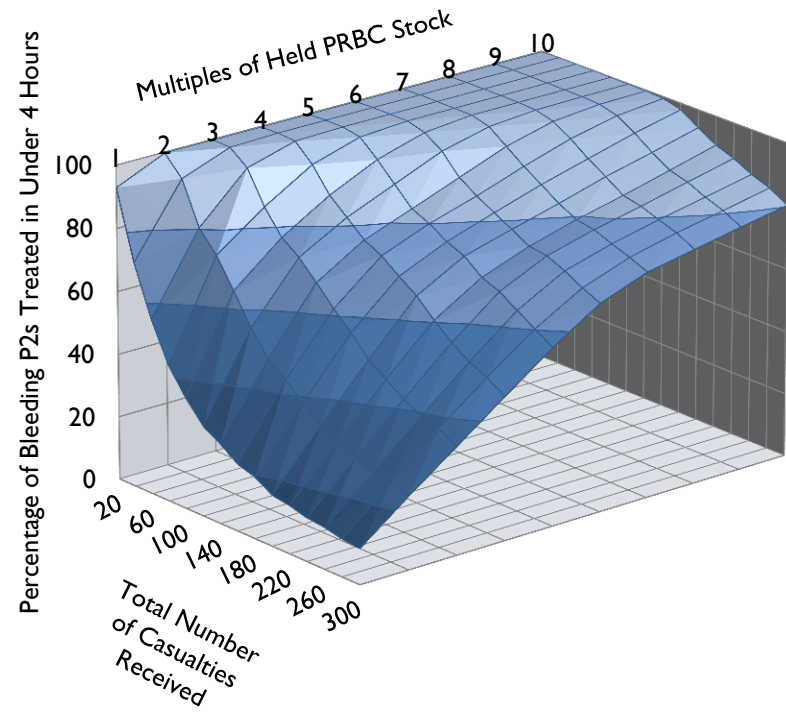
C)
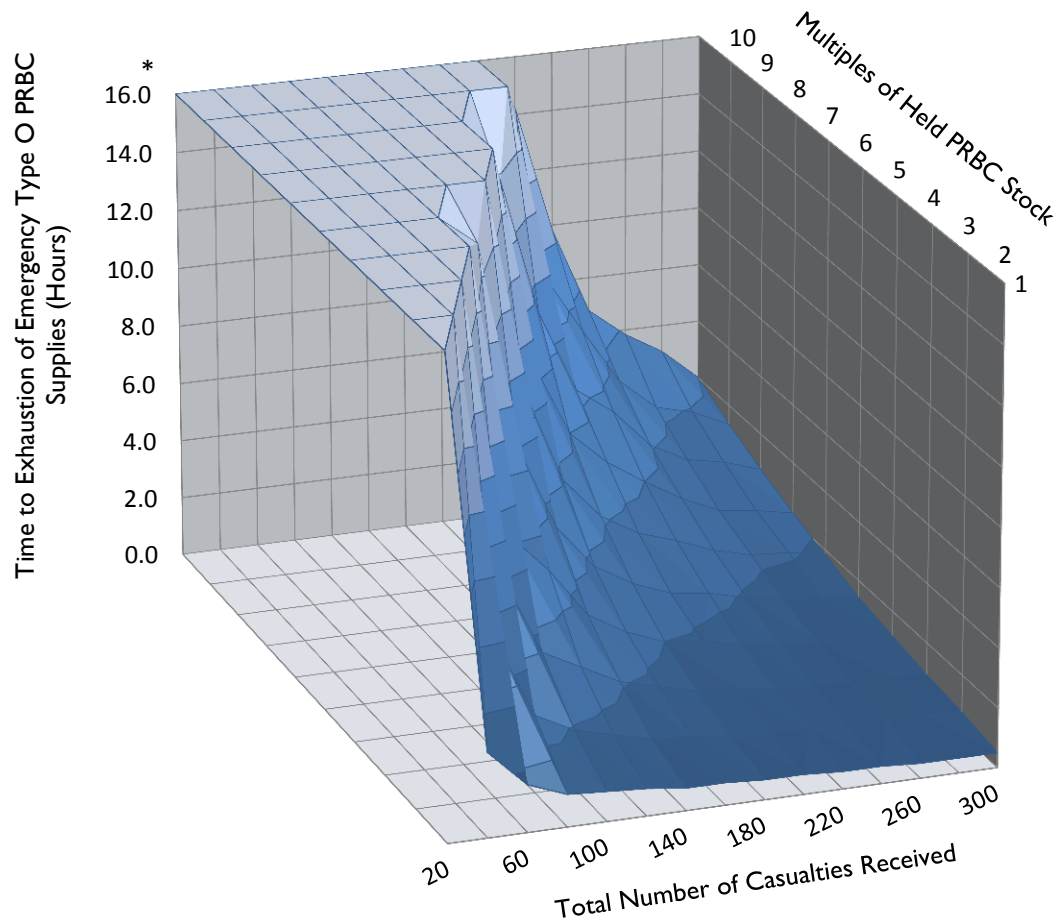
Figure 6.3 The relationship between the number of overall casualties received at the MTC, the multiples of standard all type PRBC stock held on-shelf at the centre and: A) The percentage of bleeding P1 casualties receiving full treatment within one hour, B) The percentage of bleeding P2 casualties receiving full treatment within four hours and C) The median time to exhaustion of emergency type O PRBC supplies. *Indicates stock remained available through to the end of the simulation run (72 Hours).

The effects of increasing stock on the primary outcomes can be seen instantly, with double the standard on-shelf PRBC hold enough to ensure the 100% treatment of P2s within four hours with a casualty load of 20. However, successive multiples of held stocks are required

to maintain this treatment rate with each additional 20 casualties received, up to a total of 180 casualties, where a ten-fold increase in the standard PRBC stock level is required.

In contrast, although an improvement in the treatment rate of bleeding P1s within 1 hour of arrival is seen initially in the smallest sized event with twice the standard stock level, the increased PRBC availability alone is not sufficient to fully treat all bleeding P1s regardless of the overall volume of casualties received. At a load of just 20 casualties and with double the available on-shelf stock, the treatment of bleeding P1s under one hour increases around 8% to a 73% treatment rate, however, further increases in stock hold appear to exert no further effect.

Although treatment remains incomplete amongst the P1 cohort irrespective of the PRBC inventory, an, increasingly larger stock hold does serve to maintain P1 treatment above a 50% level as the casualty load increases. As was the case with P2s, each additional 20 overall casualties received requires a further multiple of the standard baseline PRBC inventory to maintain this level of output over 50%. In order to determine whether given more than the defined hour time limit, further bleeding P1 casualties could be treated with greater stock levels, the additional outcome measure of all bleeding casualties treated within 6 and 12 hours of their arrival was also investigated (Figure 6.4 A & B).

Review of the overall percentage of all bleeding casualties treated within 6 and 12 hours of arrival confirms P1 casualties do go on to receive their full demand of PRBCs, albeit over a longer period of time with an increased stock level (Figure 6.4 A & B). The meeting of bleeding P1 PRBC demands is therefore limited by both the adequacy of blood stocks, as well as the ability to physically provide the PRBCs to bleeding P1s within the defined one hour time constraint. This limitation affecting the provision of PRBCs appears to have greatest effect within the first six hours of casualty care, as no appreciable change in treatment rates was observed within this time compared with that seen within 12 hours of arrival (Figure 6.4 A & B).
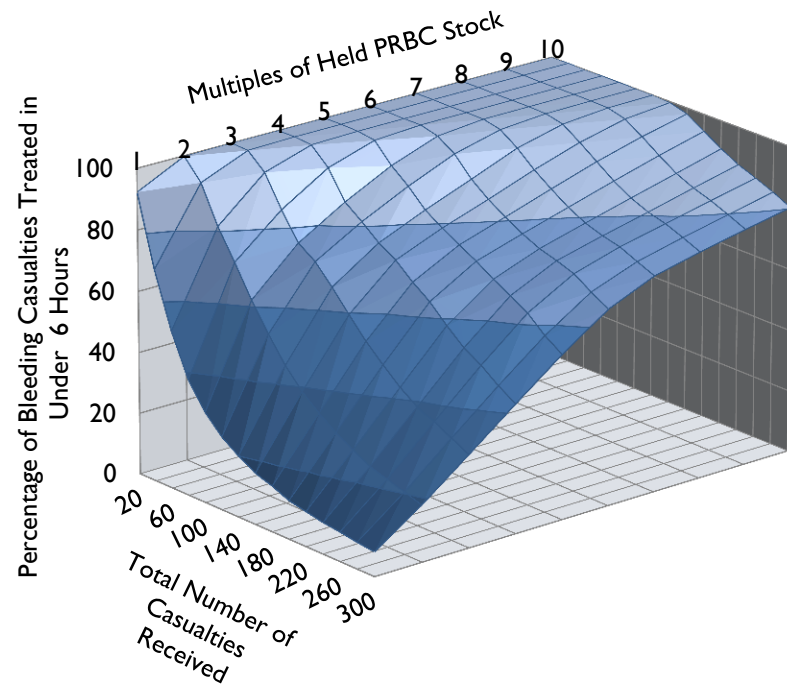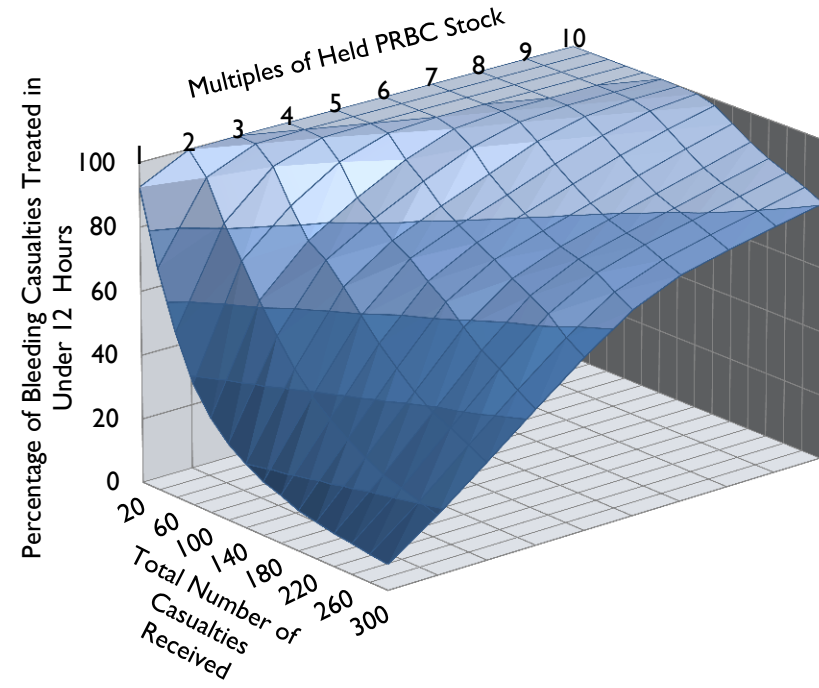
Figure 6.4 The relationship between the number of overall casualties received at the MTC, the multiples of standard all type PRBC stock held on-shelf at the centre and: A) The percentage of bleeding casualties receiving full treatment within six hours and (B) 12 hours.

The consumption of emergency type O PRBC follows a similar stepwise pattern to the P1 and P2 treatment rates, requiring greater and greater multiples of original stock to ensure adequate levels are maintained as the casualty load increases (Figure 6.3 C). Double the standard stock is required to ensure a plentiful supply of type O PRBCs in an MCE with a magnitude of 20 casualties, thereafter, another 100 units of type O are required with every further 20 casualties received to maintain this state. Further interrogation of Figure 6.3 C revealed two points of isolated early exhaustion of type O PRBC. These two premature depressions in the longevity of supplies were investigated further, however, they were found to be purely a consequence of the decimal precision applied when plotting the data graphically and therefore not of any clinical significance within the model. Without the required replenishment of PRBC supplies, a rapid exhaustion of supplies is seen to occur within hours of the first casualty arriving across all casualty loads, reiterating the dependence on emergency PRBCs early in the timeline of the event response.

In order to better understand the effects of stock and casualty numbers on study outcome measures, a number of casualty loads were selected from the simulation results and their PRBC provision examined in greater detail. Three increasingly larger event sizes were considered: A medium sized event involving 60 P1 and P2 casualties, this included an overall mean of approximately 40 casualties requiring a transfusion, a large event double the size with 120 casualties and a mean of around 80 bleeding P1 and P2s, and finally, a third event double the size again and of unprecedented proportions involving 240 P1 and P2 casualties, resulting in a mean of approximately 160 casualties requiring transfusion.

Figure 6.5 shows the specific effect increasing on-shelf stock hold has on the treatment levels of bleeding casualties across the three selected event sizes. Considering the management of P1s initially, in order to maintain a 50% treatment level of bleeding casualties within one hour, double the standard stock hold is required with a casualty load of 60, four times the standard level with 120 casualties and eight times the level for a casualty load of 240 P1 and P2s. The standard stock hold for the baseline experimental model was 210U, therefore this equates to an approximate requirement of seven units per casualty received

in order to treat half the bleeding P1s received within an hour. In order to achieve the maximum achievable treatment rate observed above of just over 70%, this figure needs to double to nearly 14U of PRBC stock per casualty received (Figure 6.5 A).

In comparison, bleeding P2s require the provision of seven units of PRBC per received casualty to ensure adequate treatment of approximately 80% of all P2s within four hours, this rises to 100% with the higher ratio of 14U per casualty received (Figure 6.5 B). A similar overall picture is observed amongst the total bleeding casualty treatment rate within 6 and 12 hours of arrival, with seven units per casualty stock hold also producing around an 80% treatment rate for both time measures (Figure 6.5 C & D). Achieving a 20% increase in the treatment rate of all bleeding casualties up to a desirable 100% within these time constraints also requires doubling the ratio of PRBCs to casualties received from 7U to nearly 14U.

A)
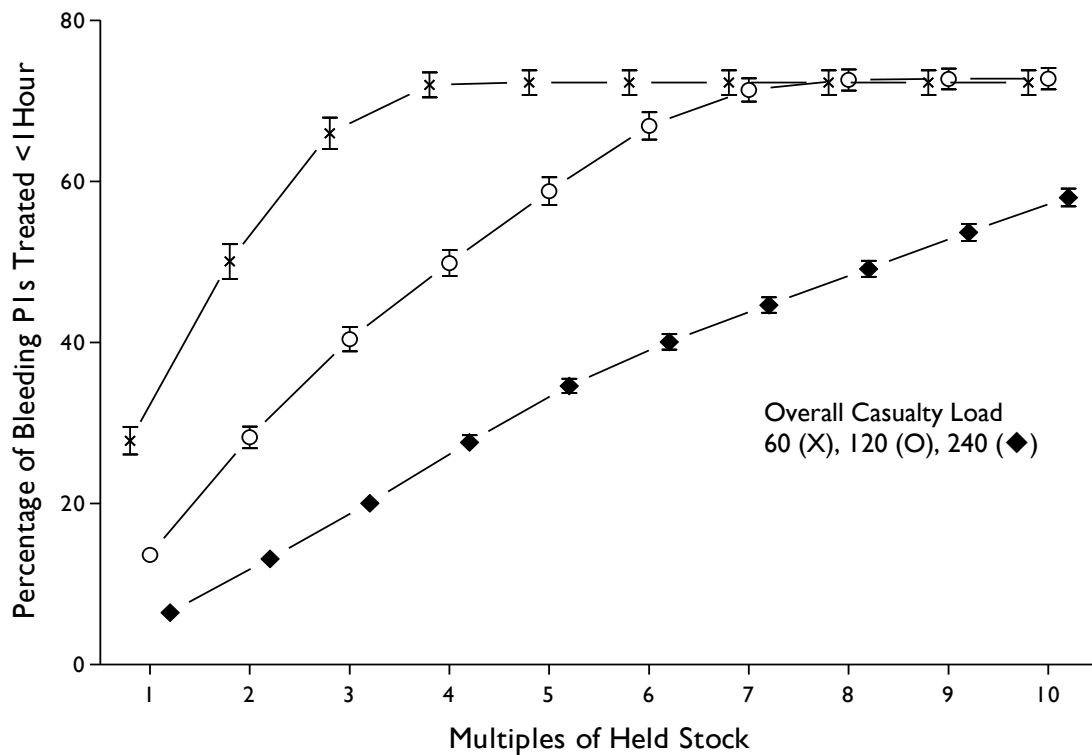
B)
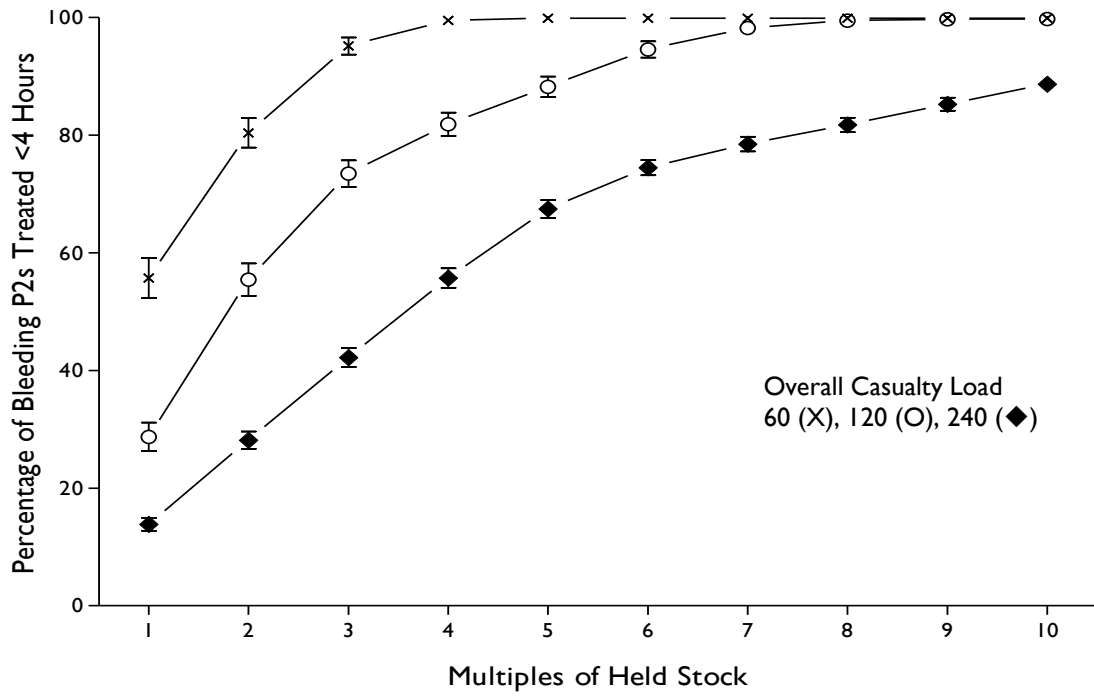
C)
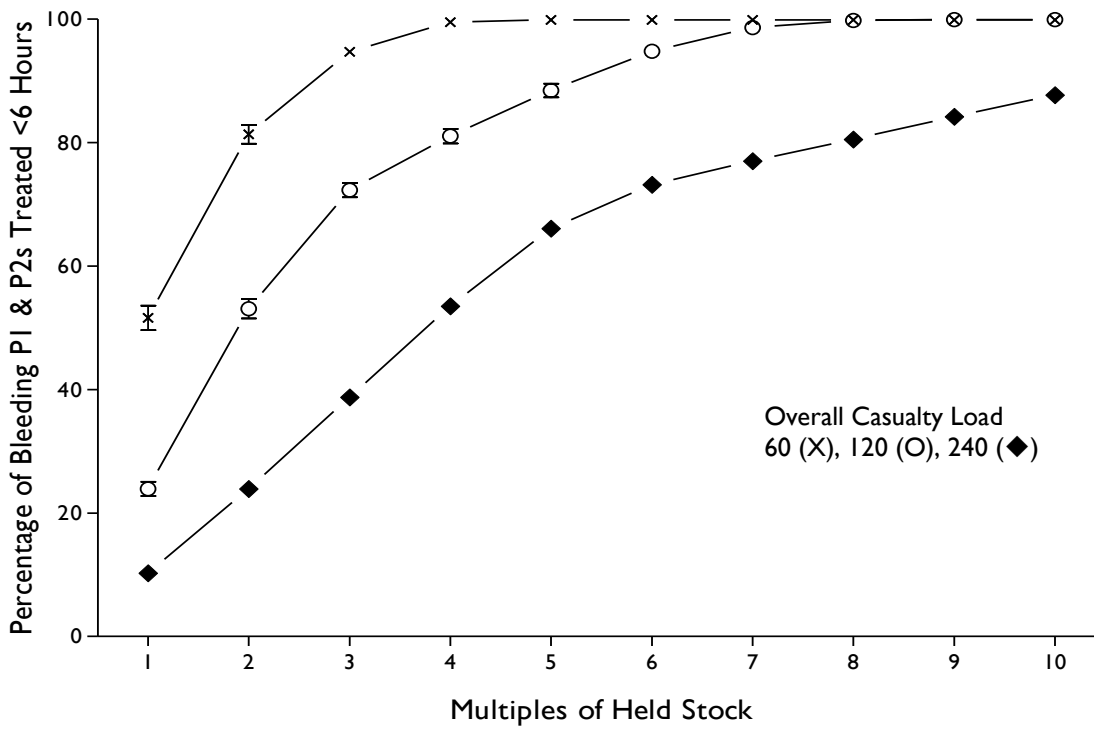
D)
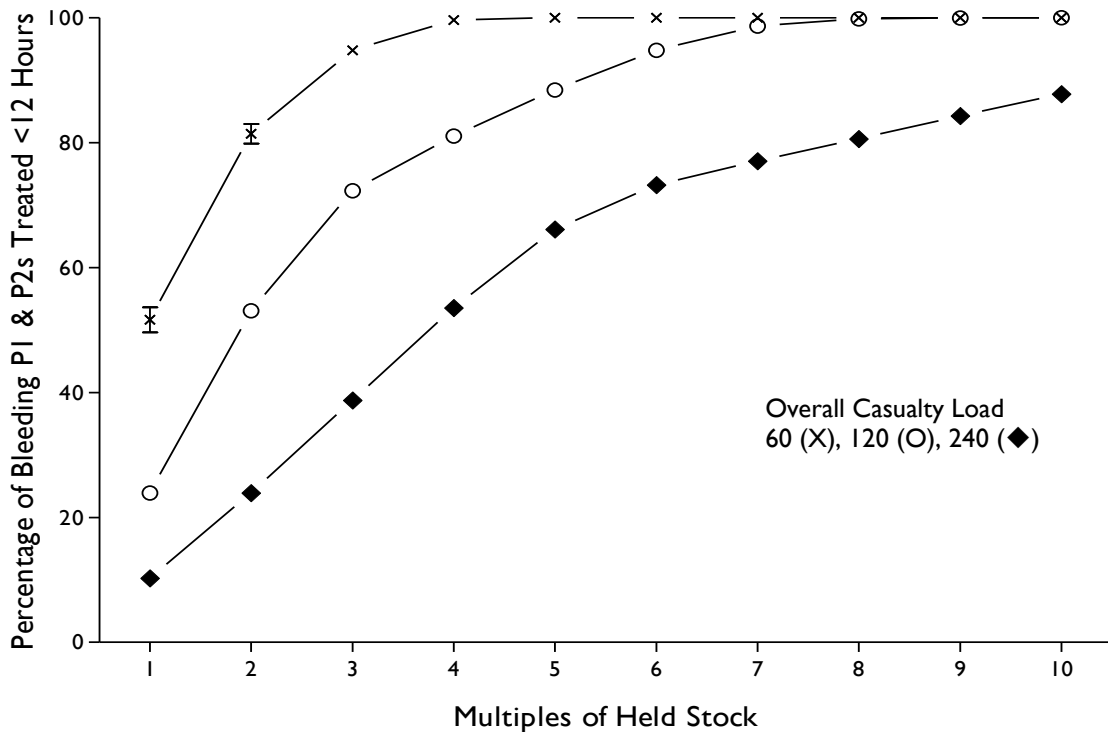
Figure 6.5 Examined over three increasing casualty loads of 60 (X), 120 (O) and 240 (◆), the effect of increasing multiples of overall PRBC stock held at an MTC on the percentage of: A) Bleeding P1s treated under 1 hour, B) Bleeding P2s treated under 4 hours, C) Bleeding P1 &2s treated under 6 hours and D) Bleeding P1 & 2s treated under 12 hours. Whiskers indicate the 95% confidence interval.

The results of the other outcome measure of time to exhaustion of emergency type O PRBC stock from receipt of the first casualty at the MTC are provided in Figure 6.6, and for further reference, Table 6.4. As expected there is early consumption of type O PRBC observed during the simulation, with supplies exhausted within a median of one hour for all events with 80 or more casualties under standard single stock hold conditions. The model indicates once stock is sufficient to last approximately 12 hours, supplies will be adequate to for the demands during the remainder of the simulation's three day duration. In the context

of achieving the 80% bleeding casualty treatment rate under six hours observed above, the seven units per casualty requirement results in a median of three and a half hours of emergency type O availability from the first casualty arrival. After this point no further new casualties would be able to be accepted as treatment would be unavailable until their blood group was known which may be too long to ensure survival.
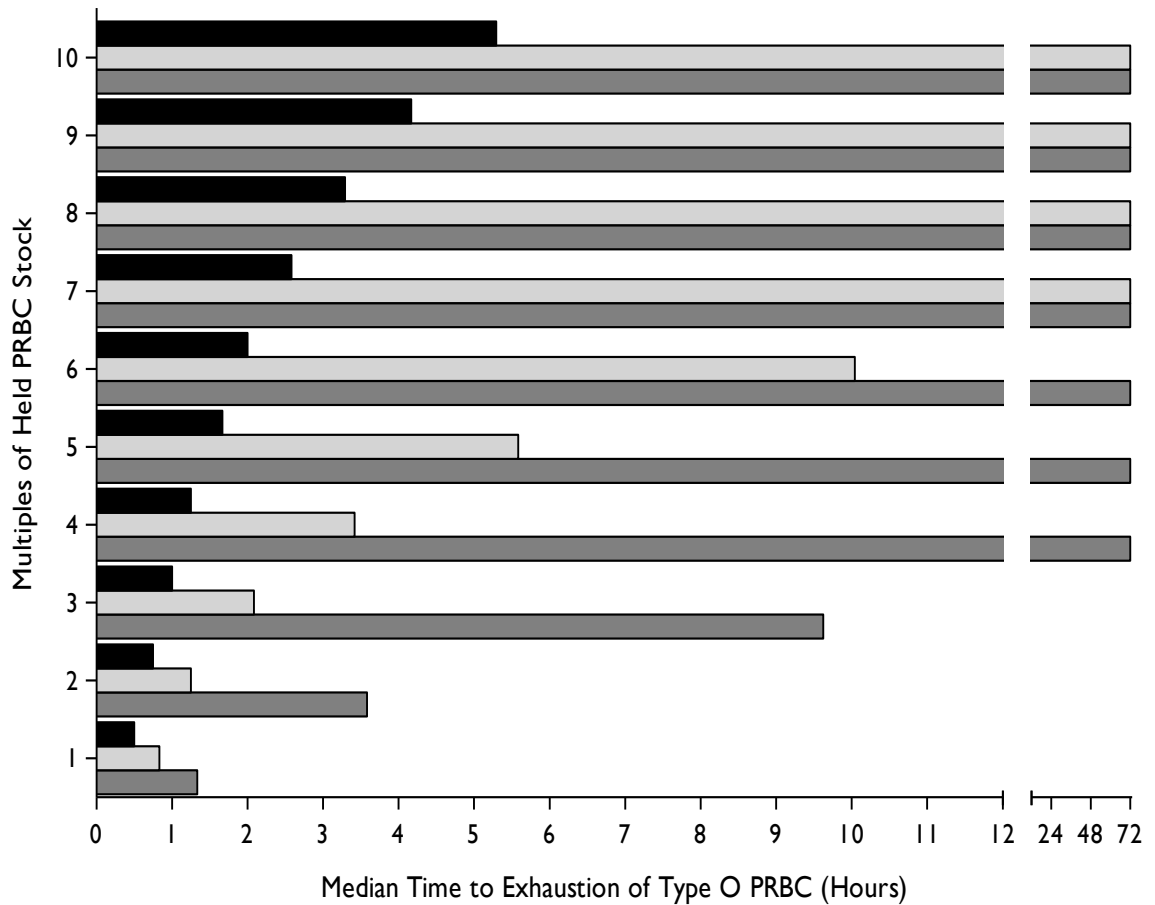
Figure 6.6 Examined with casualty loads of 60 (■), 120 (■) and 240 (■), the median effect of increasing MTC PRBC stock hold on the hours to exhaustion of type O PRBC supplies.

Table 6.4 Time (hours) from the first casualty's arrival to exhaustion of type O PRBC inventory for each casualty load and multiple of held PRBC stock. Shown as medians (IQR)

Multiples of Held Stock	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
2	* (*-*)	8.6 (5.7-*)	3.6 (2.6-4.5)	2.1 (1.7-2.5)	1.5 (1.3-1.9)	1.3 (1.1-1.6)	1.1 (1-1.3)	1 (0.9-1.1)	0.9 (0.8-1)	0.8 (0.8-0.9)	0.8 (0.8-0.9)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.7-0.8)	0.7 (0.7-0.8)
3	* (*-*)	* (*-*)	9.6 (6.8-*)	4.2 (3.3-5.4)	2.5 (2.2-3.2)	2.1 (1.8-2.5)	1.7 (1.4-2)	1.5 (1.3-1.7)	1.3 (1.1-1.3)	1.2 (1-1.3)	1.1 (1-1.2)	1 (0.9-1.1)	1 (0.9-1)	0.9 (0.8-1)	0.8 (0.8-0.9)
4	* (*-*)	* (*-*)	* (*-*)	9.3 (7-*)	4.5 (3.6-5.7)	3.4 (2.8-4.2)	2.4 (2.2-3.1)	2.1 (1.8-2.3)	1.7 (1.6-1.9)	1.5 (1.3-1.8)	1.4 (1.3-1.5)	1.3 (1.2-1.3)	1.2 (1.1-1.3)	1.1 (1-1.3)	1 (1-1.2)
5	* (*-*)	* (*-*)	* (*-*)	* (*-*)	7.7 (6-11.7)	5.6 (4.5-7)	3.7 (3.1-4.6)	2.9 (2.5-3.3)	2.3 (2.1-2.8)	2 (1.8-2.3)	1.8 (1.6-1.9)	1.7 (1.4-1.8)	1.5 (1.4-1.6)	1.3 (1.3-1.6)	1.3 (1.2-1.3)
6	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (11.5-*)	10 (8-12.9)	6 (4.6-7.6)	4.2 (3.5-4.8)	3.2 (2.8-3.8)	2.6 (2.3-3.1)	2.3 (2.1-2.5)	2 (1.8-2.3)	1.9 (1.7-2)	1.7 (1.5-1.9)	1.5 (1.4-1.7)
7	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (13.3-*)	9.5 (7.2-12.8)	6.1 (5.1-7.1)	4.2 (3.7-5.4)	3.5 (3-4.2)	2.9 (2.7-3.4)	2.6 (2.3-3)	2.3 (2.1-2.6)	2 (1.8-2.3)	1.8 (1.7-2.1)
8	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (11-*)	9.4 (7.4-11.8)	6.3 (5-8)	4.8 (4-5.7)	3.8 (3.3-4.4)	3.3 (2.8-3.8)	2.8 (2.6-3.3)	2.5 (2.3-2.9)	2.2 (2-2.5)
9	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (11.5-*)	8.8 (6.8-12.1)	6.5 (5.2-7.6)	5 (4.3-6.2)	4.2 (3.6-4.8)	3.7 (3.2-4)	3.1 (2.8-3.6)	2.7 (2.4-3)
10	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	* (*-*)	13.5 (10.5-*)	9 (7-11.3)	6.6 (5.5-8)	5.3 (4.6-6)	4.5 (3.9-5.2)	3.8 (3.3-4.4)	3.1 (2.8-3.7)

* Denotes the inventory endured to the full 72 hours and the end of the simulation run.

Having shown the effects of increasing multiples of held PRBC stock and casualty load in terms of the outcomes measures, both overall and in more detail through three specific scenarios, H_{4A} can now be proved across all the event sizes considered by showing the relationship between stock hold per casualty received and bleeding casualty outcomes. Figure 6.7 shows the relationship between the various study outcome measures and the number of units of PRBC held per casualty received. From this, planners may calculate the estimated likely outcomes from an event based on the expected casualty load and the known number of units held at an MTC.

A)
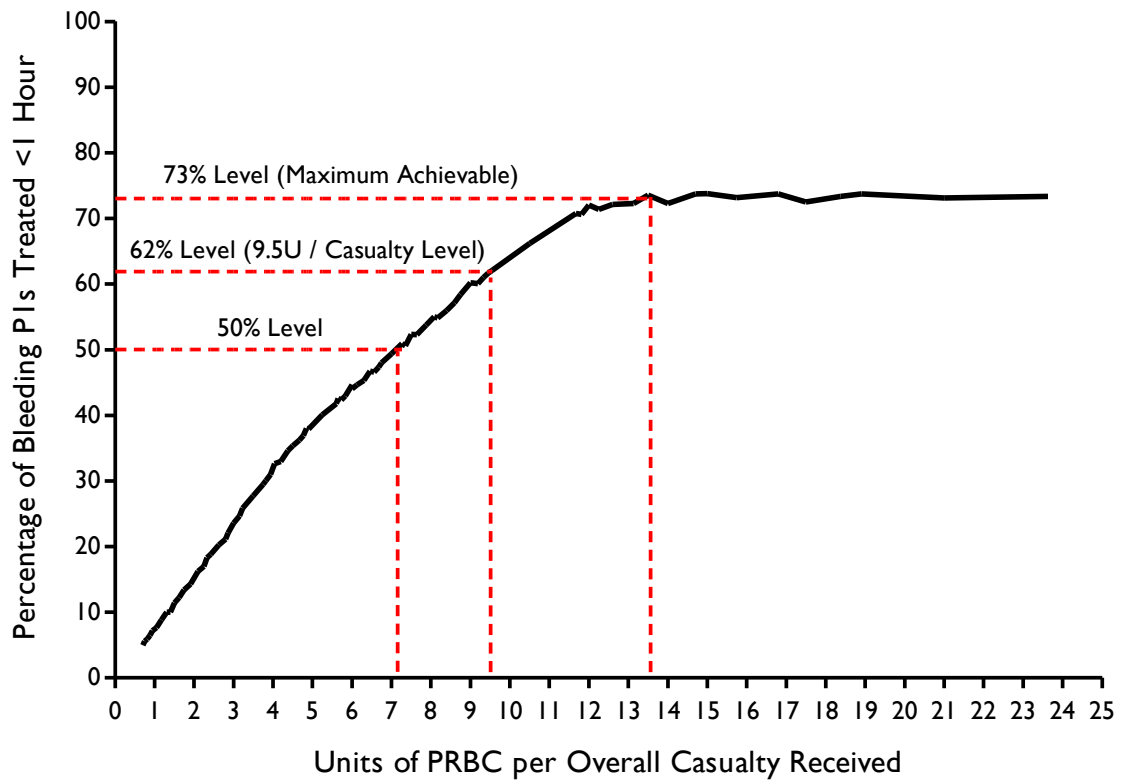
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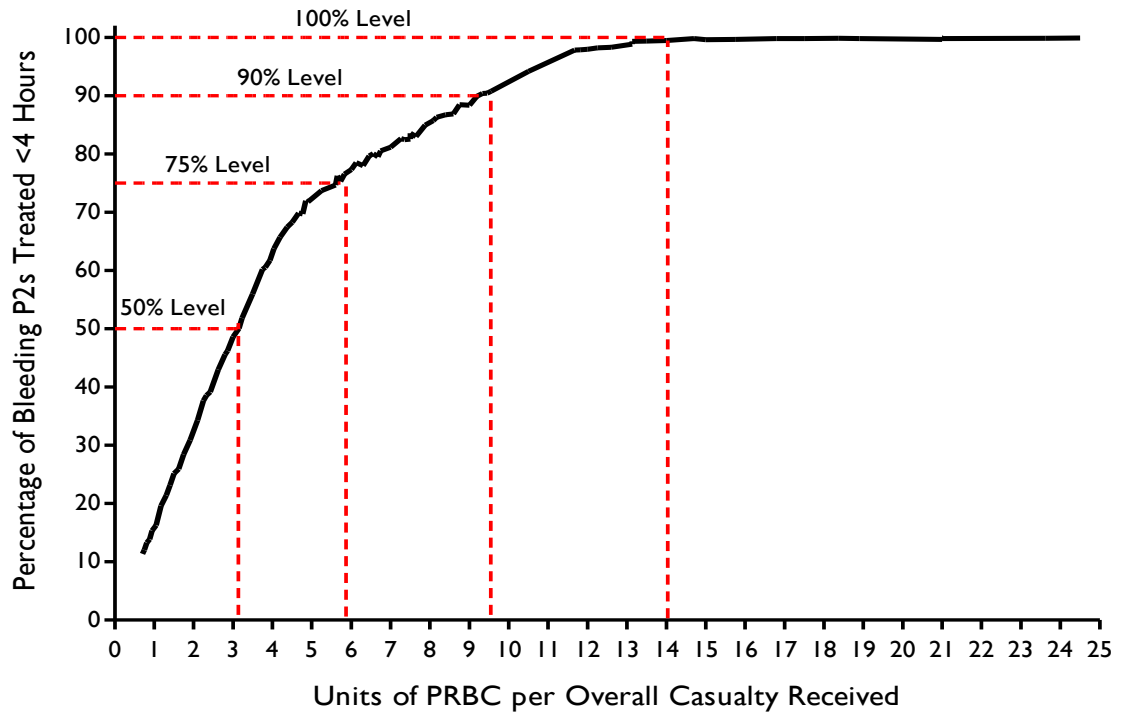
C)*
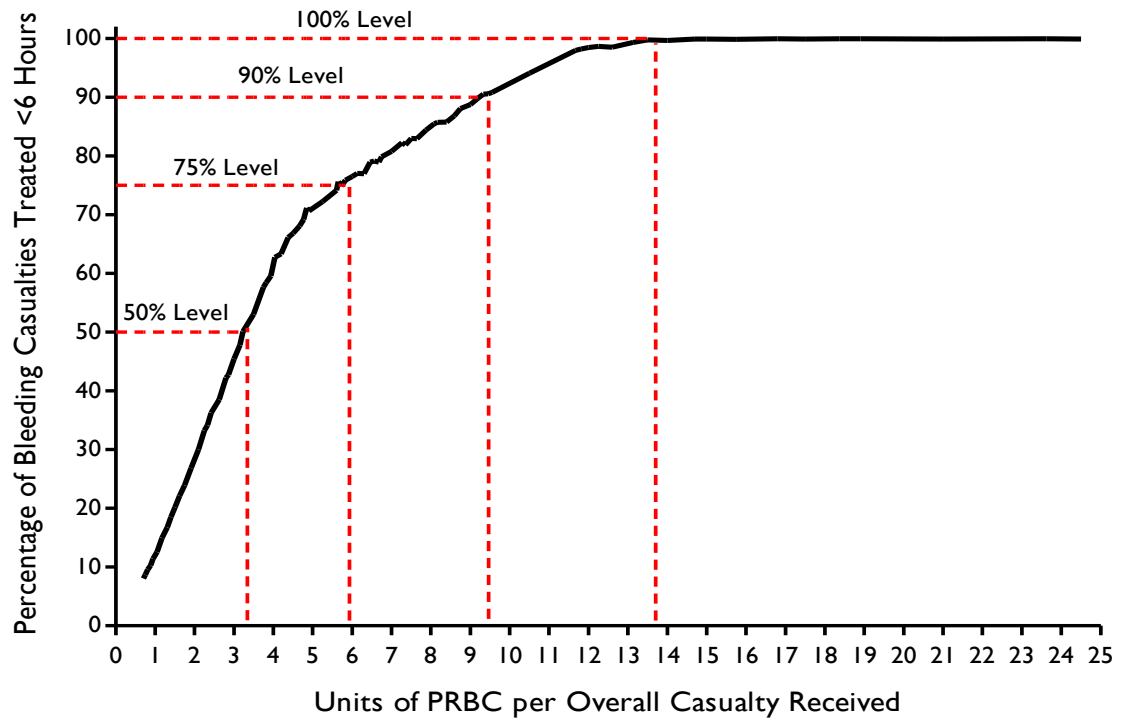
D)
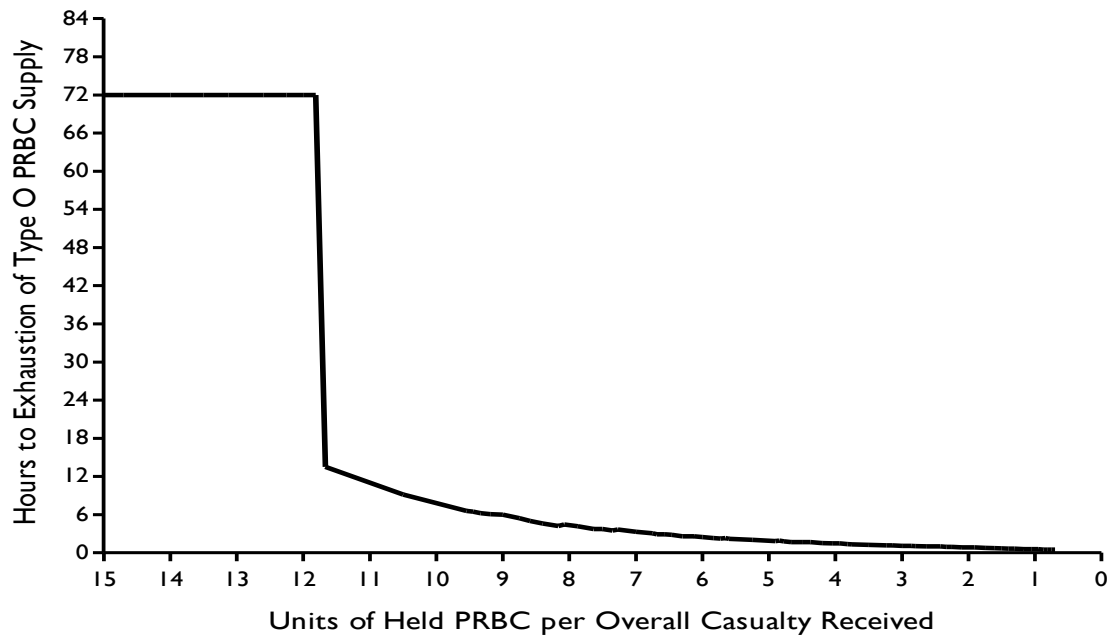
Figure 6.7 The relationship between units of PRBC held per casualty received and: A) The percentage of bleeding P1s treated within 1 hour, B) P2s within 4 hours, C) All bleeding casualties within 6 hours and D) The median time to exhaustion of type O PRBC supplies. *No significant change occurred between a 6 hour and 12 hour measurement, therefore only the 6 hour timeframe is shown.

The maximum treatment level of bleeding P1s within one hour attainable in the baseline model setup was found to be around 70%. As identified above, around 14U of PRBC per casualty received are required to maintain maximum levels of care across all measures. Taking a more universal approach and accepting a minimum treatment percentage for an event of 90% for all bleeding casualties within six hours of their arrival, the PRBC volume requirement taken from Figure 6.7 (C) falls to around 9.5U per casualty received. However, although this 9.5U level would also treat 90% of P2s within four hours (Figure 6.7 B), it would mean a fall in P1s treated within one hour of around 10% to approximately 62% (Figure 6.7 A). A critical level of units held per casualty received appears to exist within the

P2 casualty cohort at around six units per held casualty. At this level a 75% treatment rate is achievable within four hours; if this ratio is reduced further the ability to treat P2s in a timely manner rapidly deteriorates (Figure 6.7 B). In contrast the critical level for the treatment of P1 casualties is much higher with the ability to treat falling away almost immediately once the maximum treatment rate of 73% is unattainable (Figure 6.7 A). This change in the ability to treat P1s also coincides with the rapid reduction in time for Type O PRBC supplies to become exhausted (Figure 6.7 D).

Figure 6.7 D illustrates the time to exhaust type O PRBC in terms of units held per casualty received. From this, it can be recognised that, around 12U of PRBC per casualty are required to prevent exhaustion of type O supplies before the 72 hour limit of the simulation. This would also allow for close to a maximum treatment rate amongst all priority cohorts (Figure 6.7 A-C). Conversely, below this critical level type O PRBC supplies rapidly deteriorate. At a 9.5U stock hold per casualty received, type O levels only suffice for just over six hours and as a consequence beyond this time no further casualties could safely have been accepted at the MTC due to an inability to adequately treat them. The overall critical ratio of PRBC units per received casualty therefore appears to be around 12U, which ensures almost maximal attainable treatment levels as well as the endurance of type O PRBC levels for the duration of the event.

The prediction of outcomes in relation to stock hold can also be examined in the reverse manner, using the state of the system's stock hold at the time of an event to predict capacity. Figure 6.8 describes the maximum number of bleeding casualties treatable in each priority cohort and combined, based on the on-shelf stock level at the start of an event. Under baseline model conditions, whereby the total casualty load sees a 60:40 P1:P2 split with an 80% and 50% bleeding rate respectively, a 500U stock level will treat around 20 bleeding P1s and 16 bleeding P2s in under one and four hours respectively. Overall, approximately 50 bleeding casualties are treatable under six hours at this PRBC stock hold (over twice standard levels). A linear relationship between stock hold and number of treatable casualties is observed up until around 1260U of held PRBC (six times the standard level). After which, increases in stock hold begin to have a diminished effect on outcomes.

A)

B)

248
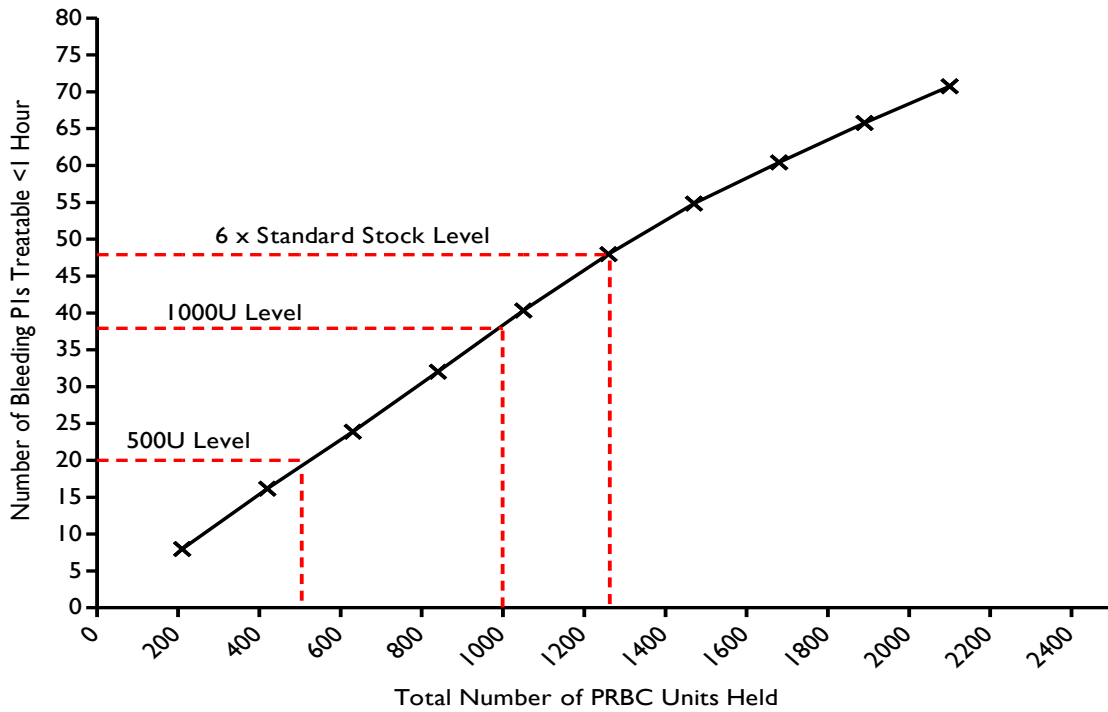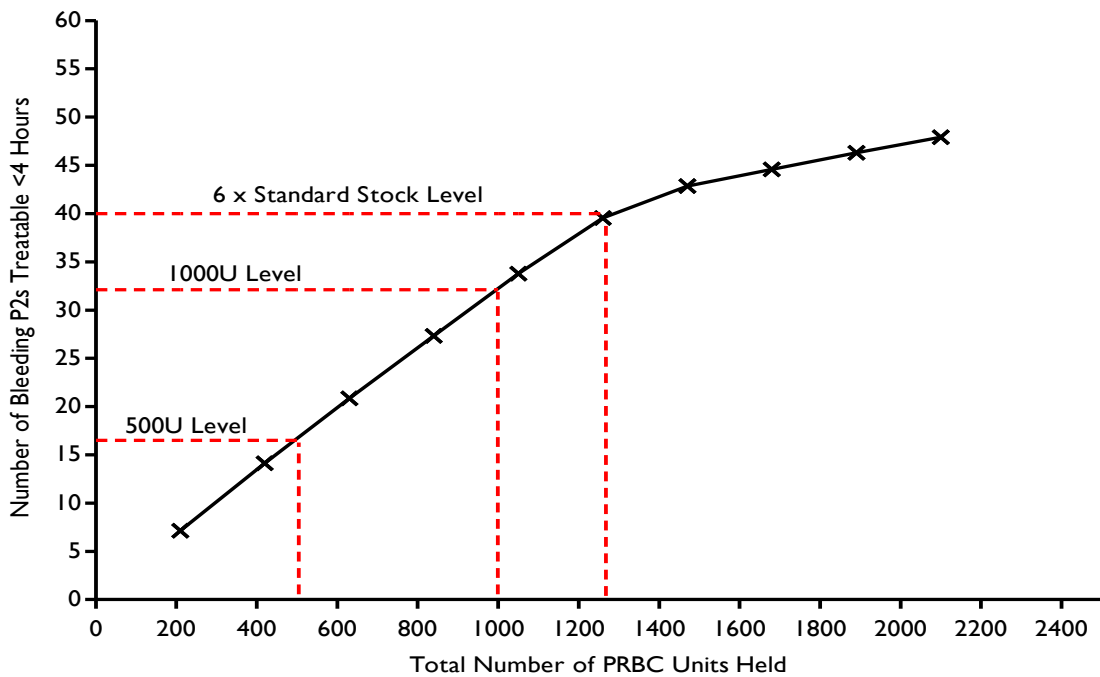
C)
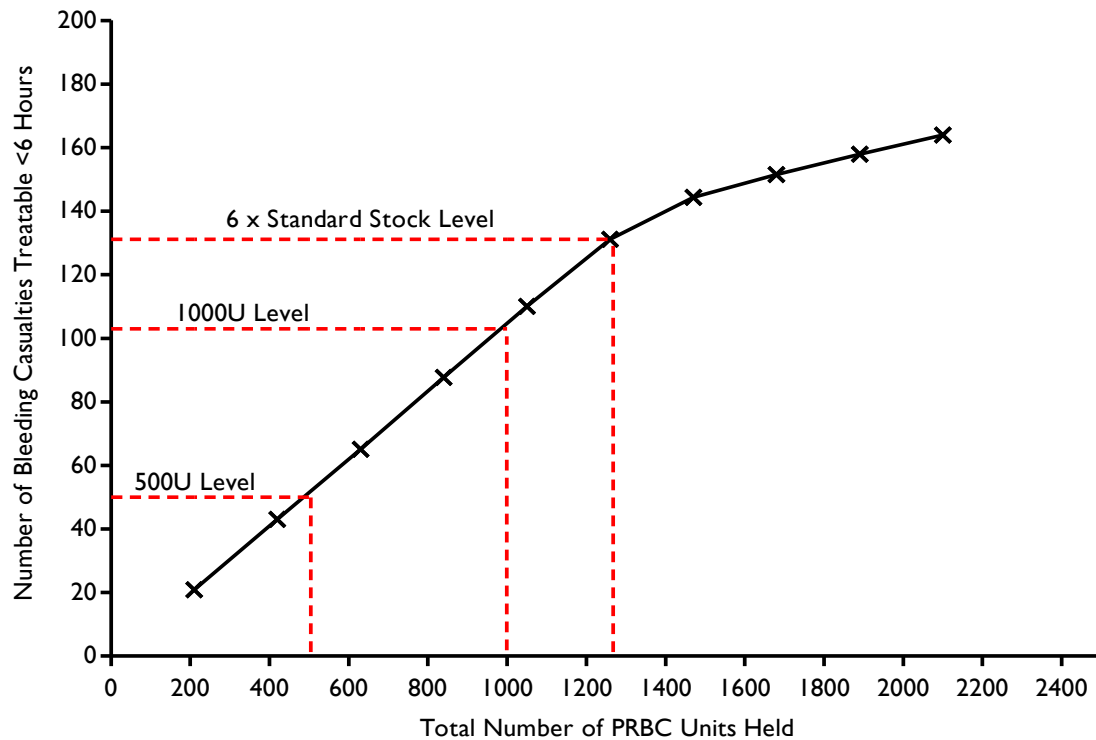
Figure 6.8 Based on the number of PRBC Units held at an MTC, the number of bleeding P1s (A), bleeding P2s (B) and overall bleeding casualties (C) treatable in under 1,4 and 6 hours respectively.

6.2.2.iii Discussion

These initial set of experiments sought to develop a clearer understanding of the system using the developed model and subsequently, characterise the relationship between the level of on-shelf PRBC stock held at an MTC and the likely treatment outcomes amongst bleeding casualties in an MCE. The experimental hypothesis was that there existed a critical ratio of MTC held PRBC stock level to the casualty load received, below which, the ability to treat bleeding casualties effectively, becomes overwhelmed.

The standard stock levels of a generic MTC were found to be inadequate in terms of achieving the maximum treatment rates possible within the model in even the smallest event sizes examined. These events and also those of much greater magnitude were simulated at various levels of increasing stock hold. The findings supported the experimental hypothesis of a critical ratio of PRBC availability to casualty load, which if not maintained, led to a rapid reduction in the ability to treat bleeding casualties in each priority cohort. Furthermore, the rate of consumption of emergency type O PRBC was found to show a similar response with increasing casualty loads and stock levels, rapidly becoming exhausted once the ability to treat P1s became overwhelmed.

The standard stock hold of 210U was found on average to be inadequate for coping at P1 and P2 casualty loads as low as 20. This appears an accurate depiction of real-world outcomes given the PRBC consumption during the validation study of the London bombings of Chapter Five was around 160U with seven bleeding P1 casualties received. Achieving acceptable levels of care following such events and indeed ones of greater magnitude, clearly requires a significant increase in stock availability. However, whilst stock hold was shown to be crucial in improving treatment rates in bleeding casualties, the volume held was not the only limiting factor in achieving a maximum level amongst the study's primary outcome measures within the model.

Despite plentiful stock, a number of bleeding P1s remained untreated within the desired one hour. Either, the ability to provide the required demand to these casualties may not be possible given the much higher individual PRBC demands present in this cohort compared with P2s, or additional factors within the model may be limiting the rate of PRBC provision. The sensitivity analysis performed in Chapter Five showed there to be a minimal effect on outcomes when the processes inherent to provision of PRBCs within the system were varied. This suggests individual PRBC demand levels to be the more likely cause of a failure to treat certain P1s in instances of adequate blood stock.

As per the experimental hypothesis H_{4A}, critical levels were identified for the treatment of both bleeding P1 and P2s, beyond which, the ability to adequately treat casualties rapidly deteriorated. The pattern of exhaustion of type O stock in terms of overall PRBC units per casualty held saw comparisons with the critical threshold for the ability to treat P1s. This level of 12U of PRBC stock per casualty received represented the point below which, there would eventually be exhaustion of type O supplies and whilst preserving adequate treatment levels of P2s, the treatment of the most severely injured P1 casualties would begin to deteriorate more rapidly. As such, this ratio may offer the best indication to planners as the point at which the system would likely fail and become overwhelmed given a casualty load and known PRBC inventory level.

Ensuring a maximum achievable treatment rate for a casualty load of around 20 would therefore require a PRBC stock hold of almost 300U based on the model results. Whilst this is a conceivable target for MTCs, events of a larger size would create stock hold demands which even at these centres, are not practical either financially or logistically in the current system. Although temporary stock builds offer a solution and are already current policy for periods of heightened risk, such as during the run-up to the Olympics, they do not offer a solution for managing the more common surprise events.

The challenge is therefore finding a manageable stock hold which provides an acceptable level of care without generating an excessive or unrealistic burden in terms of stock maintenance at an MTC. This would likely rely either on a system whereby adequate stock is available for an event of a limited size and then supplemented by early restocking, or, by making clearly defined modifications to system policy, designed to maximise the resources available for the best possible outcomes under the circumstantial constraints. Both of these possibilities are investigated and discussed during the experimentation which follows.

6.2.3 Experiment 4B – Restocking Supplies (H₄ᵦ)

'Outcomes following an MCE are greatest when a restock of an MTC's held PRBC volume occurs at the earliest opportunity in the timeline of an event.'

6.2.3.i Methods

The experimental baseline model was configured to investigate the effects of restocking the total on-shelf PRBC inventory at increasing time points from the initiation of the model. An inventory restock was set to occur at the defined time point during each simulation run, providing 100% of the total initial PRBC on-shelf inventory when activated. The restock procedure was programmed to occur only once per simulation run and at time increments of one hour up to a maximum of 12 hours from the start of the simulation.
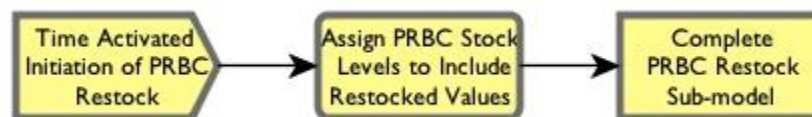
Experimental Model Inputs	
Blood Group	**Held Stock + Restock Volume Delivered at Defined Time Point**
Type O PRBC Stock	100U +100U
Type A PRBC Stock	75U + 75U
Type B PRBC Stock	25U + 25U
Type AB PRBC Stock	10U + 10U

Figure 6.9 The Inventory Restock sub-model components and changes to the model's stock values following sub-model activation at increasing hourly time points up to 12 hours from the simulation start.

In order to provide the PRBC inventory restock during a simulation run, an additional sub-model was required to be added to the experimental baseline model. This is shown in Figure 6.9 along with the tabulated effects on PRBC stock input values. The additional sub-model was designed separately from the main model and had no interaction with the main model map components. As such it exerted no additional effect on any other aspect of the model aside from increasing the level of each PRBC group held at the designated time of activation.

6.2.3.ii Results

Investigation of H_{4B} required 19,500 simulation runs and over 100 hours of computer processing time. H_{4A} illustrated the relationship between units of PRBC held on-shelf at an MTC and the ability to effectively treat casualty loads of increasing magnitude. H_{4B} stated that outcomes following an MCE are greatest when a restock of the MTC held PRBC volume occurs at the earliest opportunity following an event. The maximum stock level achieved in investigation of H_{4B} was therefore just twice the standard baseline level held. In view of this, the results focus on casualty loads up to and including 100 P1 and P2s, beyond which, the imbalance between stock and casualty demand as observed in H_{4A}, becomes limited in its interpretation with only a single inventory restock. The results for the five casualty loads considered are shown in Figure 6.10.

Amongst bleeding P1 casualties treated within an hour, paired t-test analysis showed no statistically significant difference in outcomes, between stock hold versus restocking within one hour of the simulation start, up to a casualty load of 80. However, at a two hour restock time the model displayed a statistically significant reduction in treatment rate once casualty loads reached 60 or greater. Whilst all casualty loads showed a downward trend in treatment of bleeding P1s with increasingly later restocking, the rate of bleeding P2s treated within four hours initially saw an increase above that achieved with an equivalent increased

stock hold between casualty loads of 40 and 80. This increase in treatment rate was maximal with a casualty load of 60, showing a statistically significant seven percent increase in the number of bleeding P2s treated when a complete restock was performed at four hours.

Beyond four hours there is gradual decline in bleeding P2 treatment rate in these casualty loads with increasingly delayed PRBC restocking time. This decline continues below the level of the comparison double stock hold scenario in all casualty loads above 20. The difference between the maximum and minimum treatment rates observed was just over 20% for bleeding P1s treated in the 60 casualty cohort and just over 30% for bleeding P2s treated in the 100 casualty cohort. This equates to an effective swing in treatment of seven bleeding P1s and six bleeding P2s respectively depending on when a restock occurs following an event.

Given the contrasting response in treatment rates observed between P1 and P2s following early restocking of PRBC supplies, the six hour treatment response time amongst all bleeding casualties was interrogated to determine the more general effects of restocking on model outcomes. Despite the negative trend of P1 treatment levels as restock time increases, the overall treatment rate of all bleeding casualties within six hours showed a statistically significant improvement when a restock occurred between two and six hours for casualty loads between 40 and 80 (Figure 6.10 C). The peak benefit at these casualty loads occurred with a restock at five hours. Restocking after six hours appears to represent a threshold in the model, after which, there is a decline from the optimum casualty treatment rates achievable for all casualty loads considered greater than 20 (Figure 6.10 C).

A)

Casualty Loads: 20 (□), 40 (■), 60 (X), 80 (●) and 100 (○), Equivalent Outcomes with Double Stock On-Shelf from Simulation Start Shown in Red.

B)

255

C)

Casualty Loads: 20 (□), 40 (■), 60 (X), 80 (●) and 100 (O), Equivalent Outcomes with Double Stock On-Shelf from Simulation Start Shown in Red.
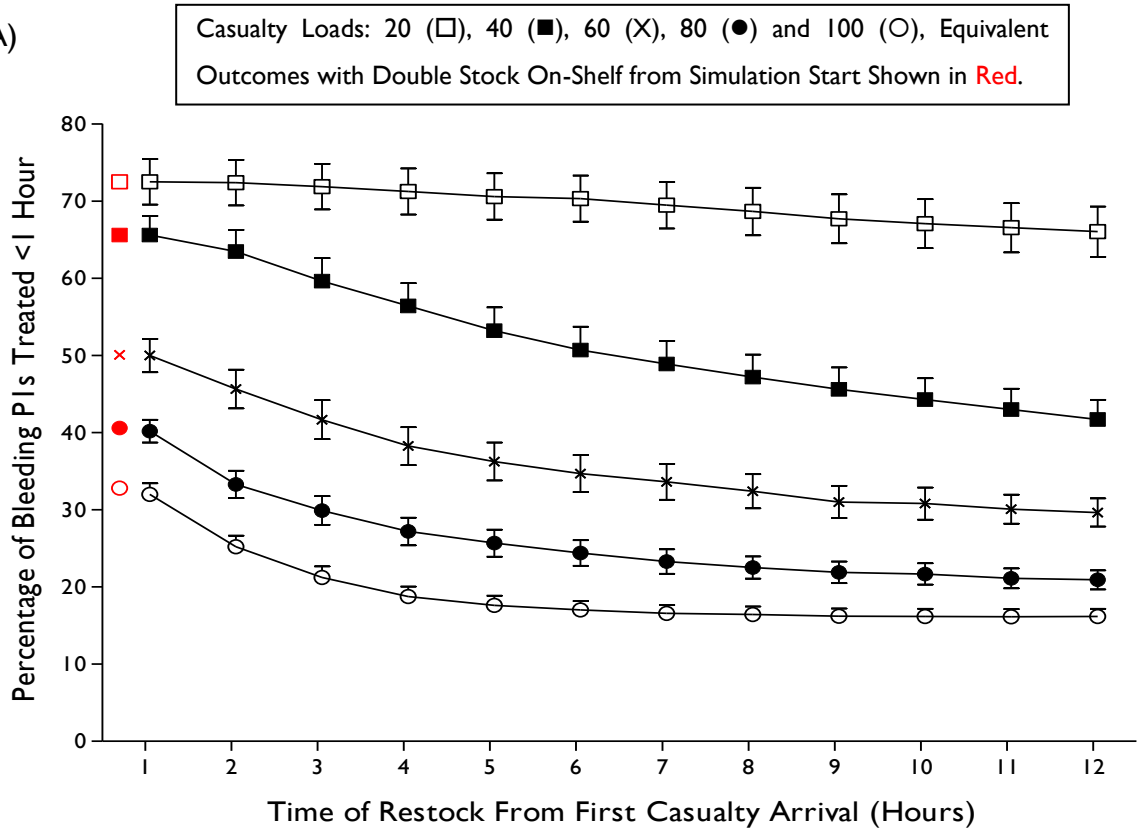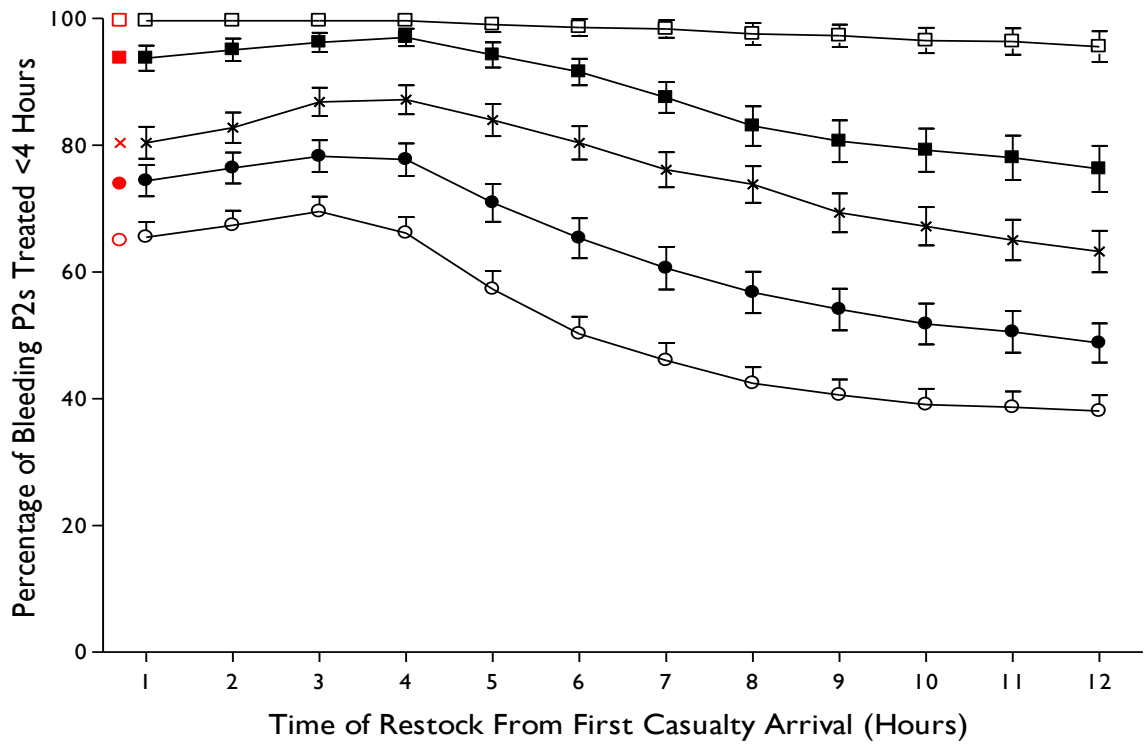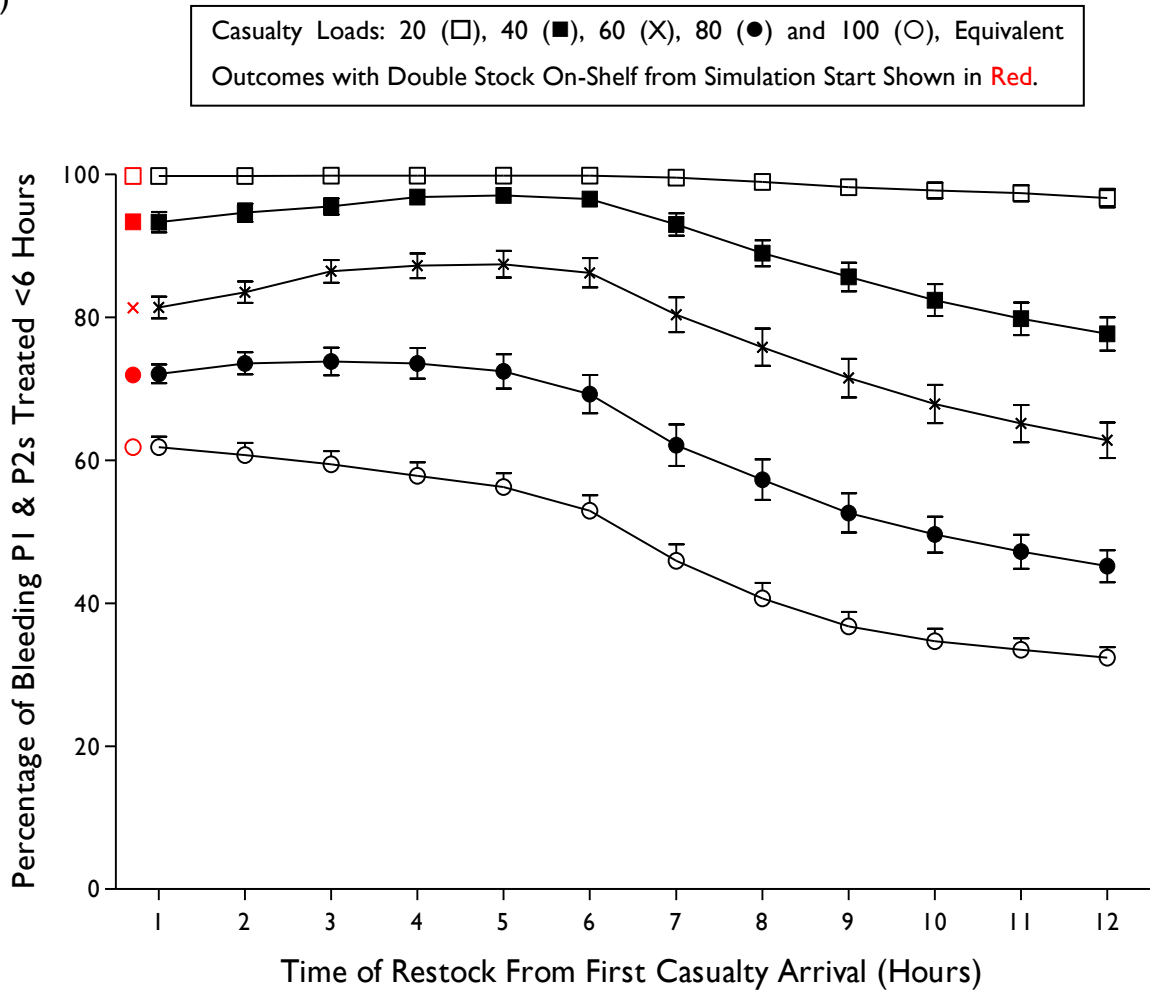
Figure 6.10 Examined through the first five casualty loads modelled of 20 (□), 40 (■), 60 (X), 80 (●) and 100 (O), the effect of restocking an MTC's PRBC inventory at increasing hourly time points from the time of first casualty arrival on: A) The percentage of bleeding P1s treated under 1 hour, B) The percentage of bleeding P2s treated under 4 hours, and C) The percentage of bleeding P1 and P2s treated under 6 hours. Values are shown as means with 95% confidence intervals. Each set of casualty load results is shown along with the corresponding mean treatment level (□, ■, X, ●, O) achieved with holding double the standard stock hold on-shelf from the start of the simulation.

The variation in P1 treatment outcomes with increasing restock time followed an expected pattern with a gradual decline in model output. Conversely, there was an unexpected initial improvement in treatment rates observed amongst P2s and in the overall population. The additional outcome measure of type O PRBC consumption was examined in order to investigate the reasons for this anomaly. The median time for all type O PRBC stock to be consumed across all casualty loads and restock times is shown in Table 6.5. This was compared with holding a double standard stock level on-shelf at the MTC from the start investigated as a component of H_{4A} above and shown in Table 6.4.

A single restock at one hour from first casualty arrival results in exhaustion of supplies of type O PRBC at approximately the same time as an increased original stock hold. A reduction in longevity of supplies of just 15 minutes was observed for all casualty loads considered. However, all restocks of PRBC performed later than the first hour resulted in exhaustion of type O supply levels prior to their additional delivery in the model. Therefore, in order to better understand the model performance with regard to treatment rates and restocking, the mean level of type O and combined levels of type A, B and AB PRBCs were examined over the first twelve hours of an event. The 60 casualty cohort simulations displayed the greatest overall percentage variation in treatment rates across individual outcome measures and therefore, this cohort was selected in which to investigate the effects of these stock fluctuations (Figure 6.11 & Figure 6.12).

Type O levels were first compared with the double on-shelf inventory reference scenario from H_{4A}, the results of which are shown in Figure 6.11. There is a consistent pattern in the consumption of emergency type O PRBCs irrespective of restock time, with the earliest restock performed within one hour leading to an equivalent outcome over the following 11 hours, as is seen when the stock is already held at the MTC prior to the event. Secondly, type O level variation in relation to the other blood group PRBC levels was examined. The restock times depicted in Figure 6.12 represent the equivalent, best and worst treatment performances amongst bleeding casualties during the 60 casualty load experiments, compared with the double on-shelf stock reference scenario from H_{4A}.

Table 6.5 Median time to exhaustion of type O PRBC levels following single PRBC inventory restocks at increasing hourly time points from the start. Displayed as medians in hours, (IQR).

Restock Time (Hours)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1	* (*-*)	8.5 (5.5-*)	3.4 (2.3-4.5)	1.9 (0.8-2.4)	0.9 (0.8-1.6)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
2	* (*-*)	1.9 (1.5-12.8)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
3	* (*-*)	1.9 (1.5-8.8)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
4	* (*-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
5	* (*-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
6	* (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
7	* (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
8	* (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
9	* (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
10	40.6 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
11	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
12	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)

* = Supply not exhausted for 72 hour simulation duration.
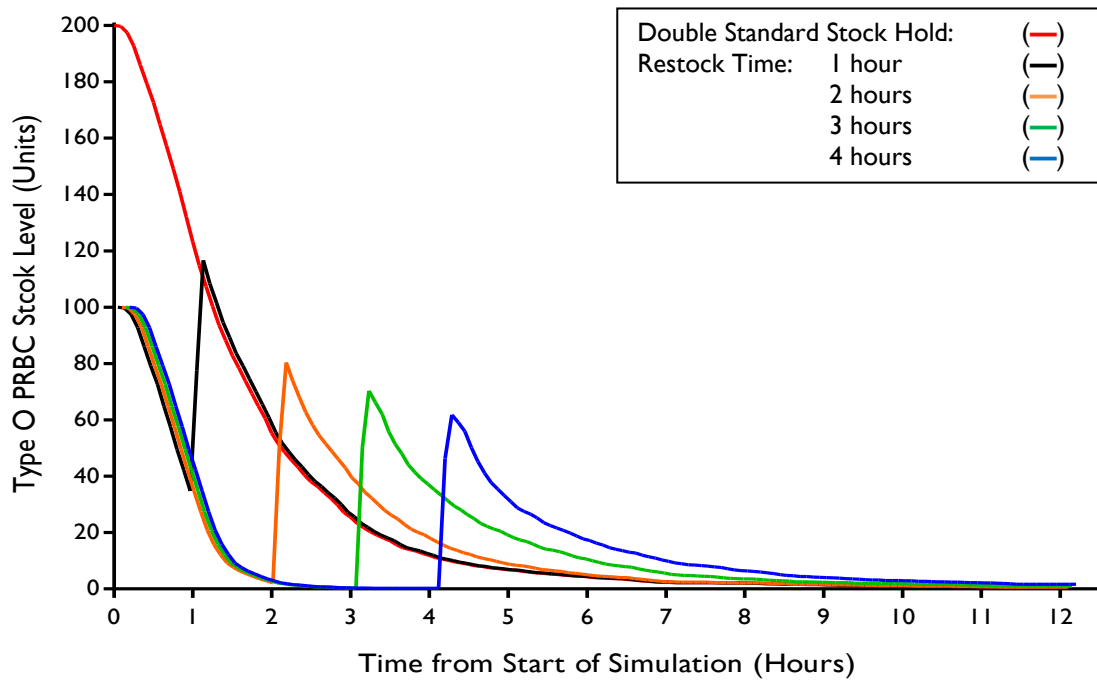
Figure 6.11 The mean use of type O PRBCs (U) over the first twelve hours of a 60 casualty MCE simulation comparing restocking time with a double initial standard stock hold.

A)
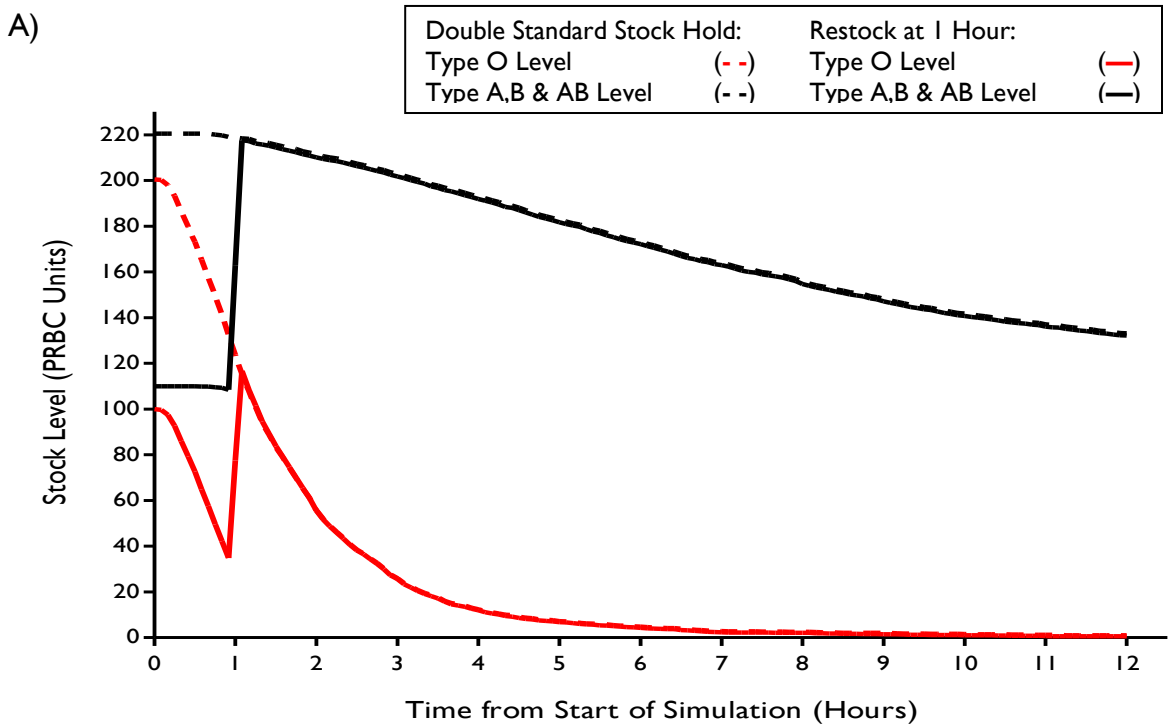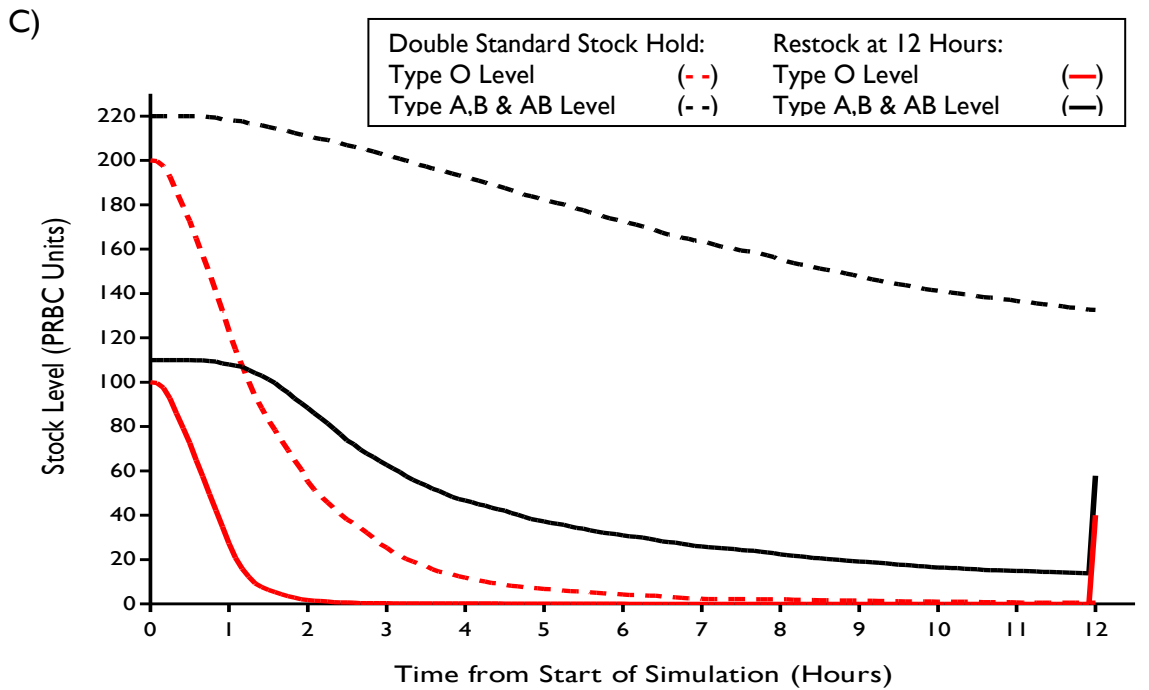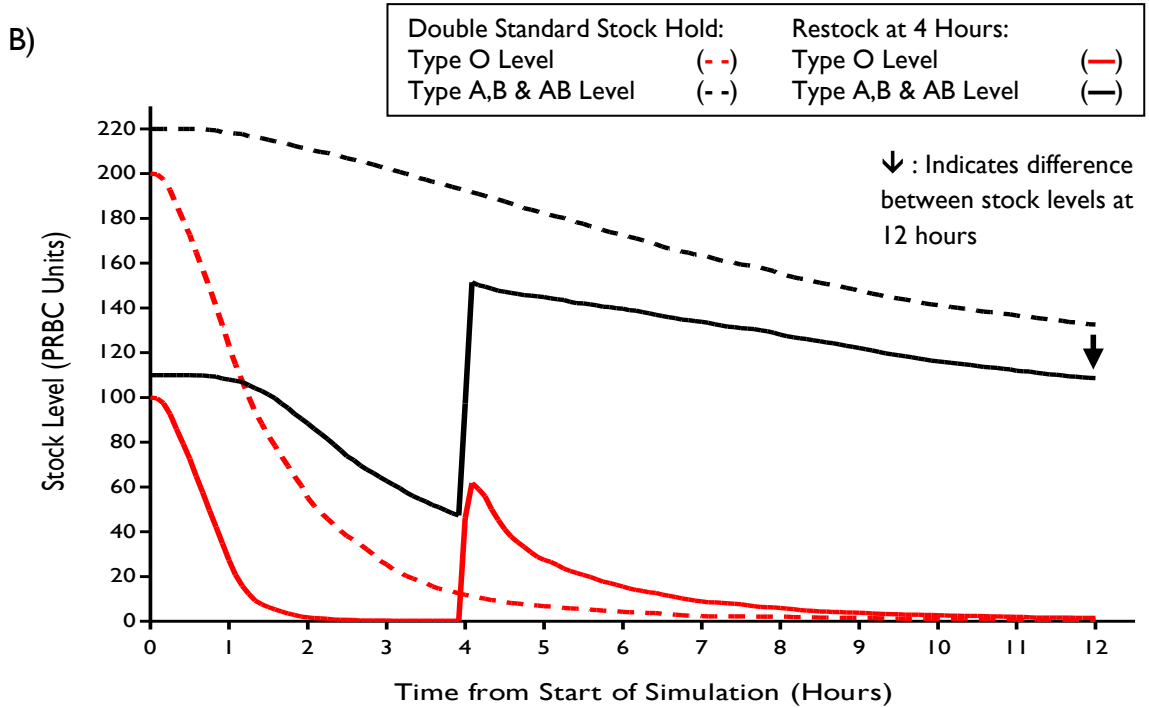
Figure 6.12 The mean use of type O PRBCs and combined all other type PRBCs over the first 12 hours of a 60 casualty MCE simulation, comparing an initial double standard level of PRBC inventory with restocking at: A) 1 hour, B) 4 hours and C) 12 hours.

The early high dependence on type O PRBCs leads to rapid exhaustion of supplies if not restocked within an hour (Figure 6.12). Upon exhaustion of the type O inventory there is a reliance on the transfer of casualties onto group-specific PRBCs for continued management of haemorrhage. Failure in the ability to provide casualties with type O PRBCs results in an increased rate of use, as well as overall consumption following an event, of all other PRBC groups (Figure 6.12 B). This response is only present when type O PRBC levels have been exhausted prior to the restock occurring. The increased rate of consumption of all other PRBC groups, without further restocking supplies eventually leads to insufficient stocks of group-specific blood to meet casualty needs, as although PRBCs may remain available, the waiting casualties may not be compatible with the stock type which remains. This scenario is best illustrated in Figure 6.12 C where the restock time is significantly delayed, and although there is increased consumption of group-specific PRBCs, the levels do not fully exhaust despite casualties remaining within the model in further need of PRBCs.

6.2.3.iii Discussion

These experiments investigated the effects of restocking PRBC supplies following an event at increasingly delayed time points. The findings appear to support the H_{4B} hypothesis with early restocking of the model MTC's PRBC inventory allowing for comparable outcomes from an event to that observed with maintenance of the equivalent stock on-shelf prior to the incident for a limited number of casualties. The simulation model also indicates that a delay in this restocking of supplies during the initial stages following the event, whilst having a detrimental effect on the treatment of bleeding P1 casualties, can actually have a beneficial effect on P2s, as well as the overall treatment outcomes following the event. This effect appears to be mediated through the increased consumption of group-specific PRBCs compared with that observed during an increased stock hold prior to the simulation start.

The ability to maintain or even improve outcomes with a restocking approach over increased stock hold is an attractive notion for future planning given the reduced burden it would place on hospital based transfusion services. The improvement in treatment rates in the model are generated through early exhaustion of type O PRBC and therefore the requirement for casualties to wait for group-specific blood to be available, leading to an increased overall consumption of group-specific PRBC. This is manageable amongst the P2 cohort, who by definition, have less urgent demands for treatment and can therefore wait for group analysis and still receive their required PRBC demand within four hours. In contrast P1s cannot afford this delay in treatment and therefore any delay in restocking beyond a single hour leads to a detrimental effect on their treatment outcomes in all but the smallest casualty loads considered.

The forced delay in treatment bought about by the exhaustion of emergency type O supplies may assist the treating clinicians in making potentially difficult decisions regarding resource allocation to bleeding casualties. As whilst adequate stocks remain available, there may be a predisposition to treat bleeding P2s with emergency type O RPBC despite their capacity to potentially hold on for group-specific blood. Strategies of controlled blood group analysis and the restriction of specific treatments as investigated in Aims Five and Six of this study, may offer further insight into this practice as a solution for improving outcomes in stock limited scenarios.

Irrespective of the potential benefit, the sufficient restocking of supplies within one to four hours may still be challenging depending on the circumstances of the event. Despite the initial improvements in care, ongoing delays eventually caused a decline in treatment levels in both individual priority groups and overall. The alternative of holding higher stock permanently at responding centres, especially to the extent suggested in H_{4A} however, may make this the only option for future event planning. Should this be the case, the emphasis from a preparedness standpoint must be on minimising the time to restock. Potential strategies to achieve this may include satellite blood centres placed within a time measured radius of responsible MTCs, or the automatic immediate dispatch of PRBC supplies at the time of an event's declaration, using a push over pull strategy.

6.2.4 Aim Four Conclusion

The experimentation of Aim Four has demonstrated the potential effect adequacy of PRBC supplies has on outcomes amongst bleeding casualties in MCEs through a simulation modelling approach. Whilst greater and greater stock volumes are able to maintain adequate rates of treatment, the logistical and financial implications of maintaining these volumes of PRBC stock at MTCs limits the viability of this solution. Restocking PRBCs during an event has been shown to generate equivalent overall outcomes from an event compared with an increased stock hold; however, this does appear to be time limited. Potential solutions for maximising treatment outcomes must therefore be identified for situations of limited stock hold capacity or when restocking within the required time constraints is not feasible. Aims Five and Six considered a number of potential such solutions.

6.3 Aim Five – Laboratory Processing

6.3.1 Introduction

Aim Four illustrated the effects of increased stock hold and ability to restock on bleeding casualty outcomes in MCEs. In contrast Aim Five and subsequently Aim Six, discuss potential system modifications which may facilitate improved outcomes during events when stock is known to be insufficient or where restocking is not possible. The sensitivity analysis performed in Chapter Five demonstrated an undetectable effect on outcomes when the number of personnel available to process PRBC samples within the transfusion laboratory is varied by a 20% margin. However, varying the overall time to process samples for the provision of group-specific PRBCs to casualties did show a degree of influence on outcomes. Although a delay in processing is possible with machine failures and human errors, increasing the rate of processing is unlikely without advances in the current technology available. Therefore, if modifications are to be made to the processing of blood samples to improve outcomes, they must come in terms of policy changes to reduce the burden on the laboratory blood processing system. The aim of this set of experiments was to investigate the influence on outcomes brought about through modifications to an MTC transfusion service's protocols for processing and providing group-specific PRBCs.

6.3.2 Experiment 5A – Priority Grouping (H_{5A})

'Outcomes from an event can be improved by prioritising the laboratory processing of P2 casualties to provide group-specific treatment whilst preserving emergency type O PRBCs exclusively for P1s.'

6.3.2.i Methods

The experimental baseline model was adapted through the addition of a number of model components within the Patient Characteristics sub-model. A Decide module was added which organised casualties by priority, with P1s continuing as per the standard baseline course and P2s entering the next additional module. This next additional module was a Record module which counts the number of bleeding P2s present in the model. The Decide module which followed determined whether or not the current bleeding P2 would be permitted emergency type O PRBCs. This decision was based on whether or not the defined threshold of received bleeding P2s had been reached in the preceding Record module.
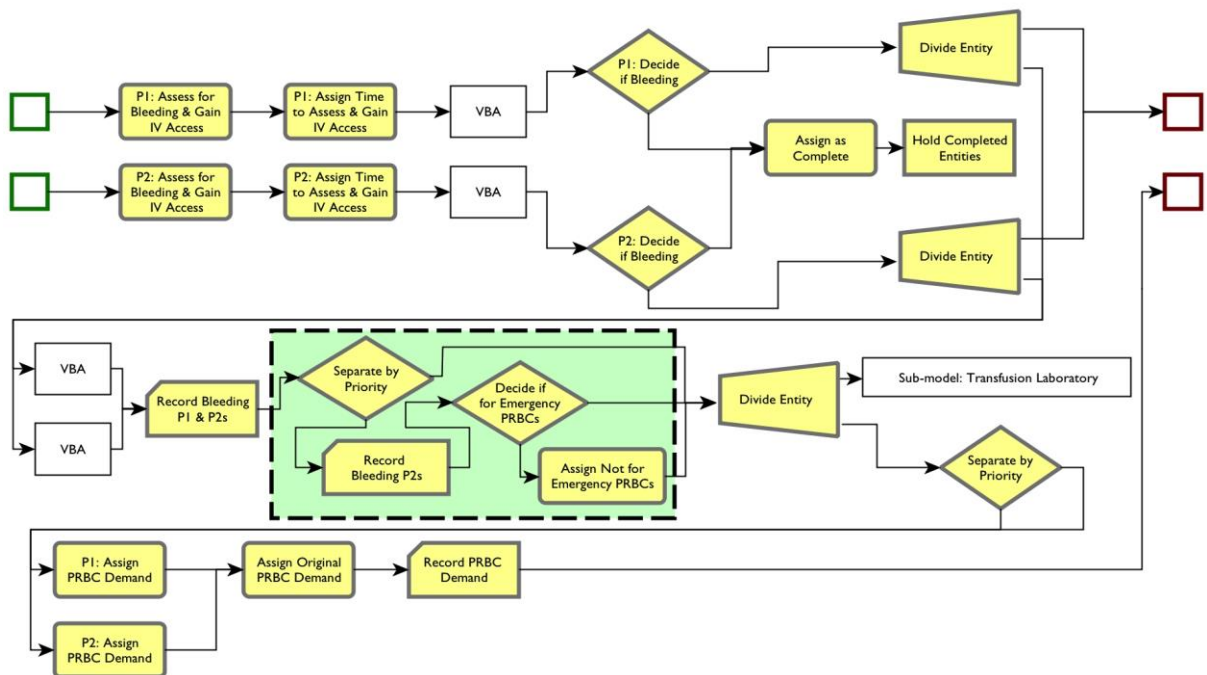
Figure 6.13 The Patient Characteristic sub-model with added components (Highlighted Green) for investigating the effects of treating P2s exclusively with group-specific PRBCs.

The threshold for allowing P2s emergency type O PRBCs was set at increments of five casualties from 5 to 30 across all casualty loads. The final supplementary module in the

Patient Characteristic sub-model was an additional Assign module to ensure the casualty did not receive emergency type O PRBCs in the Emergency PRBC Provision sub-model which followed. This sub-model also required an additional Decide module inserted to check type O emergency PRBC permission upon entry of an entity into the sub-model. The additional modules and their inclusions into both the Patient Characteristic sub-model and the Emergency PRBC Provision sub-model are shown in Figure 6.13 and Figure 6.14 respectively. The standard baseline data input values as described previously in Table 6.2 remained unchanged for all simulations performed.
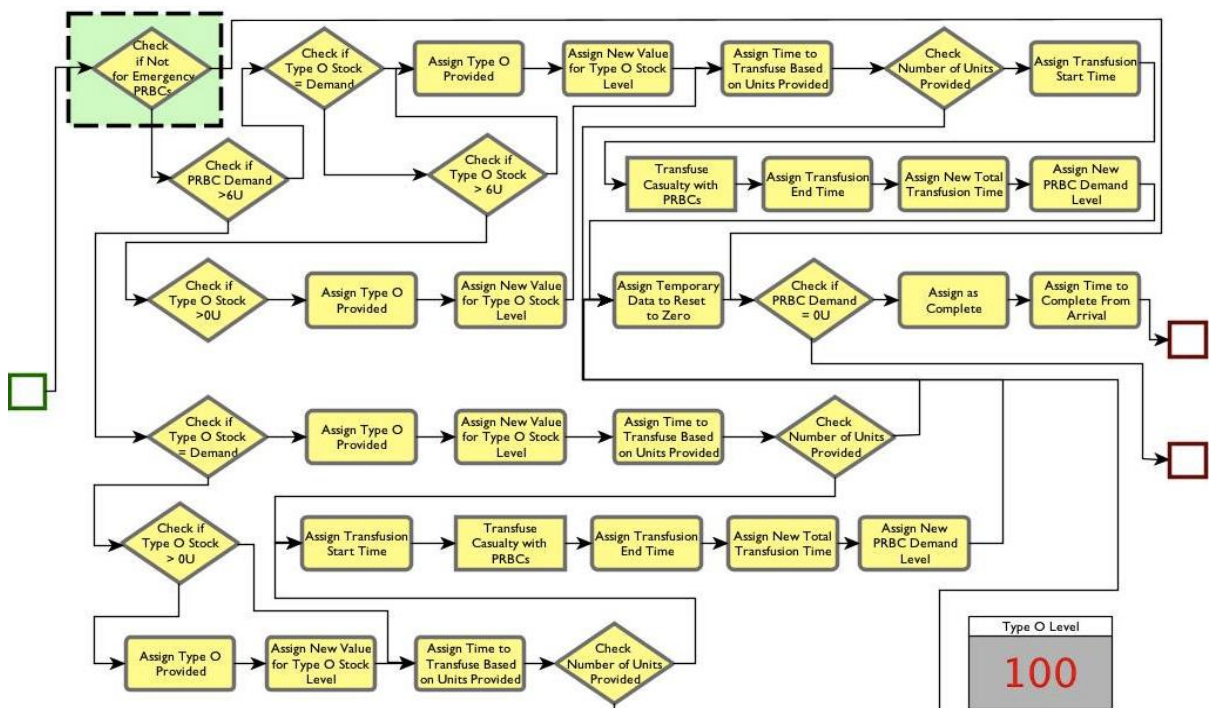
Figure 6.14 The Emergency PRBC Provision sub-model with added components (Highlighted Green) for investigating the effects of treating P2s exclusively with group-specific PRBCs.

6.3.2.ii Results

H_{5A} involved 10,500 simulations and over 50 hours of computer processing time to complete. The effects on outcomes of prioritising the group analysis of P2s whilst denying

them type O emergency PRBC use for an increasing initial volume of arriving bleeding casualties are shown in Table 6.6, Table 6.7 and Table 6.8, along with experimental baseline model results for comparison. Amongst bleeding P1s there is a universal statistically significant increase in treatment rates observed across all casualty loads with increasing restriction of P2 emergency type O PRBC allowance. This effect is greatest at smaller MCE magnitudes, ranging from a 0.6% increase at loads of 300 casualties up to 2.0% amongst the 20 casualty cohort (Table 6.6). In contrast, the restriction placed on P2s led to an overall reduction in treatment rates, greatest at a casualty load of 140, where a decline of 4.3% was observed between the baseline state and the highest number of restricted P2 casualties (Table 6.7).

Although both the increase and reduction in treatment rates of bleeding P1s and P2s respectively reached statistical significance, this equated to approximately one casualty treated over or under the level of the baseline model state. Delaying the measurement time to six hours and examining overall treatment rates of all bleeding casualties by this time point produced less variation than occurred amongst the individual priority groups across all casualty loads (Table 6.9). The difference between the greatest increase and maximal decline in treatment rates was less than two percent, with a positive deflection from the baseline level at the lowest casualty loads shifting to a negative deflection as casualty load increased beyond 40. This pattern remained unchanged with a 12 hour measurement point.

For the third outcome of time to exhaustion of type O PRBC supplies, only the 20 casualty load experiment displayed statistical significance in the variation of median time to exhaustion when comparing the baseline model with the P2 restriction models (Table 6.8). A three hour increase in longevity of type O PRBC supplies was observed when restricting provision of emergency type O PRBC to all arriving P2s in this experiment (Figure 6.15). This coincides with the greatest improvement in the bleeding P1 treatment rate observed of two percent.

Table 6.6 For MCE magnitudes ranging from 20-300 casualties, the mean percentage (95% CI) of all bleeding P1s treated in full within 1 hour of arriving at an MTC with increasing restriction of the number of P2s permitted type O PRBCs and prioritised for group analysis

Restrict to Type Specific PRBCs:	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1st 0 P2s (Baseline Model)	64.6 (61.3-67.9)	39.8 (37.3-42.3)	27.8 (26.1-29.5)	20.5 (19.3-21.7)	16.1 (15.1-17.1)	13.6 (12.8-14.4)	11.6 (11-12.3)	10 (9.5-10.6)	8.8 (8.4-9.3)	7.7 (7.2-8.1)	7.2 (6.8-7.6)	6.5 (6.1-6.9)	5.9 (5.6-6.2)	5.6 (5.3-5.9)	5 (4.7-5.3)
1st 5 P2s	66 (62.8-69.2)	42.8 (40.3-45.4)	29.2 (27.5-31)	21.9 (20.6-23.2)	17.4 (16.4-18.4)	14.8 (14-15.7)	12.8 (12.1-13.5)	10.9 (10.3-11.5)	9.6 (9.2-10.1)	8.4 (8-8.9)	7.8 (7.4-8.1)	7 (6.6-7.4)	6.2 (5.9-6.6)	6.2 (5.9-6.6)	5.5 (5.2-5.8)
1st 10 P2s	66.6 (63.5-69.8)	43 (40.4-45.6)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.1 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.9 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)
1st 15 P2s	66.6 (63.5-69.8)	43 (40.4-45.6)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.1 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.9 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)
1st 20 P2s	66.6 (63.5-69.8)	43 (40.4-45.6)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.1 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.9 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)
1st 25 P2s	66.6 (63.5-69.8)	43 (40.4-45.6)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.1 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.9 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)
1st 30 P2s	66.6 (63.5-69.8)	43 (40.4-45.6)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.1 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.9 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)

Table 6.7 For MCE magnitudes ranging from 20-300 casualties, the mean percentage (95% CI) of all bleeding P2s treated in full within 4 hours of arriving at an MTC with increasing restriction of the number of P2s permitted type O PRBCs and prioritised for group analysis

Restrict to Type Specific PRBCs:	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1st 0 P2s (Baseline Model)	92.9 (89.6-96.2)	71.5 (67.6-75.3)	55.7 (52.3-59.1)	43.2 (40.5-46)	35.2 (32.9-37.5)	28.7 (26.3-31.1)	25.4 (23.6-27.2)	21.4 (19.9-23)	19.6 (18.1-21.1)	16.3 (15-17.5)	15.3 (14.1-16.5)	13.8 (12.7-15)	13.3 (12.3-14.3)	12 (11-13.1)	11.4 (10.6-12.2)
1st 5 P2s	93 (89.6-96.4)	70.1 (65.8-74.4)	52.8 (49.3-56.2)	39.8 (37-42.6)	32 (29.8-34.3)	25.2 (22.7-27.6)	21.7 (19.8-23.5)	18.2 (16.7-19.6)	16.4 (14.9-17.8)	13.6 (12.4-14.8)	12.8 (11.6-14)	11.5 (10.4-12.5)	11.3 (10.3-12.2)	10.1 (9.2-11.1)	9.3 (8.5-10.1)
1st 10 P2s	93 (89.6-96.4)	69.6 (65.3-73.9)	52.4 (49-55.9)	39.1 (36.4-41.8)	31.6 (29.4-33.8)	24.5 (22.1-26.9)	21.2 (19.4-22.9)	17.8 (16.4-19.2)	15.8 (14.4-17.1)	13.2 (12.1-14.4)	12.5 (11.4-13.7)	11.2 (10.2-12.2)	11 (10.1-11.9)	9.9 (9-10.8)	9.1 (8.3-9.9)
1st 15 P2s	93 (89.6-96.4)	69.6 (65.3-73.9)	52.4 (49-55.9)	39.1 (36.4-41.8)	31.6 (29.4-33.8)	24.5 (22.1-26.9)	21.1 (19.4-22.9)	17.8 (16.4-19.2)	15.8 (14.4-17.1)	13.2 (12.1-14.4)	12.5 (11.4-13.7)	11.2 (10.2-12.2)	11 (10.1-11.9)	9.9 (9-10.8)	9.1 (8.3-9.9)
1st 20 P2s	93 (89.6-96.4)	69.6 (65.3-73.9)	52.4 (49-55.9)	39.1 (36.4-41.8)	31.6 (29.4-33.8)	24.5 (22.1-26.9)	21.1 (19.4-22.9)	17.8 (16.4-19.2)	15.8 (14.4-17.1)	13.2 (12.1-14.4)	12.5 (11.4-13.7)	11.2 (10.2-12.2)	11 (10.1-11.9)	9.9 (9-10.8)	9.1 (8.3-9.9)
1st 25 P2s	93 (89.6-96.4)	69.6 (65.3-73.9)	52.4 (49-55.9)	39.1 (36.4-41.8)	31.6 (29.4-33.8)	24.5 (22.1-26.9)	21.1 (19.4-22.9)	17.8 (16.4-19.2)	15.8 (14.4-17.1)	13.2 (12.1-14.4)	12.5 (11.4-13.7)	11.2 (10.2-12.2)	11 (10.1-11.9)	9.9 (9-10.8)	9.1 (8.3-9.9)
1st 30 P2s	93 (89.6-96.4)	69.6 (65.3-73.9)	52.4 (49-55.9)	39.1 (36.4-41.8)	31.6 (29.4-33.8)	24.5 (22.1-26.9)	21.1 (19.4-22.9)	17.8 (16.4-19.2)	15.8 (14.4-17.1)	13.2 (12.1-14.4)	12.5 (11.4-13.7)	11.2 (10.2-12.2)	11 (10.1-11.9)	9.9 (9-10.8)	9.1 (8.3-9.9)

Table 6.8 For MCE magnitudes ranging from 20-300 casualties, the median (IQR) time in hours to exhaustion of type O PRBC with increasing restriction of the number of P2s permitted type O PRBCs and prioritised for group analysis

Restrict to Type Specific PRBCs:	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1st 0 P2s (Baseline Model)	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
1st 5 P2s	12.5 (7.8-*)	2.2 (1.7-3.1)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
1st 10 P2s	12.8 (7.9-*)	2.2 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.8)	0.6 (0.5-0.7)	0.6 (0.5-0.7)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
1st 15 P2s	12.8 (7.9-*)	2.2 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
1st 20 P2s	12.8 (7.9-*)	2.2 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
1st 25 P2s	12.8 (7.9-*)	2.2 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
1st 30 P2s	12.8 (7.9-*)	2.2 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)

* = Supply not exhausted for 72 hour simulation duration.

Table 6.9 For MCE magnitudes ranging from 20-300 casualties, the mean percentage (95% CI) of all bleeding casualties treated in full within 6 hours of arriving at an MTC with increasing restriction of the number of P2s permitted type O PRBCs and prioritised for group analysis

Restrict to Type Specific PRBCs:	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1st 0 P2s (Baseline Model)	92.3 (90.4-94.1)	69.4 (67-71.8)	51.6 (49.6-53.6)	38 (36.5-39.5)	29.6 (28.4-30.8)	23.9 (22.7-25.1)	20 (19.2-20.8)	16.8 (16-17.5)	14.9 (14.4-15.5)	12.6 (12.1-13.1)	11.4 (11-11.8)	10.3 (9.9-10.7)	9.6 (9.2-10)	8.7 (8.3-9.1)	8 (7.7-8.4)
1st 5 P2s	93.5 (91.8-95.2)	70.7 (68.2-73.2)	50.9 (48.9-52.9)	37.4 (35.9-38.8)	29 (27.8-30.2)	23.3 (22.1-24.4)	19.4 (18.7-20.2)	16.2 (15.5-16.9)	14.4 (13.8-15)	12.1 (11.6-12.6)	11 (10.6-11.4)	9.9 (9.5-10.3)	9 (8.6-9.3)	8.5 (8.1-8.9)	7.7 (7.4-8.1)
1st 10 P2s	93.7 (92-95.4)	70.6 (68-73.1)	50.9 (48.9-52.9)	37.2 (35.8-38.7)	29 (27.8-30.2)	23.2 (22.1-24.4)	19.3 (18.5-20.1)	16.2 (15.5-16.9)	14.3 (13.8-14.9)	12.1 (11.6-12.6)	11 (10.6-11.4)	9.9 (9.5-10.3)	8.9 (8.5-9.3)	8.4 (8.1-8.8)	7.7 (7.4-8.1)
1st 15 P2s	93.7 (92-95.4)	70.6 (68-73.1)	50.9 (48.9-52.9)	37.2 (35.8-38.7)	29 (27.8-30.2)	23.2 (22.1-24.4)	19.3 (18.5-20.1)	16.2 (15.5-16.9)	14.3 (13.8-14.9)	12.1 (11.6-12.6)	11 (10.6-11.4)	9.9 (9.5-10.3)	8.9 (8.5-9.3)	8.4 (8.1-8.8)	7.7 (7.4-8.1)
1st 20 P2s	93.7 (92-95.4)	70.6 (68-73.1)	50.9 (48.9-52.9)	37.2 (35.8-38.7)	29 (27.8-30.2)	23.2 (22.1-24.4)	19.3 (18.5-20.1)	16.2 (15.5-16.9)	14.3 (13.8-14.9)	12.1 (11.6-12.6)	11 (10.6-11.4)	9.9 (9.5-10.3)	8.9 (8.5-9.3)	8.4 (8.1-8.8)	7.7 (7.4-8.1)
1st 25 P2s	93.7 (92-95.4)	70.6 (68-73.1)	50.9 (48.9-52.9)	37.2 (35.8-38.7)	29 (27.8-30.2)	23.2 (22.1-24.4)	19.3 (18.5-20.1)	16.2 (15.5-16.9)	14.3 (13.8-14.9)	12.1 (11.6-12.6)	11 (10.6-11.4)	9.9 (9.5-10.3)	8.9 (8.5-9.3)	8.4 (8.1-8.8)	7.7 (7.4-8.1)
1st 30 P2s	93.7 (92-95.4)	70.6 (68-73.1)	50.9 (48.9-52.9)	37.2 (35.8-38.7)	29 (27.8-30.2)	23.2 (22.1-24.4)	19.3 (18.5-20.1)	16.2 (15.5-16.9)	14.3 (13.8-14.9)	12.1 (11.6-12.6)	11 (10.6-11.4)	9.9 (9.5-10.3)	8.9 (8.5-9.3)	8.4 (8.1-8.8)	7.7 (7.4-8.1)

Figure 6.15 Comparison of time to exhaustion of type O PRBC under standard conditions with restriction of P2s to purely type specific PRBC treatment following an MCE producing 20 casualties. Shown as: median and IQR. *Denotes significance between results.

The experiments were repeated for all primary outcomes at both double and treble the standard held stock level in order to observe whether any limited effect would be enhanced with greater PRBC availability. However, no discernable improvement relative to the baseline model with an equivalent initial stock hold was identified beyond that of the single stock experiments.

6.3.2.iii Discussion

These experiments formed the first part of the investigation of Aim Five, studying the potential effect changes in transfusion laboratory protocols for blood sampling could have on event outcomes. The prioritisation of P2 casualty blood sample analysis whilst also reserving type O PRBC treatment exclusively for use by P1s caused a small overall

reduction in treatment rates following an event except in the most limited casualty load experiments. Where there was observed to be an improvement in event outcomes, this was also found to be extremely limited. Furthermore, only in the smallest event considered was any significant increase in longevity of type O PRBC supplies observed, indicating the application of the H_{5A} protocol to be at best, restricted in the benefit it offers planners, and at worst, detrimental to ensuring the most successful outcome possible from an event.

The additional type O units made available through denial of this resource to P2 casualties had a limited impact on improving P1 treatment levels. Reservation of type O PRBCs solely for P1s allows more of this critical resource to be available as these types of casualty arrive and therefore, improves the chances of treating them within an hour of arrival. However, the greater demand for blood P1s present with in contrast to the lesser demand the P2 casualties would otherwise consume, diminishes any potentially beneficial effects. Furthermore, a substantial proportion of P2 casualties will have been of type O blood group, whereas previously some of these casualties would have received their correct blood group by chance during the initial emergency provision period with this protocol they may not. The delay in determining their blood group may result in no suitable stock being available with which to treat them by the time this has occurred.

The predominantly negative overall effect on the treatment of bleeding casualties when applying the protocol from H_{5A} was therefore a consequence of the summative results of a marginally positive effect experienced amongst the P1 cohort, combined with the more negative treatment reaction observed in the P2 cohort. In addition, although there was almost universally no effect on type O PRBC inventory levels with instigation of the H_{5A} protocol in the model, the single instance of significant increase in longevity of supplies was accompanied by the greatest increase in treatment rates observed during these experiments. The key to overall improvement in MCE bleeding casualty outcomes may therefore lie specifically within the length of time type O supplies can remain solvent following an event in situations where restocking of supplies is not an option.

Whilst the strategy proposed by H_{5A} has been shown by the model to be an impractical solution, the experimentation has offered further insight into the processes involved in improving PRBC provision. Additional changes to the sample processing procedure following these events as explored in H_{5B} were therefore thought to have potential in maintaining or increasing the small improvements observed here, whilst also reducing their concomitantly negative effects.

6.3.3 Experiment 5B – Exclusive Treatments (H_{5B})

'In addition to prioritising the blood group analysis of P2s, overall outcomes from an event can be further improved through restricting the processing of bleeding P1 casualties altogether, providing their treatment exclusively through the use of type O emergency PRBCs.'

6.3.3.i Methods

The investigation of H_{5B} incorporated the modifications made to the experimental baseline model Patient Characteristic and Emergency PRBC Provision sub-models as described above in the methods of H_{5A} (Figure 6.13 & Figure 6.14). In addition a decision module was added which determined whether or not a casualty was processed for group-specific PRBCs based on their priority status and the current level of the preceding record module. This record module monitored the overall number of bleeding casualties in the model prior to sending a blood sample for group analysis. This ensured the same volume of bleeding P1 casualties would be treated exclusively with emergency type O PRBCs as bleeding P2s would equally be treated exclusively with group-specific PRBCs.

The experiment was repeated at increasing five casualty thresholds across all casualty loads up to a maximum of 30 bleeding P1s and 30 bleeding P2s. The modified Patient Characteristic sub-model for these sets of experiments is shown in Figure 6.16, whereas, the Emergency PRBC Provision sub-model remained unchanged from that shown in Figure 6.14. The standard baseline data input values as described previously in Table 6.2 remained unchanged for all simulations performed.
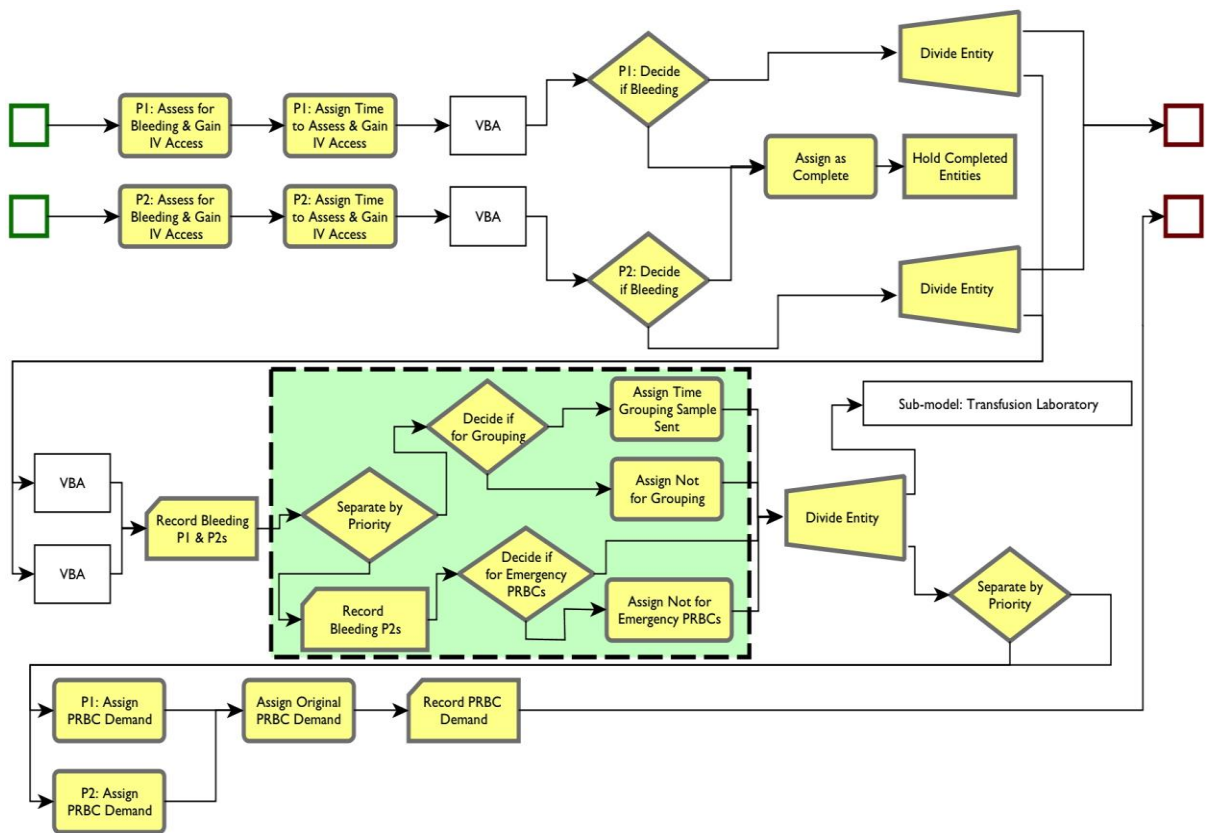
Figure 6.16 The Patient Characteristic sub-model with added components (Highlighted Green) for investigating the effects of treating P2s exclusively with group-specific PRBCs and P1s exclusively with emergency type O PRBCs.

6.3.3.ii Results

Investigation of H_{5B} required 10,500 runs of the simulation and approximately 50 hours of computer processing time to complete. The treatment response across all casualty loads to an increasing restriction of P1 blood group analysis was investigated in combination with the P2 protocol from H_{5A}. Application of both protocols displayed contrasting effects amongst P1 and P2 casualties depending on the volume of arriving casualties to which it was applied (Figure 6.17). Applying the protocol to the first five bleeding P1 and P2s produced a net positive and net negative effect on treatment rates across all casualty loads respectively.

As the protocol was applied to a greater number of casualties a reciprocal effect was observed up to the maximum number of the first 30 bleeding casualties from each cohort. The greatest increase amongst bleeding P1 casualties was seen with a casualty load of 40 and a restriction in processing of the first five casualties, this generated an increase in percentage of bleeding P1s treated within an hour of just fewer than three percent (Figure 6.17 A). Conversely, a casualty load of 80 combined with processing restriction of the first 30 casualties provided the greatest increase in treatment amongst bleeding P2s, with almost a 16% increase from the baseline model (Figure 6.17 B).

Figure 6.17 C combines both P1 and P2 outcomes, showing the total treatment rate for all bleeding casualties within six hours. The overall effect at casualty loads less than 100 is a decline in the treatment response when the protocol is applied to any number of initially arriving casualties up to 30. The worst outcome being nearly a 20% decline in treatment when the protocol is initiated for the first 30 casualties in a 40 casualty total MCE. At loads of 100 casualties there is a substantial decline in any treatment response. Although a positive response above that of the baseline mode was detected at these higher casualty loads, the variation between maximum and minimum treatment levels was just under three percent. In addition, no further change in the response pattern was detected at a 12 hour time point of measurement.

A)

Percentage of Bleeding P1s Treated <1 Hour in Relation to Baseline Model

B)

Percentage of Bleeding P2s Treated <4 Hours in Relation to Baseline Model

C)
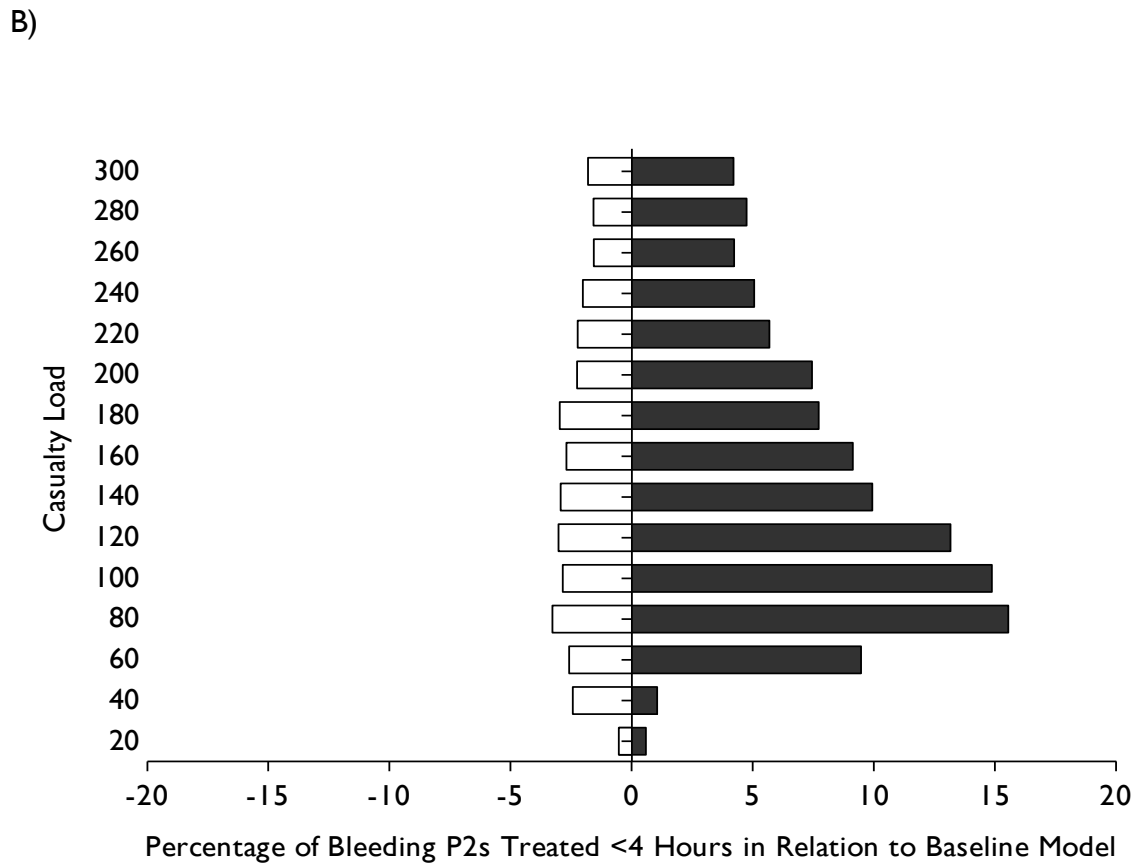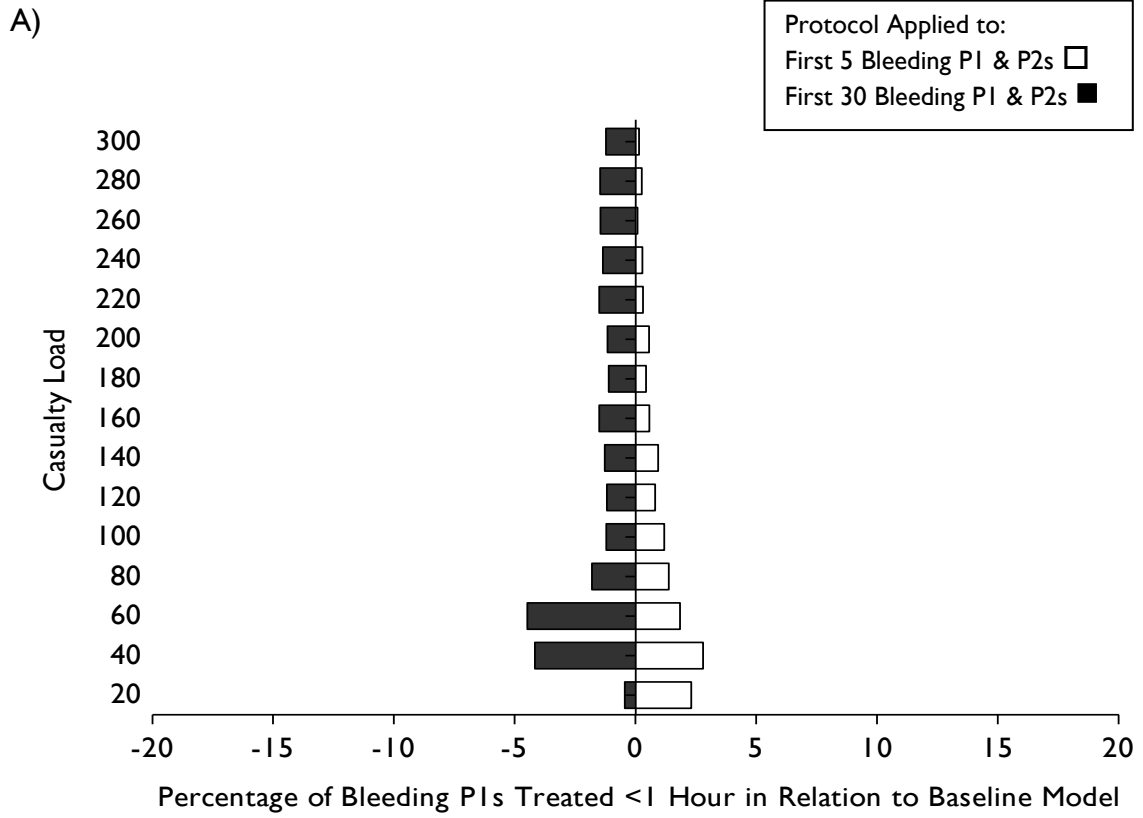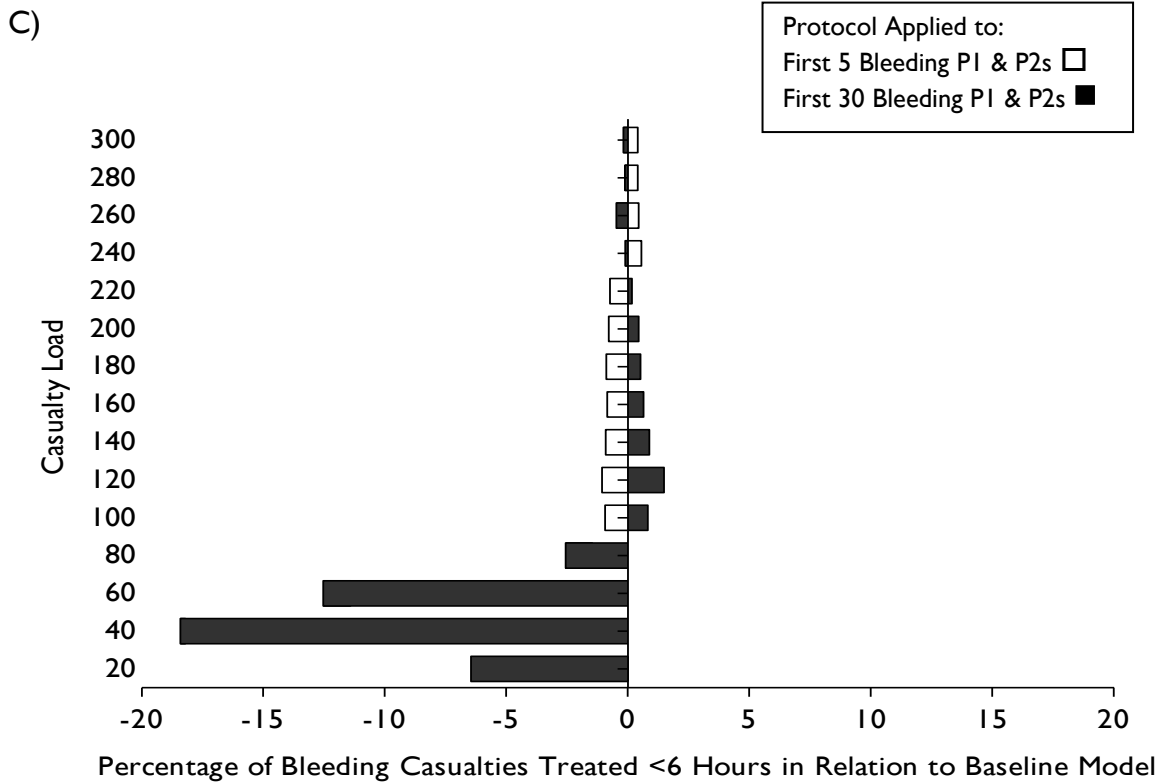
Figure 6.17 The mean variation in percentage of casualties treated in relation to the baseline model following application of the sample processing protocol to the first 5 (□) and first 30 (■) bleeding P1 and P2 casualties received following an event in terms of: A) Bleeding P1 casualties treated within 1 hour of arrival, B) Bleeding P2 casualties treated within 4 hours of arrival and C) All Bleeding casualties treated within 6 hours of arrival.

As all model experiments carried out during the investigation of H_{5B} maintained all other characteristics of the baseline model, there was potential for the lack of overall stock within the system to mask any possible benefit a sample processing protocol may provide. Therefore, in order to determine whether or not the overall negative effect on treatment rates experienced through application of the H_{5B} protocol varied with greater stock hold, the experiments were repeated with both double and treble the initial on-shelf PRBC stock levels. The results were compared with the baseline model with an equivalent PRBC inventory and the treble stock hold comparison is shown in Figure 6.18. The greater stock hold reduced the variability in treatment response observed across different sizes of MCEs

when the sample processing protocol was applied. However, despite an increase in stock availability of both double and treble the standard PRBC level, the trend across all casualty loads continued to show an overall decline in treatment levels. Although a positive effect was detected in certain cases when the lowest volumes of casualties were protocolled, the maximum improvement observed from the baseline was just under one percent.
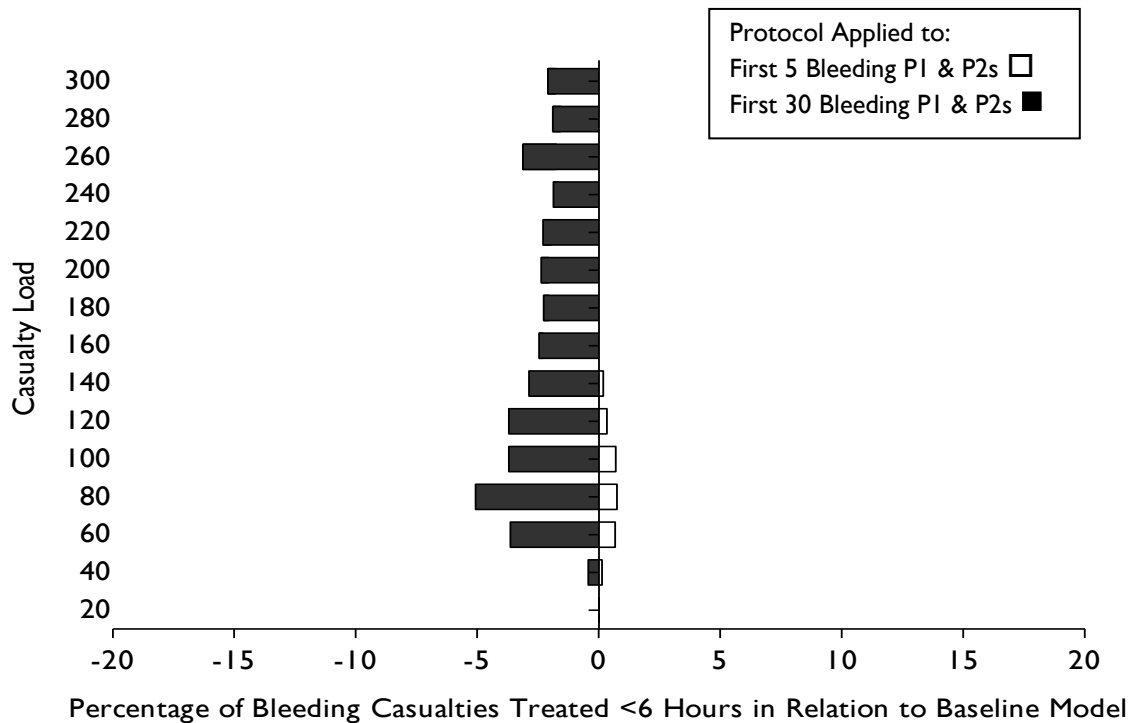
Figure 6.18 The mean variation in percentage of casualties treated in relation to the baseline model following application of the sample processing protocol shown in terms of all Bleeding casualties treated within 6 hours of arrival and with treble the standard on-shelf PRBC stock level.

Overall, the time to exhaust emergency type O PRBC supplies was only minimally affected by instigation of the sample processing protocol (Table 6.10). Although an increase in the median time to exhaustion was observed amongst the lower casualty loads experimented with, the variation from the baseline time was not found to be statistically significant, even at the smallest 20 casualty level. This was in contrast to the variation observed in the same scenario during investigation of H_{4A}.

Table 6.10 For MCE magnitudes ranging from 20-300 casualties, the median (IQR) time in hours to exhaustion of type O PRBC with increasing application of the sample processing protocol to arriving bleeding P1 and P2 casualties

Protocol Applied to 1st:	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
1st 0 P1 & P2s (Baseline Model)	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
5 P1 & P2s	11 (5.8-*)	2 (1.6-3)	1.4 (1.3-1.7)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
10 P1 & P2s	9.5 (5.2-*)	2.1 (1.6-3)	1.4 (1.3-1.7)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
15 P1 & P2s	9.5 (5.2-*)	2.1 (1.6-3)	1.4 (1.3-1.7)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
20 P1 & P2s	9.5 (5.2-*)	2.1 (1.6-3)	1.4 (1.3-1.7)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
25 P1 & P2s	9.5 (5.2-*)	2.1 (1.6-3)	1.4 (1.3-1.7)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
30 P1 & P2s	9.5 (5.2-*)	2.1 (1.6-3)	1.4 (1.3-1.7)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.8 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)

* = Supply not exhausted for 72 hour simulation duration.

6.3.3.iii Discussion

These experiments sought to determine if restricting the sample analysis of P1 casualties and providing their treatment exclusively through type O PRBCs, whilst also treating P2s solely with group-specific blood could improve outcomes from MCEs through a simulation modelling approach. A varied response was observed between the number of casualties to which the protocol was applied and the size of the MCE considered. Despite individual benefit amongst the different priority groups, the reciprocal nature of these responses meant the overall consequences of such a protocol were found to be detrimental in smaller events and equivocal to standard protocol outcomes in larger events. Thus the H_{5B} hypothesis could not be supported.

Preventing the grouping of P1 casualties showed an overall reduction in their treatment rate across experiments, whilst they may receive more type O PRBC units than under standard conditions, should this not satisfy their demand and without a known blood group, they are left untreatable following exhaustion of type O stock. Essentially, any PRBC delivered to these casualties has been wasted on ultimately unsalvageable cases, whereas it could have potentially satisfied many more P2s given their lesser PRBC demands. This conclusion is further supported by the tempering of the overall response with increased stock loads. This eventually extends to a partly beneficial effect recognised with greater stock availability in the smaller event sizes; however, these relatively small increments in treatment do not appear enough to warrant any universal application of this policy.

No significant change in the longevity of type O PRBC supplies was found to occur during these experiments. The rapid consumption of this resource observed under standard conditions clearly continues with the H_{5B} protocol without however, maintaining the same level of overall outcomes from the event. The practice of preventing grouping of P1 casualties in addition to treating P2s exclusively with grouped PRBC in an effort to reduce additional or unnecessary burden on the transfusion laboratory, it would seem, only serves

to waste precious PRBC supplies with a consequential detrimental effect on overall event outcomes.

6.3.4 Aim Five Conclusion

The experimentation of Aim Five has demonstrated the potential effects on treatment outcomes of applying various strategies of sample processing during an event. Although responses in treatment levels were identified within individual priority cohorts, the net effect of these was predominantly negative in nature compared with the results where standard operating procedures were applied. As such, neither hypothesis postulated in Aim Five could be supported based on the output of this model. In order to identify strategies for maximising treatment outcomes in instances of inadequate stock hold or restricted restocking capability, alternative approaches need to be considered. Aim Six, which follows below, discusses an alternative approach to managing transfusion systems during an MCE in an effort to ensure the greatest benefit possible is realised from the resources available.

6.4 Aim Six – Rationing Individual Casualty Treatment

6.4.1 Introduction

The preceding experimentation of Aim Four illustrated the dependence on stock and the ability to restock supplies during an event to ensure optimal bleeding casualty outcomes. Subsequently, Aim Five investigated the effects of modifying blood sample processing procedures on outcomes, in an effort to maximise overall care when stock was limited and could not be replenished. Such procedures were however found to be ineffective in significantly improving event outcomes. The alternative approach postulated by this study to maximising use of a limited stock hold was to use strategies which limit individual PRBC provision. These strategies formed the basis of Aim Six of this thesis.

The literature review and case study of the Olympics indicated the substantial PRBC demands of a minority of casualties. In fact, there have been reports both in civilian and military trauma settings of survival of casualties following massive transfusion (MT) of over 50U or even 100U of PRBCs (70-73). Although survival of these casualties has been reported as high as 70%, the effect on stock and therefore subsequent casualties received should this occur in an MCE could be catastrophic (70). Rationing of service provision is observed as a necessary evil in the initial pre-hospital setting, yet rarely discussed where in-hospital care is concerned. There could be substantial benefit in such an approach, especially with regard to larger events where individual demand may lead to greater extremes in individual PRBC demand. These experiments aimed to investigate the effect of rationing PRBC provision on event outcomes.

6.4.1 Experiment 6A – Limiting All Packed Red Blood Cell Provision (H$_{6A}$)

'Limiting individual casualty overall PRBC provision can improve overall outcomes following an event.'

6.4.2.i Methods

The experimental baseline model was adapted through the addition of a further two components within the Patient Characteristics sub-model and two within the main model. The Patient Characteristic sub-model was supplemented with a decision module separating casualties by whether or not their assigned PRBC demand was greater than the defined limit of PRBC provision for the run. Those casualties with a PRBC demand over the allowed limit entered a second additional module. This assigned them as a PRBC regulated casualty and reset their PRBC demand to the maximum permissible volume for the run. This ensured they still received PRBCs up to the allowed limit but not their full original demand.
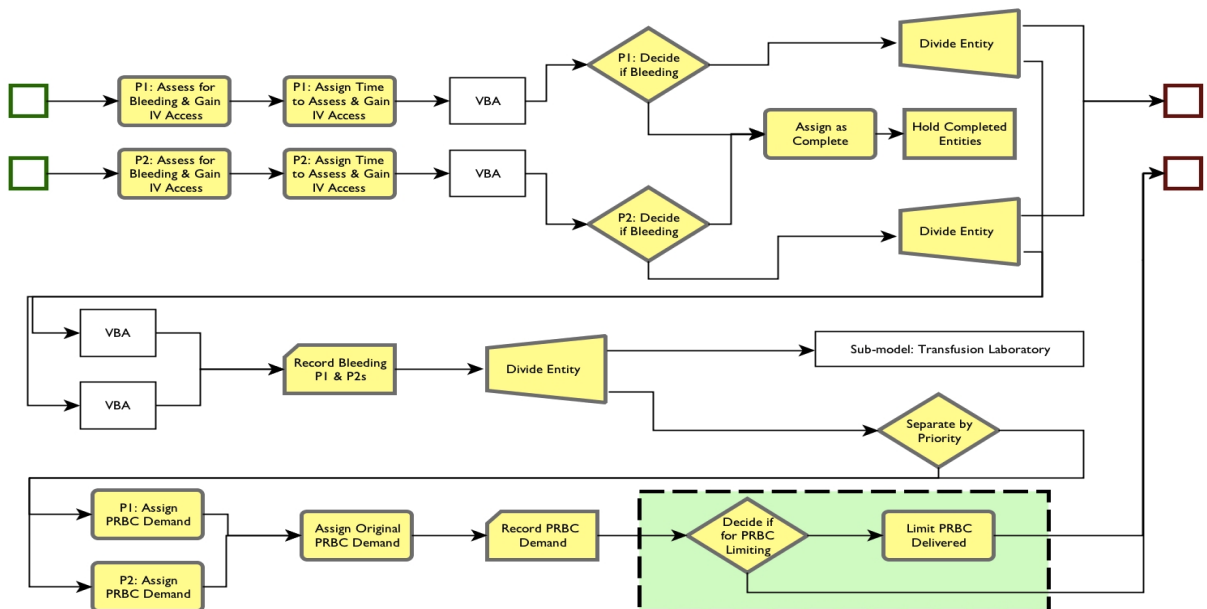
Figure 6.19 The modified (Highlighted Green) Patient Characteristic sub-model for investigating the effects of limiting individual PRBC provision to a defined threshold.

As PRBC limited casualties could no longer be recorded as receiving full treatment they were captured upon exiting the model with the addition of two components to the main model. The first of these was a Decide module, which checked for casualties whose PRBC provision had been limited and the second was a Hold module, which prevented them being recorded as treated in full by the data collection modules at the end of the run. The additional modules and their incorporation into the sub and main model are shown in Figure 6.19 and Figure 6.20 respectively. The experiment was run for all casualty loads with PRBC provision limits at increments of six PRBC unit packs starting above the mean P1 PRBC demand of 10.7U and including: 12, 18 and 24U of PRBCs. Limits were applied regardless of priority status. The standard baseline data input values as described previously in Table 6.2 remained unchanged for all simulations performed.
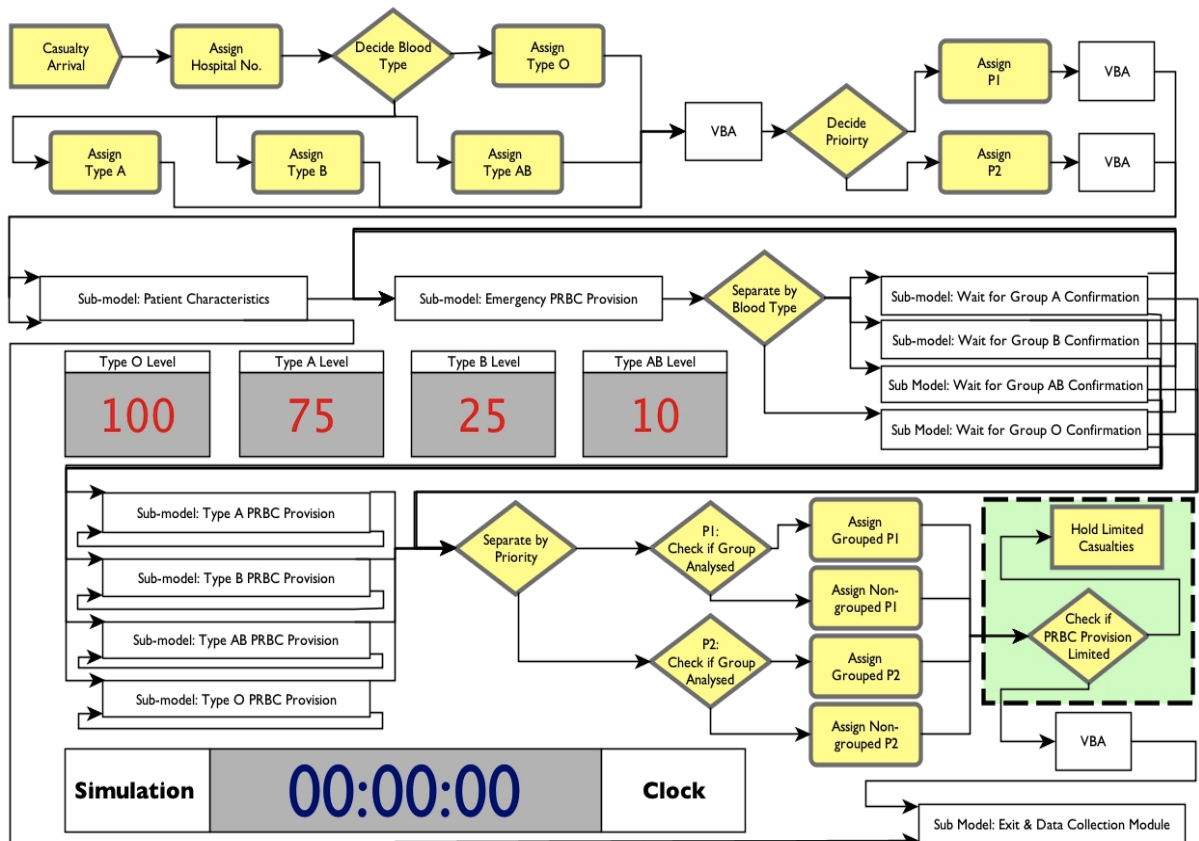
Figure 6.20 The main model including the supplementary components (Highlighted Green) added for investigating the effects of limiting individual PRBC provision to a defined threshold.

6.4.2.ii Results

The investigation of H_{6A} involved 6,000 simulations over 32 hours of computer processing time. For understanding and simplicity, the results are presented in terms of the three casualty loads applied during the description of H_{4A}: A medium sized event of 60 P1 and P2 casualties, a large event twice the size with 120 casualties and a third event double in size again involving 240 P1 and P2 casualties. Limiting the PRBC provision to individual bleeding casualties following an event to a 12, 18 or 24U maximum had no detrimental effect on the treatment rates of bleeding P1 or P2 casualties either individually, or overall, when compared with the baseline unrestricted model. A statistically significant improvement was detected amongst the principal outcome measures of both P1 treatment rates within an hour for all three event sizes and P2 treatment rates within four hours for the 120 and 240 casualty events when a 12U PRBC limit was imposed (Figure 6.21 A & B). Limitation of overall PRBC provision at the higher thresholds of 18U and 24U resulted in no statistically significant improvement or deterioration from the baseline model.

A)
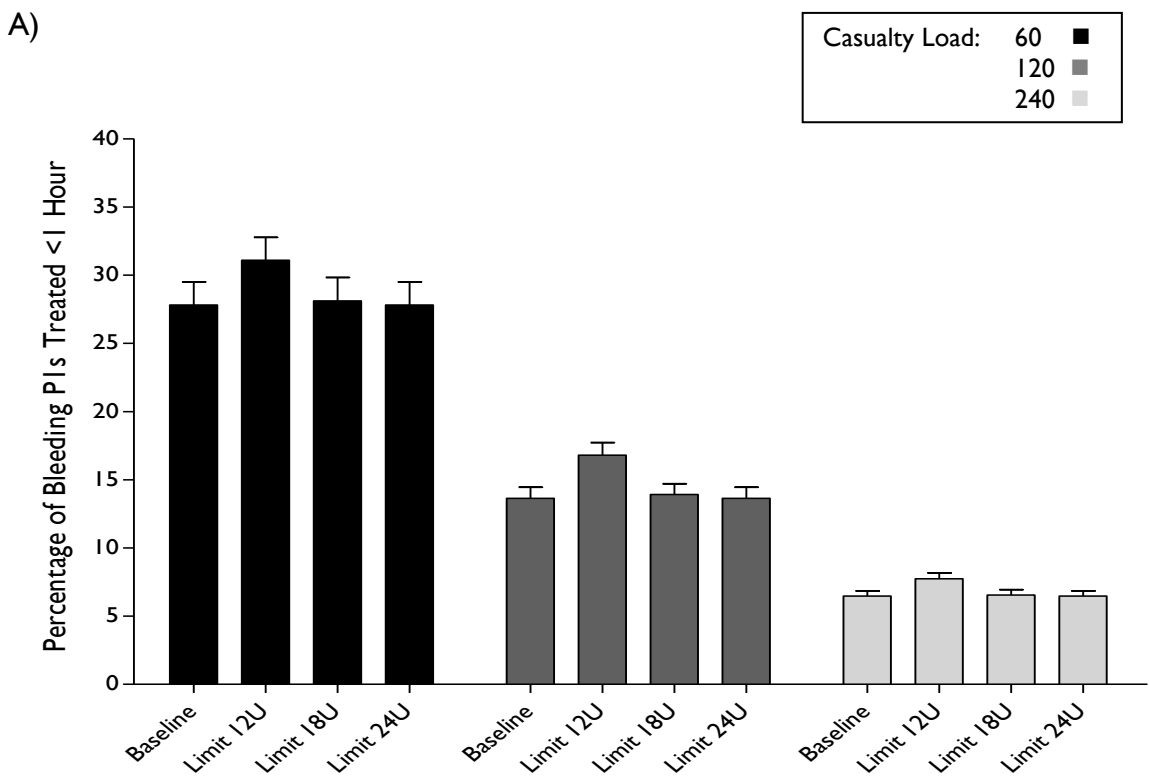
B)
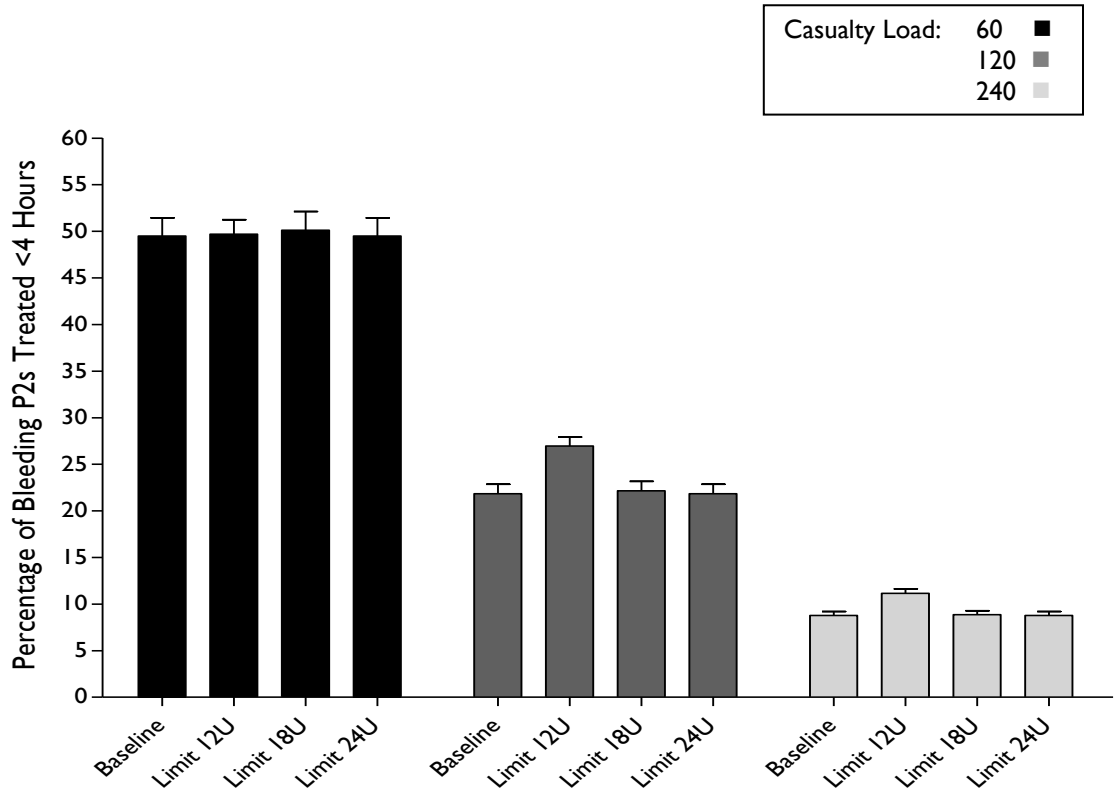
C)
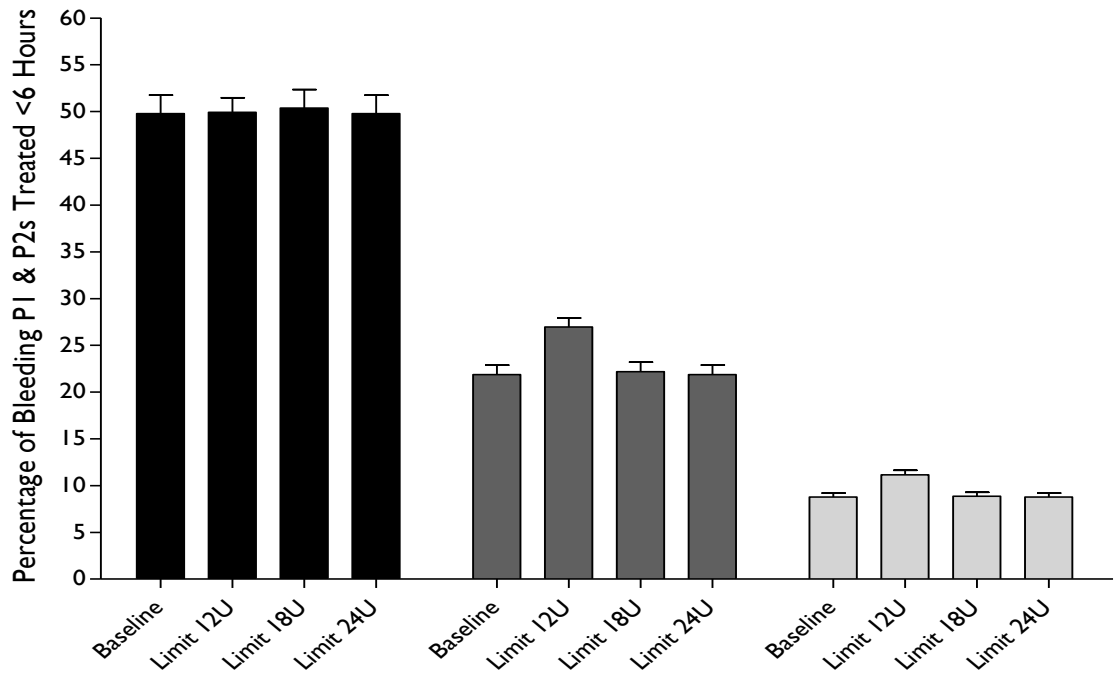
D)
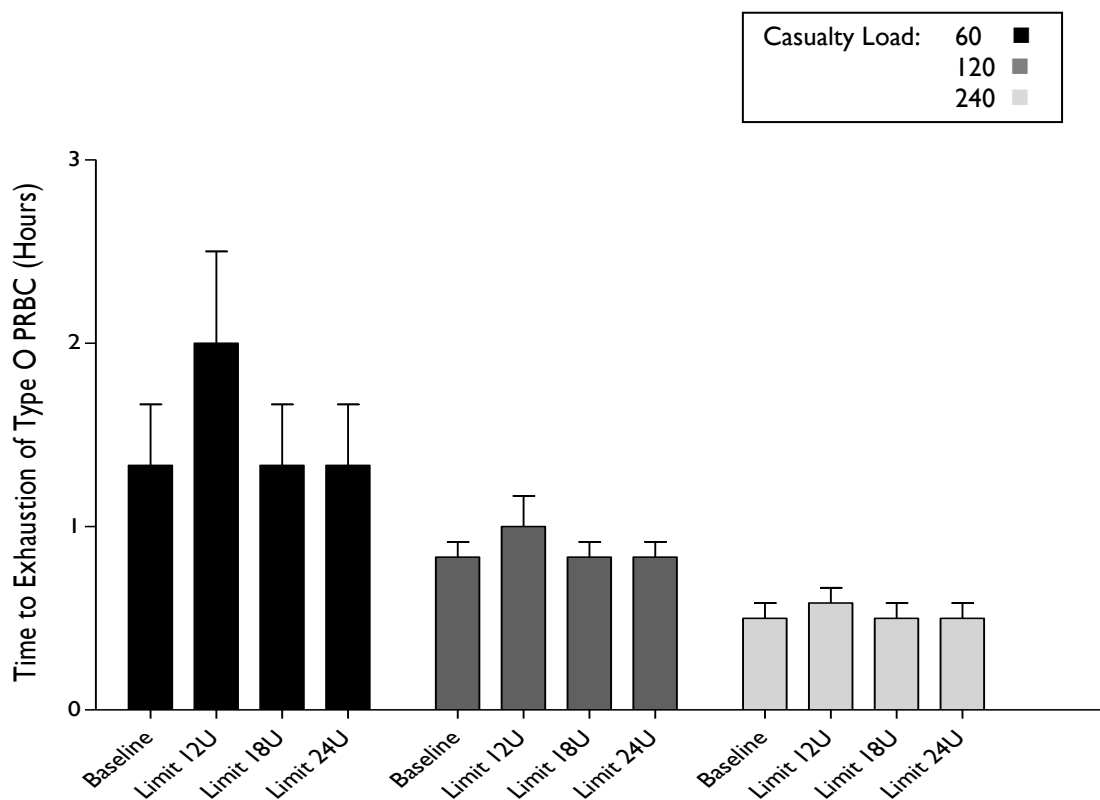
Figure 6.21 For casualty loads of 60 (■), 120 (■) and 240 (□), under increasingly restricted individual casualty PRBC allowance: A) The mean percentage of bleeding P1s treated under 1 hour, B) The mean percentage of bleeding P2s treated under 4 hours, C) The mean percentage of bleeding casualties treated under 6 hours, and D) The median time to exhaustion of type O PRBC supplies in hours from arrival of the first casualty into the model. Data are shown as means (95% CI) or medians (IQR) respectively.

Overall treatment rates within six hours were also considered and showed statistically significant increases of just over 5% and 2% respectively in the larger two of the three events considered with a 12U limit (Figure 6.21 C). This effect was also maintained when measured within 12 hours of arrival (Full tabulated results for all outcome measures considered across all casualty loads are provided in Appendix V). Furthermore, the 12U PRBC limit also displayed a statistically significant increase in the median longevity of type O PRBC supplies for all three event sizes beyond that observed under baseline conditions (Figure 6.21 D). This effect was greatest in the smaller of the three event sizes (60 casualty load) with supplies lasting around a third longer than under standard conditions.

The 12U limit performed the best when considering the three casualty loads described above, however, in smaller sized MCEs involving 20 or 40 total casualties, there was a detrimental effect observed amongst the overall bleeding casualty treatment rate by six hours (Figure 6.22). The treatment of bleeding P1s in less than an hour was observed to be significantly less than the baseline only once across all experiments, this was with a 12U limit and a 20 casualty load. For P2s treated under four hours this was exclusively the case in the 20 and 40 casualty loads and again with a 12U overall PRBC limit (Appendix V). The 60 casualty cohort appears to be the transition point in the model whereby imposing a limit on PRBC provision to individual casualties begins to improve overall outcomes from an event. This improvement is felt maximally at a casualty load of 120, where an over five percent gain in treatment of all bleeding casualties is observed. This would equate to the salvage of approximately a further four casualties out of around 80 suffering haemorrhage.
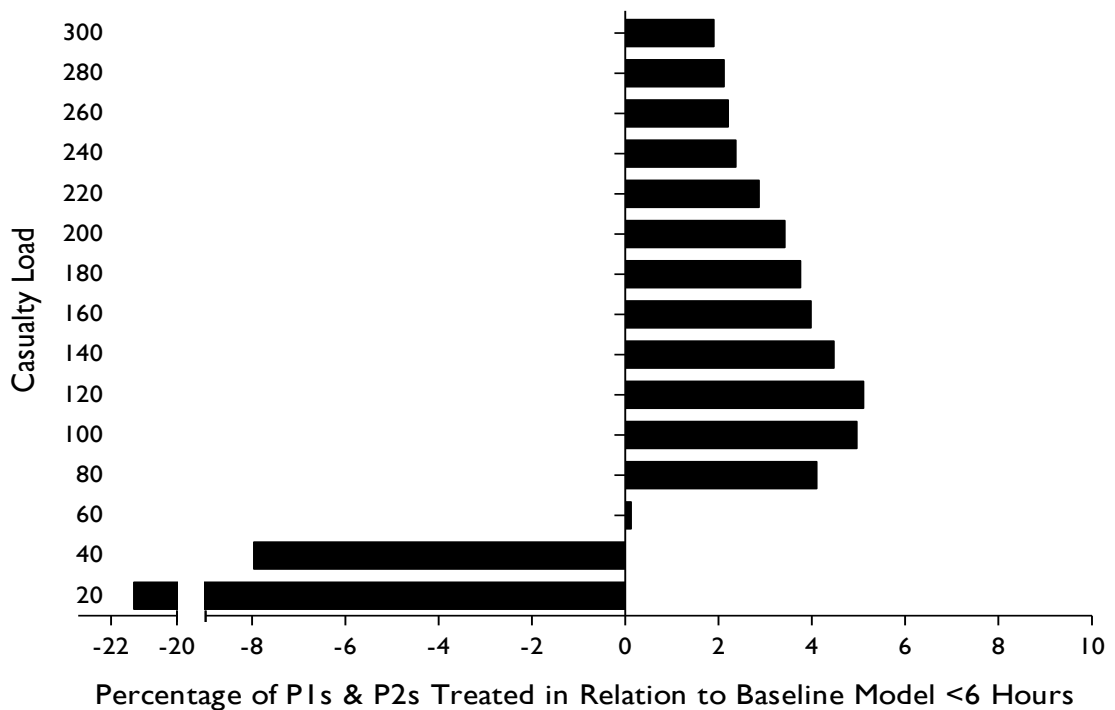
Figure 6.22 The mean percentage variation from the baseline model level for bleeding casualties treated within 6 hours of arrival at an MTC across casualty loads from 20-300 with a restriction of a maximum 12U PRBC permitted per individual casualty requiring transfusion.

6.4.2.iii Discussion

H_{6A} examined limiting individual bleeding casualties to a set volume of overall PRBCs received. The basis of this approach being to ensure the salvage of the greatest number of casualties possible in instances of limited stock, either through inadequate on-shelf supplies or an inability to restock them. A statistically significant improvement in all outcome measures was observed when PRBC supplies were rationed, supporting the first hypothesis of Aim Six. Although, whilst this practice produced a predominantly positive effect on outcomes, there remained a propensity for a detrimental effect on treatment levels to occur when the most effective strategy was employed in the smallest event sizes considered.

The model showed that applying a limit of 12U total PRBC provision to each bleeding casualty in events of magnitude greater than 40 has the potential to maximise available stock and achieve improved outcomes from an event compared with standard practice. Greater thresholds of PRBC limitation appeared to result in the loss of this perceived benefit, although without leading to any detrimental effects. This suggests that the volume of casualties with an individual PRBC demand in the model greater than 12U, is insufficient to compromise the demands of others. Events generating an increased mean individual PRBC demand may therefore shift the optimum threshold for limiting PRBC provision higher in order to maintain any improvement in overall outcomes.

The rationing of treatment in any healthcare scenario is contentious. Whilst the practice is common place in the pre-hospital setting of MCEs with regard to triage, in-hospital rationing of care is less well described. The primary issue with employing a strategy of limiting the PRBC allowance to arriving casualties at an MTC is that the gravity of the event, in terms of overall expected casualties, is often unclear during these early stages. As was described in Chapter One during the account of the London bombings of 2005, there was an announcement of a second wave of casualties expected from the event several hours after the initial attack. This information proved to be incorrect, but is an example of how

misinformation with the instigation of rationing strategies could have serious consequences on casualty outcomes.

Based on this, the benefit from a rationing protocol with regard to PRBC provision may come from ensuring only extreme cases are identified for limited treatment protocols, by setting the threshold at a more substantial level. The aim here would not be to necessarily improve outcomes by a small percentage, but prevent an outlying anomaly in terms of PRBC demands, from jeopardising overall casualty care through excessive consumption of available stock. An alternative measure may be to focus rationing techniques more on the supply of emergency type O PRBCs, especially given their critical importance in maintaining and improving outcomes illustrated throughout this study. The second hypothesis of Aim Six which follows investiagted the addition of this approach.

6.4.2 Experiment 6B – Limiting Type O Packed Red Blood Cell Provision (H_{6B})

'Overall outcomes can be further improved through additionally limiting all P1s to one 6U pack of emergency type O PRBCs, whilst also denying P2s treatment with this particular resource altogether.'

6.4.3.i Methods

The experimental model from H_{6A} was modified to ensure type O emergency PRBC provision was limited to P1s only and restricted to one pack of six units of PRBCs per casualty. This required the inclusion of five further components to the Emergency PRBC Provision sub-model. Firstly, two Decide modules were added at the entry and exit of the sub-model which checked the level of emergency type O PRBCs already provided. The entry Decide module prevented casualties progressing through the sub-model if they had

already reached the defined limit of provision. The exit Decide module led to an additional Assign module to label casualties as having reached the limit of provision if this was the case.

Secondly, two separate Assign modules were added within the body of the sub-model to update the level of emergency type O PRBC as it was provided. This ensured the defined experimental threshold was not exceeded as casualties were transfused. The same additional modules were added to all sub-models involving the provision of group-specific PRBCs where inability to meet demand would, under normal circumstances, be supplemented by any available emergency type O PRBCs. The additional modules in the context of the Emergency PRBC Provision sub-model are shown in Figure 6.23.
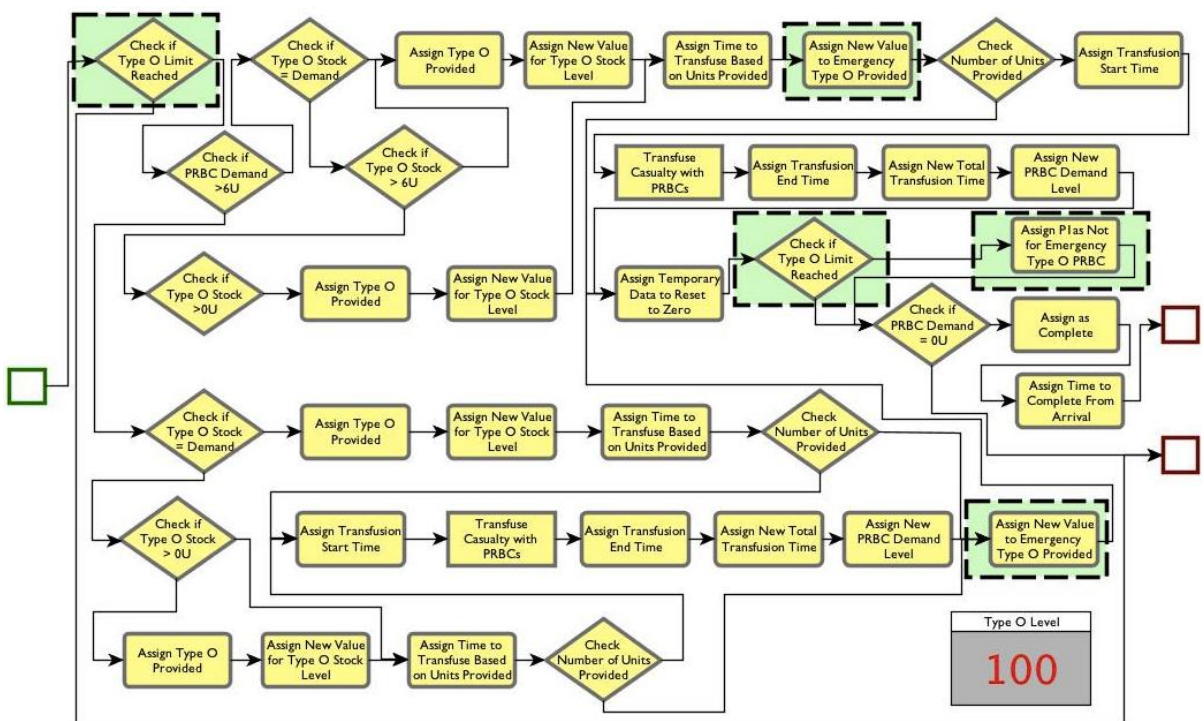
Figure 6.23 The Emergency PRBC Provision sub-model with added components (Highlighted Green) for investigating the effects of limiting emergency type O and overall PRBC supply.

The investigation of H_{6B} also required the further addition of two model components to the previously modified main model from H_{6A}. These were required in order to prevent P2

casualties from receiving emergency type O PRBCs. The first additional module was a Decide module to separate P1 and P2 casualties following the Patient Characteristic sub-model and prior to their progression to initial transfusion. The P1 casualties would continue as normal, albeit limited in their emergency type O PRBC provision, whereas the P2 casualties would enter the second additional module.

This second module was another Assign module used to mark P2s as having already reached their limit of emergency type O provision. This process therefore ensured P2s would only receive group-specific PRBCs as and when available (including type O where applicable). These two additional model components are shown in Figure 6.24. The experimentation was performed across all casualty loads with application of 12, 18 and 24U overall PRBC limits as per H_{6A}. The standard baseline data input values as described previously in Table 6.2 remained unchanged for all simulations performed.
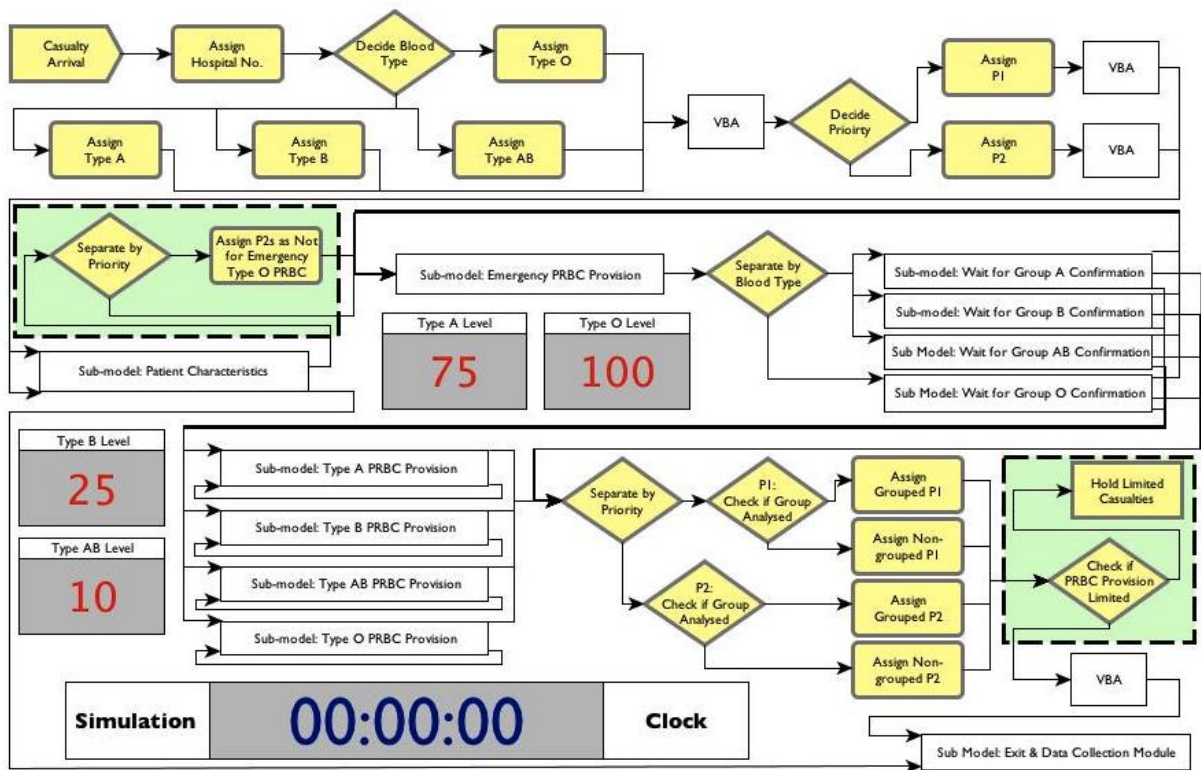
Figure 6.24 The main model with all added components (Highlighted Green) for investigating the effects of limiting emergency type O and overall PRBC supply.

6.4.3.ii Results

The investigation of H_{6B} required 6,000 simulation runs and over 32 hours of computer processing time to complete. For continuity, the three casualty loads applied during the description of H_{6A} of 60, 120 and 240 P1 and P2 casualties are applied again here to describe the effect of additionally restricting emergency type O PRBC provision. Application of this extended rationing protocol resulted in a further overall increase in treatment rates. There was a statistically significant increase detected with a 12U overall PRBC limit for all three casualty loads across all P1, P2 and combination treatment measures (Figure 6.25).

As was the case in H_{6A}, although limiting overall PRBC delivery to either 18U or 24U produced no statistical advantage over the unlimited baseline system, neither were there any detrimental effects observed with these restrictions at casualty loads greater than 40. The full experimental results of H_{6B} for all casualty loads from 20-300 are provided in tabular form in Appendix V.

The greatest improvement in treatment of P1s was observed in the 80 casualty load with a 12U limit, producing a six percent rise in bleeding P1s treated in full within one hour (Appendix V). This was double the largest improvement detected amongst the P1 casualties during investigation of H_{6A}. In addition, over a five percent improvement from the baseline model was observed in the treatment of P2s with the same casualty load of 80, equivalent to the largest advance observed amongst P2s in H_{6A}. Analysis of the combined treatment of bleeding casualties within the six hour measurement point also showed a universal statistically significant improvement. The addition of the emergency type O PRBC restrictions compared with both the baseline and the H_{6A} models for this outcome measure is shown through a selection of casualty loads in Figure 6.26.

A)

B)

C)
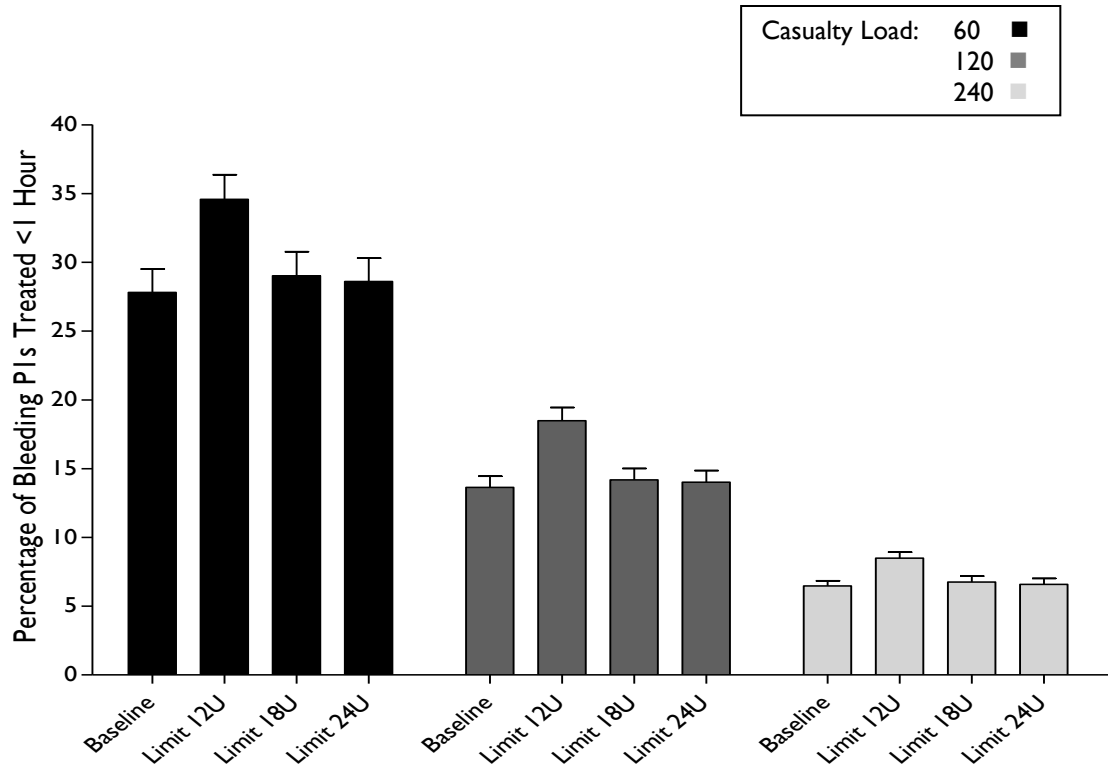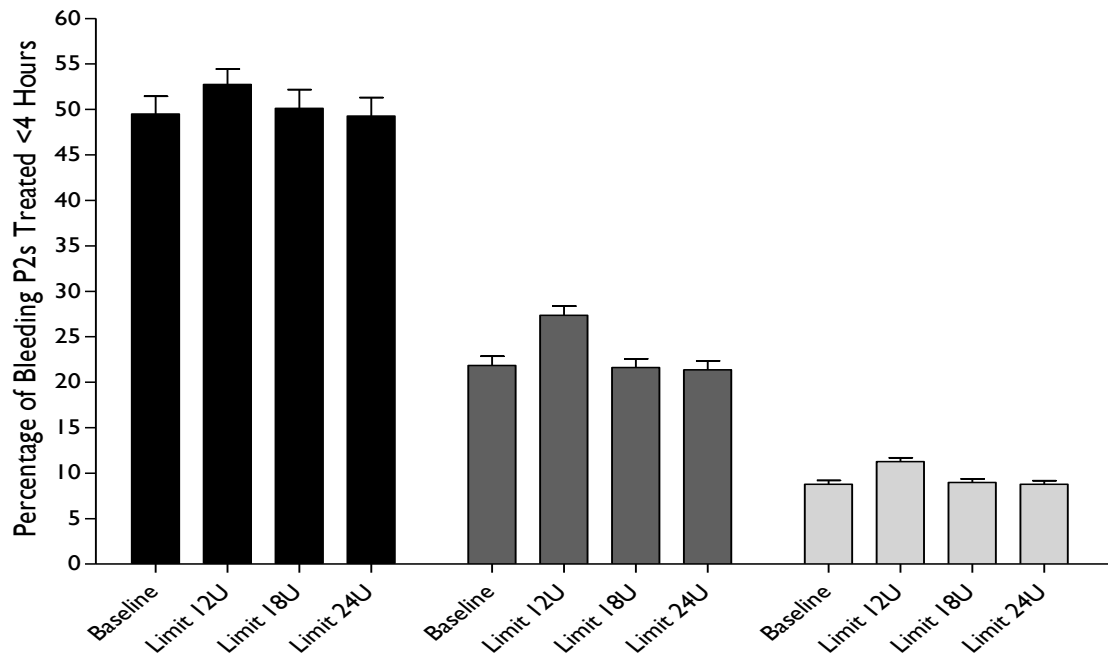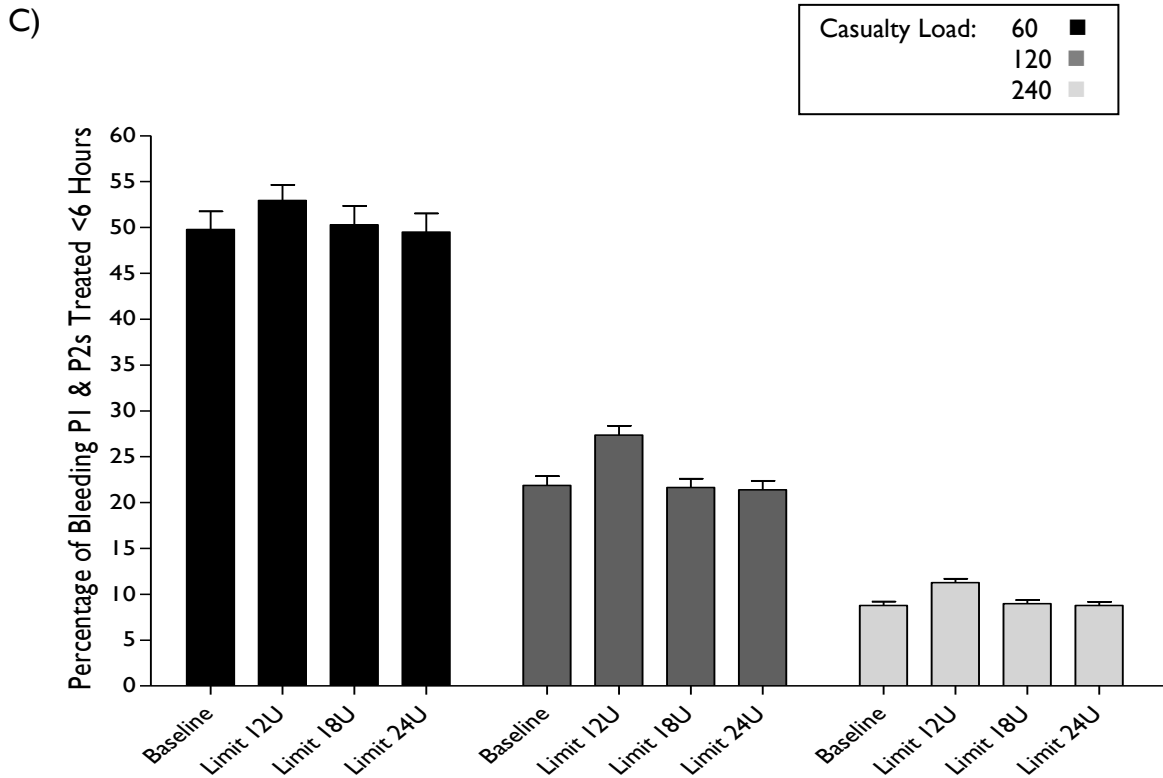
Figure 6.25 For casualty loads of 60 (■), 120 (■) and 240 (□), restriction of emergency type O PRBC provision to a maximum of 6U to P1s and denial of emergency type O to P2s in addition to an increasing overall PRBC provision restriction: A) The mean percentage of bleeding P1s treated under 1 hour, B) The mean percentage of bleeding P2s treated under 4 hours, and C) The mean percentage of bleeding casualties treated under 6 hours. Data are shown as means (95% CI).

The other principal study outcome measure of type O PRBC longevity was increased with limiting overall PRBC provision to 12U in H_{6A}, this was found to be further increased with the addition of the emergency type O restrictions of H_{6B} (Figure 6.27). Type O levels lasted approximately two and a half times longer than the baseline model and a third longer than that seen with a total PRBC limit alone. Furthermore, although no significant variation was detected in casualty treatment levels with higher limits of PRBC provision and emergency type O restrictions, there was a significant increase in time to exhaustion of type O stock at both the 18 and 24U limits compared to the baseline model.
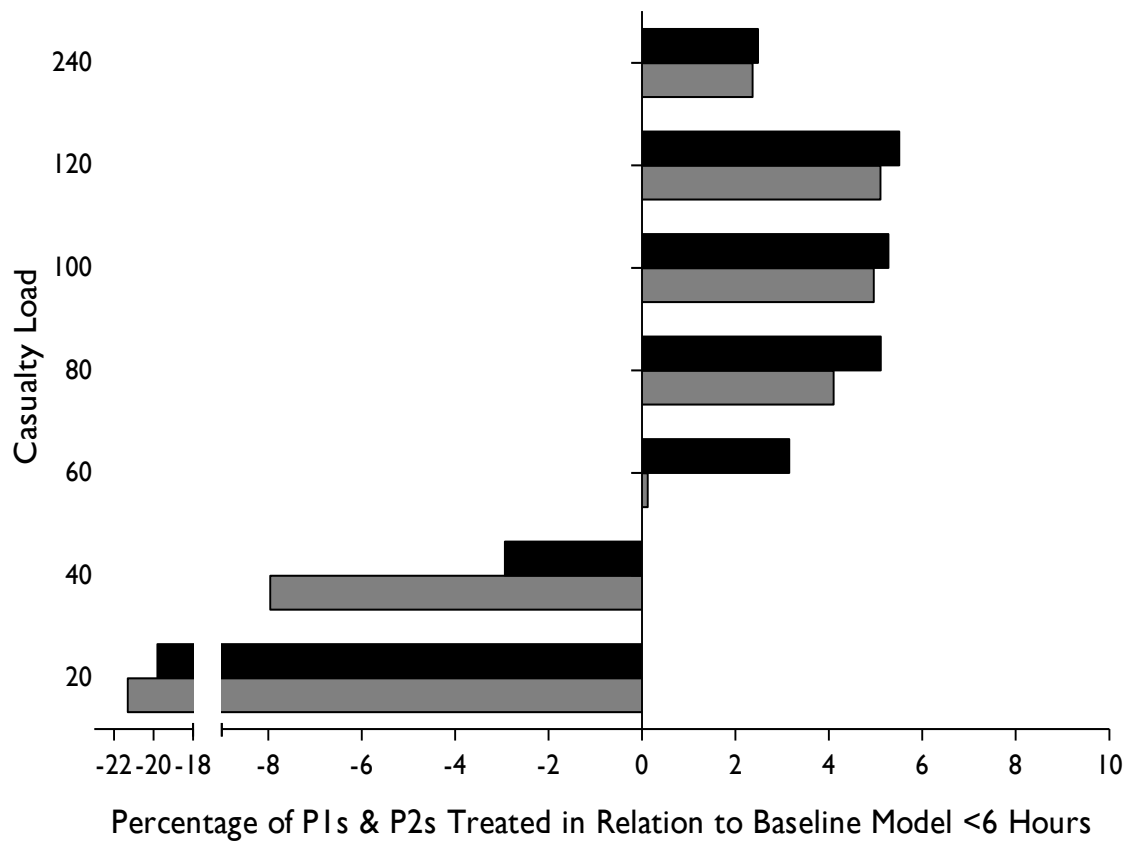
Figure 6.26 The mean percentage variation from the baseline of all bleeding casualties treated within 6 hours from arrival with limited overall PRBC provision (H_{6A}) (■) and limited overall PRBC provision as well as emergency type O PRBC restrictions (H_{6B}) (■).
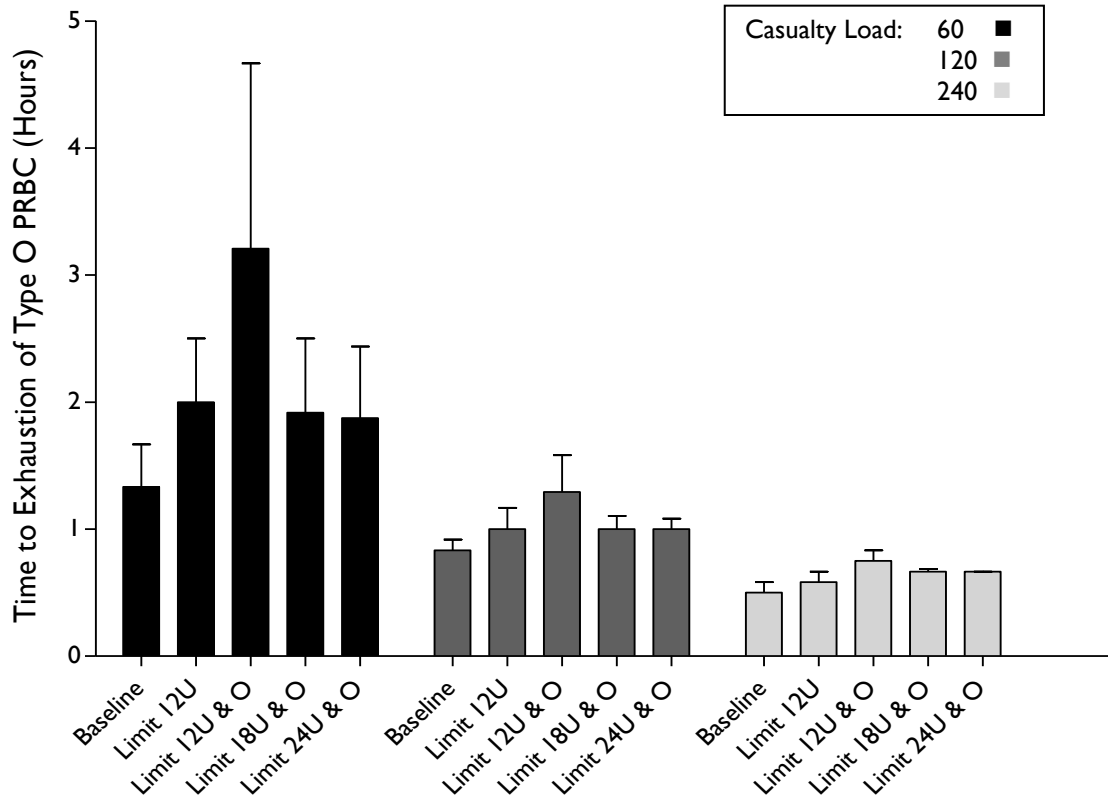
Figure 6.27 For the three casualty loads, the median (IQR) time to exhaustion of type O PRBC supplies in hours from first casualty arrival in relation to: The baseline model with no PRBC limits, The best performing experiment of H_{6A} with a 12U overall PRBC limit, and The restriction of emergency type O PRBC provision in addition to increasing overall limits (H_{6B}).

6.4.3.iii Discussion

These set of experiments overall support the H_{6B} hypothesis, having again shown in terms of the model, that limiting provision of PRBCs and in particular, valuable type O PRBCs can improve outcomes following an event when finite levels of stock are available. The addition of a limited provision of type O PRBCs caused an earlier shift towards a significant positive treatment response at lower casualty loads than observed in H_{6A}. In addition, it was possible

to significantly extend the longevity of type O PRBC supplies through application of the protocol; this would allow continued receipt of casualties requiring emergency transfusion following an event, where previously alternative treatment units would have needed to be sought.

The findings of this study have highlighted again the dependence the system has on levels of type O PRBC, an issue confounded by the high prevalence of this blood type in the population the model was designed around. Interestingly, the denial of type O PRBCs in an emergency form to P2s, failed to have any negative impact on their treatment levels within the defined four hours. As was identified in the restocking exercise of H_{4B}, P2s appear to tolerate the delay to determine their blood group without suffering significant treatment failures in the process. As discussed in the first part of Aim Six, rationing of supplies in-hospital is a contentious issue, however, the restriction of one aspect of PRBC provision in withholding type O PRBCs may offer a potential compromise planners and care providers would be willing to consider.

6.4.3 Aim Six Conclusion

Aim Six has identified potential strategies for maximising the use of available PRBC stock to improve outcomes under conditions of restricted stock. The results of the various experiments limiting individual casualty provision with all type and specifically emergency type O PRBCs appear to largely support the two hypotheses proposed. Although these practices are controversial given the unpredictable nature of MCEs, they offer greater insight into understanding the levers within the transfusion system which have the greatest influence on casualty outcomes. Whilst this investigation has satisfied the final aim of the thesis, there are a number of further possibilities which could be explored using this versatile model. Some of these are discussed along with the limitations of this work in the final chapter which follows.

CHAPTER SEVEN

Conclusion

7.1 Summary of Findings

This research study set out to achieve a specific objective; this was to improve understanding of blood use in mass casualty events (MCEs) and develop strategies to improve packed red blood cell (PRBC) provision to casualties across a range of event sizes and applied conditions using a mathematical modelling approach. The rationale for the study and its relevance to the field was established in Chapter One. This introduction described the concept of trauma as a disease process and its consequences in the context of MCEs, from both a financial and morbidity and mortality perspective. The description highlighted the potential burden of haemorrhage in these events and the importance of ensuring adequate in-hospital PRBC provision, in order to meet demand and minimise MCE associated mortality (38, 51). The imbalance between MCE based transfusion service contingency planning and the attention afforded to other blood planning emergencies such as pandemic influenza and seasonal blood shortages was also illustrated (140-149). Finally, Chapter One identified a series of six interconnected aims for: establishing a detailed understanding of MCE blood provision, developing a suitable and sound methodology with which to investigate the system and then, applying this methodology to cultivate potential strategies for improving outcomes, therefore satisfying the overall study objective.

Chapter Two accomplished the first aim of investigating the use of blood in MCEs from a historical perspective in order to understand the challenges and controversies associated with casualty blood provision. This involved performing a comprehensive literature review spanning 100 years of events. An imbalance between the number of reported events and their discussion of blood product provision, especially concerning non-red cell components was identified. Despite this, the study was able to establish an association between the volume of severely injured casualties and the overall PRBC demand during related events. Notably, the majority of this PRBC demand ($^2/_3 - ^3/_4$) was found to occur within the first four hours. This early strain on the system, combined with increased emphasis on the use of

major haemorrhage protocols (MHP) in trauma has the potential to challenge, if not completely overwhelm, the treating ability of responding centres, a belief previously thought inconceivable (205).

Chapter Three discussed the modelling strategy and the design of a discrete event simulation (DES) model for experimenting with the system. This would allow the development of transfusion based strategies for coping with the MCE related issues identified in Chapter Two. The chapter highlighted the benefits of a mathematical modelling approach to the problem given the practice's financial and resource efficiency, inherent versatility and the experimental freedom it offers investigators (163, 174, 243). A suitable software program in the form of Arena Simulation (Rockwell Automation, Pittsburgh, USA) was then selected based upon the study objective and application of industry recommended guidelines for evaluating potential software candidates. The theoretical design of the model was subsequently described in detail along with the method by which it was translated into the Arena modelling environment. This process provided a framework for the model which in order to function effectively, required populating with the various data inputs necessary to drive it. Only then could the model be fully evaluated for experimentation.

Chapter Four established the inputs for all definable fields within the model framework developed in Chapter Three. This included all resource numbers, probability distributions and mean values required to ensure the model provided a realistic representation of the real-world system. This exercise produced a working mathematical model of in-hospital MCE PRBC provision and therefore fulfilled Aim Two of the thesis. The process involved several sub-studies in its completion, including a further literature review, interrogation of both civilian and military trauma datasets and a questionnaire based study of all four London major trauma centres (MTC(s)).

As well as supporting previously held beliefs regarding MCEs, such as the early surge in arrivals following an event, these studies also led to a number of original findings. Firstly, individual priority one (P1) and two (P2) casualty PRBC demands were characterised, establishing a mean demand in the distribution of over ten and four units respectively per

casualty. Secondly, a significantly high rate of haemorrhage was identified amongst the P1 cohort, with 80% requiring a transfusion and emphasising why haemorrhage represents such a major source of potentially preventable mortality in these events. Finally, the variation in ratio of P1 to P2 casualties amongst overall MCE casualty loads was revealed, showing a preponderance towards P1s specifically in terror related MCEs, which along with the data on MCE casualty transfusion processing times, has not been previously reported in the literature. Having developed the working model and established the inputs to drive it, an evaluation of model performance could be undertaken; this therefore formed the focus of Chapter Five.

Chapter Five satisfied Aim Three of the study through a rigorous evaluation of the model, applying industry set guidelines to verify, test and validate the methodology for the experimentation process. The model performed to an acceptable standard when directly compared to the largest UK based MCE in recent history. Both bleeding casualty treatment times and end levels of individually grouped PRBC stock showed no significant difference between real life and the model, developing greater overall confidence in the model's performance.

The final part of the evaluation process included a sensitivity analysis, which comprised the first experimental exercises to be performed using the model. The principal study outcome measures of the percentage of bleeding casualties treated and time to type O PRBC exhaustion, showed greatest sensitivity to variations in the P1:P2 ratio, the total casualty load, the casualty bleeding rate, the level of individual PRBC demand and the initial on-shelf PRBC stock hold. These findings not only fostered a greater understanding of PRBC provision in MCEs, but also provided an early insight into which of the proposed strategies suggested in the final three study aims, had greatest potential for improving overall outcomes from an event.

Chapter Six saw the completion of Aims Four, Five and Six of the thesis through the investigation of their respective experimental hypotheses. This experimentation phase of the study involved approximately 70,000 individual simulations and required over 400 hours

of computer processing time to complete. Each of the final three aims centred on a particular theme in the provision of PRBC during an MCE. Aim Four was concerned with stock management in terms of the volume held on-shelf and the ability to restock supply. The stock hold at an MTC was one of the five leading influencing factors in the sensitivity analysis of Chapter Five and of these, the most accessible for planners to control for future events.

Standard MTC on-shelf stock levels were found to be inadequate even in the smallest event sizes considered, with a critical ratio of PRBC availability to casualty load identified. The model indicated a requirement of approximately 12U of PRBC per P1 and P2 casualty received at an MTC to avoid rapid exhaustion of emergency type O supplies and therefore overwhelming a centre's capacity to respond. Contextualising this, the RLH, the busiest of all MTCs involved during the London bombings of 7th July 2005, utilised 164U of PRBC during the initial event response. This volume of PRBCs was consumed by just seven casualties suffering acute haemorrhage, all of whom were categorised as P1s. Although the RLH received three restocks of PRBC on the first day, given the starting on-shelf volume was over 300U of PRBC, the available volume of PRBC including type O emergency PRBC would have been sufficient to manage the casualty load without additional supplies.

Comparing that event with the smallest MCE experimented with in this study of 20 P1 and P2 casualties, equivalent to approximately 14 bleeding casualties (10P1 and 4P2) and therefore twice that of 2005, the minimum requirement of on-shelf PRBC to meet a critical demand volume of 12U per P1 and P2 received, equates to around 240U. Bearing in mind the level of PRBC held on-shelf across all MTCs in the UK has fallen over the past decade, with current levels approximately two thirds that of 2005, this illustrates both the relative accuracy of the model in its overall demand predication, as well as, the present potential danger today for MTC blood systems to become overwhelmed with an event only marginally larger than that of the London bombings.

This would suggest restocking supplies during an event is therefore crucial to ensuring optimal event outcomes. The reliance on this solution may explain why there is a lack of

declared PRBC supply exhaustion reported in the historical literature (118, 124, 126, 129, 153). This practice may however be challenged in future events with more prolonged periods of threat, as seen in Mumbai, Oslo and most recently Paris, which could potentially prevent any restocking of supplies from taking place (159-161). Experimentation with the restocking of PRBC supplies during an event was found to be effective if performed in a timely enough manner to meet the early surge in demand these events create. Delays experienced whilst PRBC supply centres wait for hospital requests for blood could potentially jeopardise overall outcomes from events and moving to a push over pull approach to restocking may help in ameliorating this threat.

Aims Five and Six focused on strategies for improving outcomes primarily in settings of limited stock or, as in the scenarios alluded above of a reduced restocking capability. Aim Five followed a theme investigating transfusion laboratory processing, examining two approaches to modifying the handling of blood samples to improve overall event outcomes. The first of these involved prioritising the grouping of P2 casualty blood samples over P1s to reduce their consumption of valuable type O stock. The second approach was based on P1 casualties' dependence on this type O stock for meeting their demands within a highly restricted time window. This experiment investigated whether given this; bypassing P1 blood group analysis altogether would relieve the laboratory work burden generating a more efficient system.

Whilst a statistically significant improvement was identified in the former, the practical application did not appear to translate into a meaningful improvement worthy of policy change. Conversely, the latter experiment showed an overall detrimental effect on overall outcomes, suggesting the predominantly automatic nature of blood sample processing does not present a major bottleneck in the system. A theory supported by the sensitivity analysis of Chapter Five.

The final theme surrounding the experiments of Aim Six was focused on the rationing of resources, applying the MCE mantra of providing 'the greatest good for the greatest number' (84, 87, 102) . Firstly, through limiting overall PRBC provision to any single casualty

and secondly, through additionally restricting initial access to emergency type O PRBCs. Both policies resulted in significant improvements at a specified limit of provision, with the addition of an emergency type O restriction displaying a further benefit to an overall individual PRBC limit. The advantage of the first strategy appeared to come from concentrating on those few casualties whose individual demand for PRBCs far exceeded the population mean – an occurrence well documented in the literature (70-73). Whereas the second strategy further improved outcomes through allowing access to emergency PRBCs for a restricted time, effectively bridging the gap till blood type could be confirmed and group specific treatment initiated. The challenge here however, is the applicability of such a solution given the limited accuracy of any information predicting expected casualty numbers, especially early in an event when any such rationing protocol would be most effective.

7.2   Study Limitations

This study applied mathematical modelling techniques in investigating the provision of PRBCs to bleeding casualties following an MCE. In accomplishing the overall study objective through the individual aims discussed in the previous section, a number of specific limitations were recognised in the methods employed during the study and through their experimental application. These were acknowledged in each respective chapter; however, in addition, there are a number of more general limitations to the overall study design which should be appreciated when interpreting the results of this work.

First and foremost of these is the need to appreciate that the study results for the final three aims of this thesis relate to a model of an MTC transfusion system. They do not represent experiments performed in real life and therefore, must be interpreted in the context of the system as a whole, including accounting for external influences which lay outside of the explicit boundaries of the model. This issue may be heightened by the use of

software programs such as Arena, which incorporates a visual interactive simulation (VIS) approach. This method is known to increase the susceptibility of the user to interpreting the simulation outputs as reality, having directly observed the passage and behaviour of entities as they advanced through the model (163).

Secondly, it is important to discuss the outcome measures utilised within the model. The definition applied to represent an adequate level of care for bleeding casualties was that of full receipt of their PRBC demand within one hour for P1s and four hours for P2s. These defined timescales adapted from the literature are in reality, the period of time during which a casualty's required medical intervention (such as transfusion) must commence, as opposed to necessarily completing it (87). This was reflected in the model outputs through the inability to completely treat all P1s within one hour despite a plentiful supply of PRBCs being available. Nevertheless, applying this adapted standard as an assessment of casualty care, provided a suitable treatment target and a quantifiable measure for interpreting system performance and comparing outcomes between the various scenarios considered.

The final general limitation of the study to mention surrounds the assumptions and boundaries applied to the model. Many of the assumptions discussed in the model's development were applied in order to maintain simplicity in the system. This was done to meet the objective of, not only developing transfusion based strategies for MCEs, but also, to improve our understanding of the system as a whole. For instance, capacity in terms of medical staffing was not incorporated into the model, despite the fact this would likely become a significant issue when considering the more extreme casualty loads experimented with. Conversely, system elements which were not included in the model but could be significant even in more conservatively sized events include system errors and the provision of components other than PRBCs.

System errors such as blood sampling mistakes are not uncommon in these events and with dependence on automated systems there is always the potential for machinery to breakdown or malfunction (138). The latter could have potentially catastrophic effects on system capacity and efficiency, as tasks are required to be performed manually by a limited

number of staff. The impact of a change in staff numbers in this instance could be much more significant than observed during the model's sensitivity analysis of Chapter Five. In order to determine the effectiveness of the proposed improvement strategies, it was felt experimentation would be most appropriately performed under error-free system conditions. Then, should an applicable solution be identified, such errors could be introduced. This was therefore an aspect of the model considered for future work as discussed in the following section of this chapter.

The decision to model exclusively the provision of red cells was in the first instance to determine whether an MCE based transfusion model would work and be practical in terms of future planning. The other rationale for this was that given the relatively recent advances in managing traumatic haemorrhage through early coagulation therapies, accurate data with which to inform any such inclusive model would be highly limited, a theory which was subsequently confirmed in Chapter Two. Nevertheless, it must be recognised that current damage control resuscitative techniques rely heavily on the provision of components such as fresh frozen plasma, cryoprecipitate and platelets, without which, PRBC consumption may be significantly increased along with event critical mortality (28, 69, 73).

Despite these limitations a practical model of an MTC transfusion system was designed and developed in-line with the study objective through a fully transparent process using industry recommended best-practice guidelines. The model was thoroughly verified, tested and validated to ensure it was fit for purpose and the conclusions drawn from the experimental results suggest it to be accurate representation of reality.

7.3 Recommendations and Future Work

This research has developed our overall understanding of the provision of PRBCs in MCEs and identified areas of potential development for improving outcomes from these challenging events. Specifically, the model was used to examine system performance through modifications to stock management, transfusion laboratory processing and individual casualty resource provision policies. Future work in this field should aim to develop these themes as well as the methodology of mathematically modelling MCE blood provision further, especially with regard to the whole spectrum of blood products utilised in the management of traumatic haemorrhage.

The apparent inability to meet the PRBC demands of bleeding casualties under standard stock conditions even in the smallest event sizes considered would suggest events of an even lesser size should be investigated in greater detail. This should include examining non-MTC type centres to ascertain their capability to assist in an MCE response. The results of early restocking of supplies observed in the model were encouraging for avoiding the necessity of holding excessive on-shelf stocks in readiness for an event, however, further work should be considered into the logistics and challenges of adopting a push over pull approach between MTCs and regional blood providers.

Although variations in laboratory processing procedures in the model exerted little effect on outcomes a variety of areas warrant greater investigation. As alluded to in the limitations of the study, the current MTC system is highly dependent on automated machine processes. Investigation of the effect of machine and human errors on casualty treatment rates would assist in establishing robust contingency plans for future such failures during an event. The study of manual processing would also benefit those institutions with less advanced technology in determining optimum staffing levels should the need arise for such centres to respond to these events.

Rationing of any in-hospital resource is controversial, however in certain circumstances, such as an inability to restock supplies or an overwhelming demand from casualties, such strategies may become necessary and understanding optimal thresholds in these instances would be crucial to optimising outcomes. The issue with this is the lack of accurate information available early in the event. Development of improved predictors of expected casualty loads and severities may ameliorate this issue allowing such resource rationing policies to be instigated. For the time being, alternative strategies should be sought.

The model analysis indicated that along with stock availability, the proportion of P1 casualties received is one of the leading factors in determining treatment levels. Rather than rationing care in-hospital, rationing hospital access may be more effective. This would involve the triaging of only P1s to resource rich MTCs where most emergency type O PRBC is available. P2s would instead be transferred to second tier trauma centres for treatment using group specific PRBCs, capitalising on the extended time window within which these casualties require treatment.

In terms of developing the model, this research has clearly illustrated the financial and logistical benefits of applying a simulation modelling methodology to blood planning. The evolving practice of treating major haemorrhage with protocol driven high dose coagulation therapy demands the consideration of non-red cell components in any future model of this type and represents the most important step in any further addition to the simulation architecture. Modelling the provision of frozen blood components such as plasma or cryoprecipitate during periods of demand surge would require the inclusion of a blood component thawing process within the simulation. This has the potential to have far reaching effects in terms of meeting overall blood demands as well as doing so within the time constraints applied throughout this study.

Furthermore, whilst frozen products may be available in their required quantity and the limiting factor in their provision focused around their pre-provision preparation, other products such as platelets are in much more finite supply. Meeting the demand volume required to provide a 1:1:1 transfusion strategy of PRBCs, plasma and platelets as

recommended in certain studies may therefore be impossible in MCE scenarios (59-61). The combined effect of these factors could ultimately increase mean PRBC requirements of individual casualties and therefore the time required to treat them. Based on the findings of this study, a simulation modelling approach maybe the most suitable approach for solving such a complex system.

7.4   Closing Remarks

MCEs have increased in frequency, severity and longevity in recent years. There is a risk that in the future the provision of current transfusion therapy will be overwhelmed by casualty demand. Contingency planning strategies are required to respond to this demand as well as for managing the response during scenarios of limited resource availability. Computer models such as the one developed here using DES, offer advantages both financially and logistically to planners in emergency preparedness and MCE response. This research has provided greater insight into MCE transfusion systems and the levers within these systems which can effect greatest change. Further development of this methodology has the potential to reduce critical morbidity and mortality from these destructive events.

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APPENDIX I

Full Search strategy for the comprehensive literature search of historical blood provision and use following civilian MCEs performed as a part of Chapter Two .

Population: Victims of Mass Casualty Events (MCEs)

- Free-text search terms:

  "Mass Casualty" OR "Mass Casualties" OR "Multiple Casualty" OR "Multiple Casualty" OR Emergenc* OR Disaster* OR Attack* OR Fight* OR Battle* OR War OR Conflict* OR Catastroph* OR Bomb* Terror* OR Collapse OR Explosi* OR Blast OR Blasts OR Shoot* OR Destroy* OR Suicide OR Fire OR Crash* OR Incident* OR Accident* OR Crowd OR Gathering OR Casualt* OR Riot* OR Protest* OR Violen*.

'AND'

Intervention: Blood descriptors, provision or indication of requirement

- Free-text search terms:

  Blood* OR "Red Cell" OR "Red Cells" OR Bleed* OR H?emorrhage OR Transfus* OR Wounds OR Wounded* OR Injur*.

Boolean operators were applied between search terms and subject groups as above with the use of truncation (*) to allow for similar terminology and wildcards (?) for language variations.

Applicable MeSH headings encompassing the free-text terms above were additionally applied in PubMed and Medline via the NCBI and NHS Evidence search engines respectively. These included:

(Violence[MeSH Terms]) OR (War[MeSH Terms]) OR (Weapons[MeSH Terms]) OR (Disaster[MeSH Terms]) OR (Civil Defense[MeSH Terms])

'AND'

(Blood[MeSH Terms]) OR (Transfusion[MeSH Terms]) OR (Hemorrhage[MeSH Terms])

Limitations: The following limits were applied across all searches where possible:

- Publication date (online or in print) had to lie between 01-11-1911 – 31-10-2011 inclusive
- Articles had to be in the English language
- Only humans based studies were permitted
- Described events were required to be predominantly civilian in nature

Results:

Search Engine	Citations
PubMed	(5043)
Medline	(7453)
AMED	(140)
BNI	(82)
CINAHL	(3474)
EMBASE	(8011)
Health Business Elite	(421)
HMIC	(137)
NYAM	(7)
Google Scholar	(6250)
BASE	(238)
ERIC	(7)
Total Results	**31,263**

Literature Search Total Results: 31,263

Total Articles Excluded: 2,020

Results Post Removal of Exlcusions & Duplicates: 29,243

Total Articles Excluded: 29,671

Abstracts Shortlisted from Search Results: 1,592

Total Articles Excluded: 31,001

Additional Articles Reviewed from Full Text Reference Lists: 15

Total Full Text Articles Independently Reviewed: 262

Total Articles Excluded: 31,244

Total Articles Included in Literature Review: 34

Critical appraisal by two independent reviewers was performed in line with the recommendations laid out by the Critical Appraisal and Skills Programme (CASP), Oxford, UK (http://www.casp-uk.net/).

APPENDIX II

The long-list of simulation software packages considered for the study

Software	Vendor
aGPSS	Beliber AB
Analytica 4.4	Lumina Decision Sytems Inc.
AnyLogic Simulation Software and Services	AnyLogic North America
ArenaSimulation Software	Rockwell Automation
Bluesss Simulation System	Stanislaw Raczynski
Capacity Planning Simulator	ProModel Corporation
Clinical Trials Simulator	ProModel Corporation
CSIM20	Mesquite Software, Inc.
Enterprise Dynamics	INCONTROL Simulation Solutions
Enterprise Dynamics Airport	INCONTROL Simulation Solutions
Enterprise Dynamics Logistics	INCONTROL Simulation Solutions
Enterprise Dynamics Plato	INCONTROL Simulation Solutions
Enterprise Portfolio Simulator (EPS)	ProModel Corporation
ExpertFit	Averill M. Law & Associates
ExtendSim AT	Imagine That Inc.
ExtendSim OR	Imagine That Inc.
ExtendSim Suite	Imagine That Inc.
FlexSim	FlexSim Software Products Inc.
FlexSim Healthcare	FlexSim Software Products Inc.
Fluid Flow Simulator	Stanislaw Raczynski
ForeTell-DSS	DecisionPath, Inc.
GoldSim	GoldSim Technology Group
Integrated Performance Modelling Environment (IPME)	Alion Science and Technology MA&D Operation
LABAMS	LABAMS
MAST	CMS Reasearch Inc.
MedModel Optimization Suite	ProModel Corporation
Micro Saint Sharp	Alion Science and Technology
Oracle Crystal Ball Suite	Oracle Americas Inc.
Patient Flow Simulator	ProModel Corporation
Portfolio Simulator	ProModel Corporation
Process Simulator	ProModel Corporation
Project Simulator	ProModel Corporation
ProModel Optimization Suite	ProModel Corporation
Proof 3D	Wolverine Software
Proof 5 (2D Animation)	Wolverine Software
QMS (Quantitative Methods for Management)	QuantMethods
SAIL	CMS Reasearch Inc.
SAS Simulation Studio	SAS
Service Model Optimization Suite	ProModel Corporation
ShowFlow	Webb Systems Ltd.
Simcad Online	CreateASoft Inc.
Simcad Pro	CreateASoft Inc.
Simio Design/Team Edition	Simio LLC
Simio Express Edition	Simio LLC
Simio Scheduling / Risk Analysis	Simio LLC
SIMPROCESS	CACI
SIMSCRIPT III	CACI
SimTrack Real Time Visibility and Analysis	CreateASoft Inc.
SIMUL8 Professional	SIMUL8 Corporation
SIMUL8 Standard	SIMUL8 Corporation
SIMUL8 Web	SIMUL8 Corporation
SLIM	MJC2
SLX	Wolverine Software
Vanguard Business Analytics Suite	Vanguard Software
Vanguard System	Vanguard Software
Vector Economics Platform	Vector Economics Inc

List collated from the eighth edition of the INFORMS simulation software survey 2011 (179).

APPENDIX III

The probability distributions available in Arena from which model components may be programmed to sample from during a simulation run. The distributions given here are also available in Arena's Input Analyzer for fitting external datasets to an applicable sampling distribution.

Beta (BETA)

Probability Density Function

Inputs: (β, α)

$$f(x) = \frac{x^{\beta-1}(1-x)^{\alpha-1}}{\mathrm{B}(\beta, \alpha)}$$

$$(for\ 0 < x < 1)$$

Continuous (CONT)
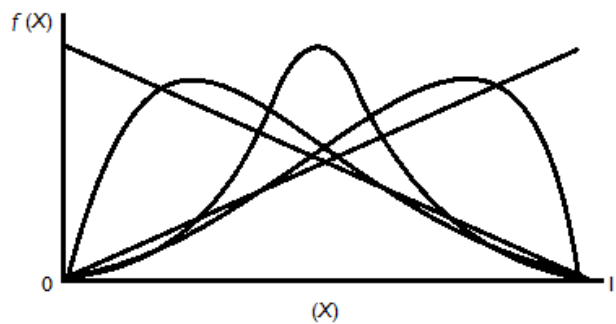
Cumulative Distribution Function

Inputs:

$(Cumulative\ Probability\ 1, Value\ 1 ....)$

$$f(x) = c_1\ \ if\ x = x_1$$

$$(a\ probability\ of\ c_1\ at\ x_1)$$

Discrete (DISC)

Cumulative Distribution Function
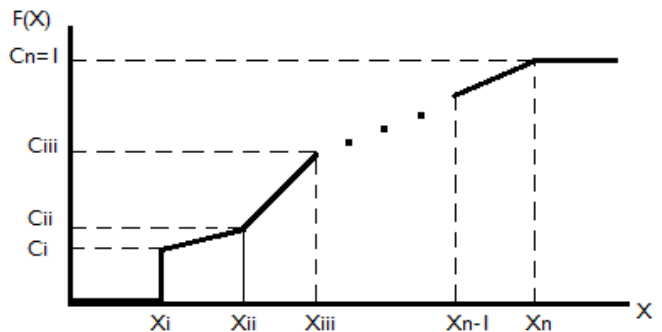
Inputs:

$(Cumulative\ Probability\ 1, Value\ 1 ....)$

$$p(x_j) = c_{1j} - c_{j-1}$$

$$(where\ c_0 = 0$$
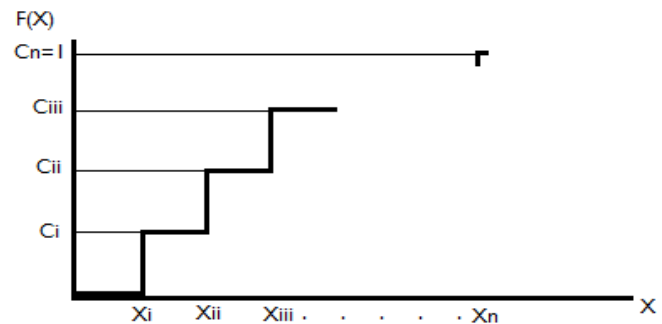
Erlang (ERLA)

Inputs: $(ExpMean, \kappa)$

$$f(x) = \frac{\beta^{-\kappa} x^{\kappa-1} e^{-\frac{x}{\beta}}}{(\kappa - 1)!}$$

$$(for\ x > 0)$$

Probability Density Function
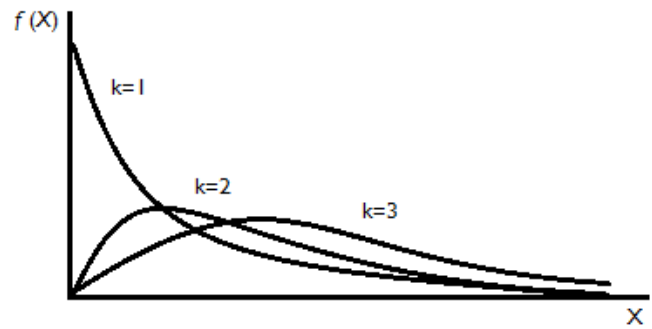
Exponential (EXPO)

Inputs: $(ExpMean, \kappa)$

$$f(x) = \frac{1}{\beta} e^{-\frac{x}{\beta}}$$

$$(for\ x > 0)$$

Probability Density Function
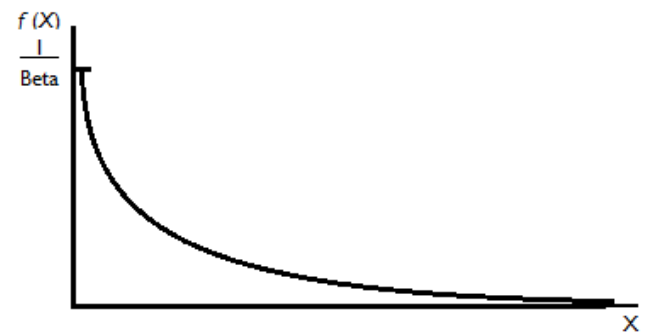
Gamma (GAMM)

Inputs: (β, α)

$$f(x) = \frac{\beta^{-\alpha} x^{\alpha-1} e^{-\frac{x}{\beta}}}{\Gamma(\alpha)}$$

$$(for\ x > 0)$$

Probability Density Function
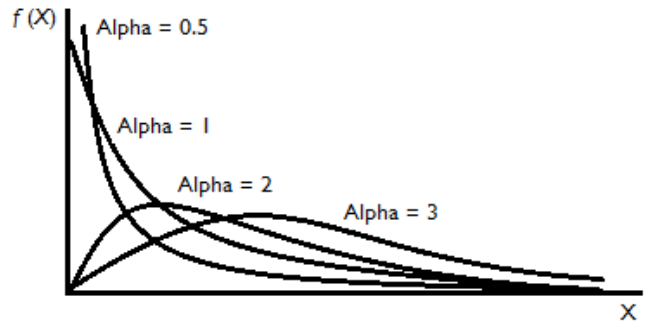
Johnson (JOHN)

Inputs: $(\gamma, \delta, \lambda, \xi)$

$$\gamma, \delta - shape$$
$$\lambda - scale$$
$$\xi - X_i\ location$$

Probability Density Function

Bounded   Unbounded
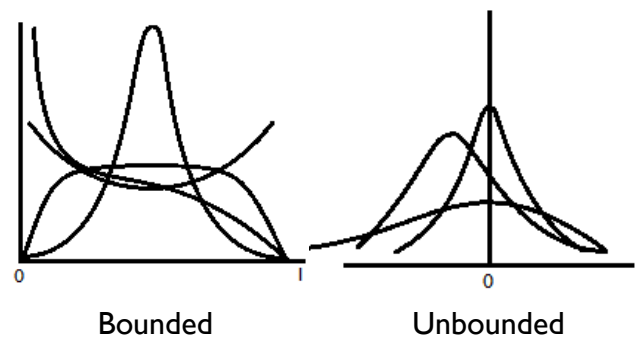
Lognormal (LOGN)

Inputs: $(LogMean, LogStd)$

$$f(x) = \frac{1}{\sigma x \sqrt{2\pi}}\, e^{-(\ln(x) - \mu^2/(2\sigma^2)}$$

$$(for\ x > 0)$$

Probability Density Function
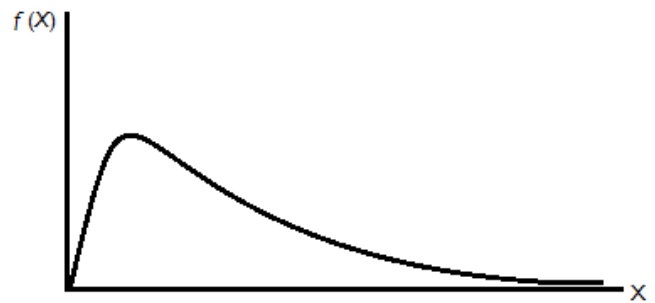
Normal (NORM)

Inputs: $(Mean, StdDev)$

$$f(x) = \frac{1}{\sigma \sqrt{2\pi}}\, e^{-(x-\mu)^2/(2\sigma^2)}$$

$$(for\ all\ x)$$

Probability Density Function
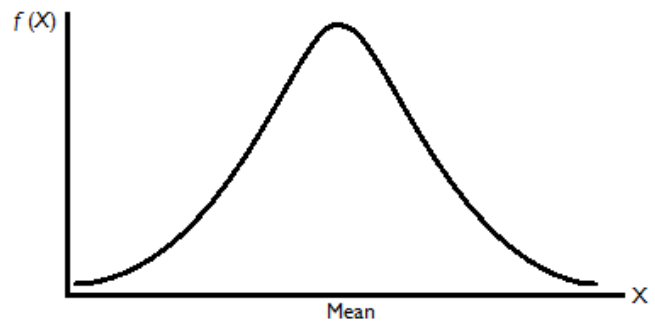
Poisson (POIS)

Inputs: $(Mean)$

$$p(x) = \frac{e^{-\lambda}\lambda^x}{x!}$$

$$(for\ x\varepsilon\ \{0,1,....\})$$

Probability Mass Function
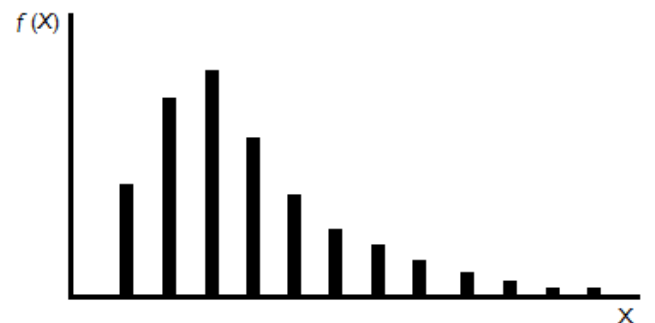
Triangular (TRIA)

Inputs: $(Min, Mode, Max)$

$$f(x) = \frac{2(x-a)}{(m-a)(b-a)}\ (for\ a \le x \le m)$$

$$f(x) = \frac{2(b-x)}{(b-m)(b-a)}\ (for\ m \le x \le b)$$

Probability Density Function

Uniform (UNIF)   Probability Density Function
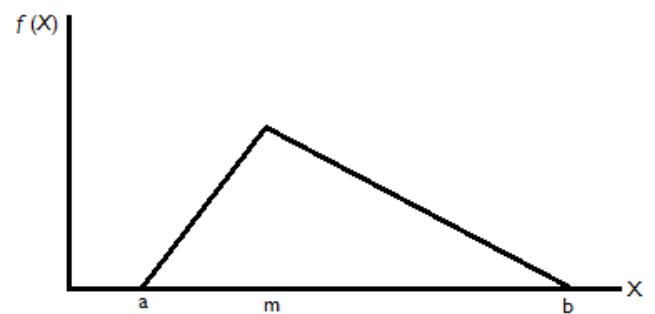
Inputs: (Min, Max)

$$f(x) = \frac{1}{b-a}$$

$$(for\ a{\leq}x{\leq}b)$$
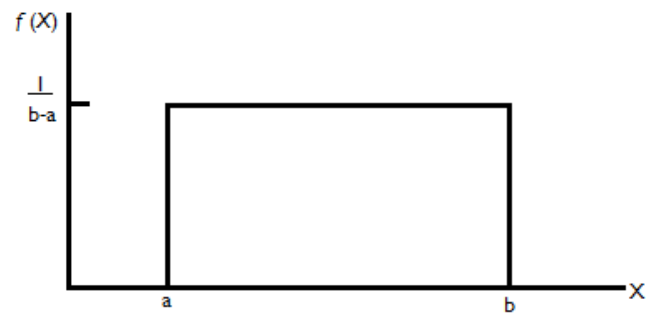
Weibull (WEIB)   Probability Density Function

Inputs: (β, α)

$$f(x) = \alpha\beta^{-\alpha}x^{\alpha-1}e^{-(\frac{x}{\beta})\alpha}$$

$$(for\ x > 0)$$
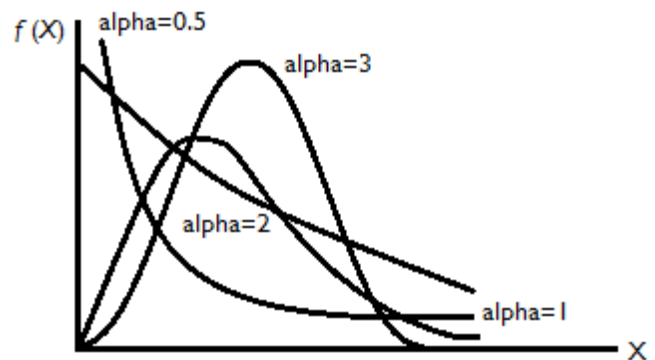
Adapted from: Simulation with Arena, Second edition, Kelton, Sadowski and Sadowski, McGraw Hill Publishing.

A number of sampling shapes are available within each distribution depending on the values of the definable parameters. Where applicable, an indication of the variability within each probability distribution is provided above in order to illustrate the effects of varying these parameter values.

APPENDIX IV

Transfusion Laboratory Survey of Blood Processing and Resources Required for the Provision of Packed Red Blood Cells During a Mass Casualty Event

Please answer all of the following questions providing as much detail as possible with regard to your unit's practices and procedures:

1. Please provide the average daily stock level held at the major trauma centre for each packed red blood cell grouping.
2. Please indicate in which locations and in what volumes emergency type O PRBCs are held at the major trauma centre.
3. Please quantify the number of blood processing and portering staff available on a standard working day and the maximum available staff which could assist in the case of a mass casualty event.
4. Please provide a description of your blood processing procedure (from sample received through to dispensing type specific blood) with typical times or time ranges for each procedure as well as the number of staff required in performing the process. Include in the description any sample verification and authorisation steps which are required.
5. Please detail any procedures specifically instigated during mass casualty events including modifications to sample processing and alterations to the roles performed by transfusion staff.
6. Please provide details of the equipment required to process blood samples in terms of number, sample capacity and the provision for continuous machine loading of samples.
7. Please indicate the additional steps, timings and resources involved in providing fully cross-matched PRBCs to patients.
8. Please describe the release of PRBCs to individual patients including remote issue availability and number of units released simultaneously.
9. Please confirm the hierarchical order in which grouped blood is provided in the event of a patients' specific group type being unavailable.
10. Finally, please provide any further information deemed relevant to this study not covered above.

APPENDIX V

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding P1 casualties treated in full within 1 hour of arrival with increasingly restricted individual casualty overall PRBC allowance (H_{6A})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	64.6 (61.3-67.9)	39.8 (37.3-42.3)	27.8 (26.1-29.5)	20.5 (19.3-21.7)	16.1 (15.1-17.1)	13.6 (12.8-14.4)	11.6 (11-12.3)	10 (9.5-10.6)	8.8 (8.4-9.3)	7.7 (7.2-8.1)	7.2 (6.8-7.6)	6.5 (6.1-6.9)	5.9 (5.6-6.2)	5.6 (5.3-5.9)	5 (4.7-5.3)
Limit 12U	54.2 (51.1-57.3)	41.2 (39.1-43.4)	31.1 (29.4-32.8)	24 (22.7-25.3)	19.3 (18.2-20.3)	16.8 (15.9-17.7)	13.8 (13.1-14.5)	11.8 (11.3-12.4)	10.8 (10.2-11.3)	9.7 (9.3-10.1)	8.7 (8.3-9.1)	7.7 (7.3-8.2)	7.1 (6.8-7.5)	6.9 (6.6-7.3)	6.2 (5.9-6.6)
Limit 18U	64.6 (61.4-67.8)	40 (37.6-42.5)	28.1 (26.4-29.8)	20.8 (19.6-22.1)	16.2 (15.2-17.2)	13.9 (13.1-14.7)	11.7 (11.1-12.4)	10.1 (9.6-10.7)	8.9 (8.4-9.3)	7.8 (7.4-8.2)	7.3 (6.9-7.6)	6.6 (6.2-7)	6 (5.6-6.3)	5.6 (5.3-6)	5 (4.7-5.3)
Limit 24U	64.6 (61.3-67.9)	39.8 (37.3-42.3)	27.8 (26.1-29.5)	20.5 (19.3-21.7)	16.1 (15.1-17.1)	13.6 (12.8-14.4)	11.6 (11-12.3)	10 (9.5-10.6)	8.8 (8.4-9.2)	7.7 (7.2-8.1)	7.2 (6.8-7.6)	6.5 (6.1-6.9)	5.9 (5.6-6.2)	5.6 (5.3-5.9)	5 (4.7-5.3)

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding P2 casualties treated in full within 4 hours of arrival with increasingly restricted individual casualty overall PRBC allowance (H_{6A})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	91 (88.9-93.1)	67.9 (65.4-70.5)	49.5 (47.5-51.5)	35.6 (34.2-37.1)	27.1 (25.9-28.4)	21.8 (20.8-22.9)	17.9 (17.1-18.6)	14.8 (14.1-15.4)	13 (12.4-13.5)	11.1 (10.6-11.6)	9.8 (9.4-10.2)	8.8 (8.4-9.2)	8 (7.6-8.4)	7.3 (7-7.7)	6.7 (6.4-7)
Limit 12U	70.3 (67.5-73)	60.2 (57.9-62.5)	49.7 (48.1-51.3)	39.7 (38.4-41.1)	32.1 (30.9-33.3)	27 (26-27.9)	22.3 (21.6-23.1)	18.7 (18-19.4)	16.7 (16.1-17.4)	14.5 (13.9-15)	12.7 (12.2-13.2)	11.2 (10.7-11.6)	10.2 (9.8-10.6)	9.5 (9.1-9.8)	8.6 (8.2-9)
Limit 18U	90.2 (88.1-92.3)	68 (65.4-70.5)	50.1 (48.1-52.1)	36.2 (34.7-37.7)	27.5 (26.3-28.8)	22.2 (21.2-23.2)	18.2 (17.5-18.9)	15.1 (14.5-15.8)	13.1 (12.5-13.6)	11.3 (10.8-11.8)	10 (9.6-10.4)	8.9 (8.4-9.3)	8.1 (7.7-8.5)	7.5 (7.1-7.8)	6.8 (6.5-7.1)
Limit 24U	91 (88.9-93.1)	67.9 (65.4-70.5)	49.5 (47.5-51.5)	35.7 (34.2-37.1)	27.1 (25.9-28.4)	21.8 (20.8-22.9)	17.9 (17.1-18.6)	14.8 (14.1-15.4)	13 (12.4-13.5)	11.1 (10.6-11.6)	9.8 (9.4-10.2)	8.8 (8.4-9.2)	8 (7.6-8.4)	7.3 (7-7.7)	6.7 (6.4-7)

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding casualties treated in full within 6 hours of arrival with increasingly restricted individual casualty overall PRBC allowance (H_{6A})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	91.8 (89.7-93.9)	68.3 (65.8-70.9)	49.8 (47.8-51.8)	35.7 (34.3-37.2)	27.1 (25.9-28.4)	21.9 (20.8-22.9)	17.9 (17.1-18.6)	14.8 (14.1-15.4)	13 (12.4-13.5)	11.1 (10.6-11.6)	9.8 (9.4-10.2)	8.8 (8.4-9.2)	8 (7.6-8.4)	7.3 (7-7.7)	6.7 (6.4-7)
Limit 12U	70.5 (67.7-73.2)	60.4 (58-62.7)	49.9 (48.3-51.5)	39.8 (38.5-41.2)	32.1 (30.9-33.3)	27 (26-27.9)	22.3 (21.6-23.1)	18.7 (18.1-19.4)	16.7 (16.1-17.4)	14.5 (13.9-15)	12.7 (12.2-13.2)	11.2 (10.7-11.6)	10.2 (9.8-10.6)	9.5 (9.1-9.8)	8.6 (8.2-9)
Limit 18U	90.7 (88.6-92.9)	68.4 (65.8-70.9)	50.4 (48.4-52.4)	36.3 (34.9-37.8)	27.5 (26.3-28.8)	22.2 (21.2-23.2)	18.2 (17.5-18.9)	15.1 (14.5-15.8)	13.1 (12.5-13.7)	11.3 (10.8-11.8)	10 (9.6-10.4)	8.9 (8.4-9.3)	8.1 (7.7-8.5)	7.5 (7.1-7.8)	6.8 (6.5-7.1)
Limit 24U	91.8 (89.7-93.9)	68.3 (65.8-70.9)	49.8 (47.8-51.8)	35.8 (34.3-37.2)	27.1 (25.9-28.4)	21.9 (20.8-22.9)	17.9 (17.1-18.6)	14.8 (14.1-15.4)	13 (12.4-13.5)	11.1 (10.6-11.6)	9.8 (9.4-10.2)	8.8 (8.4-9.2)	8 (7.6-8.4)	7.3 (7-7.7)	6.7 (6.4-7)

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding casualties treated in full within 12 hours of arrival with increasingly restricted individual casualty overall PRBC allowance (H_{6A})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	91.9 (89.8-94)	68.3 (65.8-70.9)	49.8 (47.9-51.8)	35.7 (34.3-37.2)	27.1 (25.9-28.4)	21.9 (20.8-22.9)	17.9 (17.1-18.6)	14.8 (14.1-15.4)	13 (12.4-13.5)	11.1 (10.6-11.6)	9.8 (9.4-10.2)	8.8 (8.4-9.2)	8 (7.6-8.4)	7.3 (7-7.7)	6.7 (6.4-7)
Limit 12U	70.5 (67.7-73.2)	60.4 (58-62.7)	49.9 (48.3-51.5)	39.8 (38.5-41.2)	32.1 (30.9-33.3)	27 (26-27.9)	22.3 (21.6-23.1)	18.7 (18.1-19.4)	16.7 (16.1-17.4)	14.5 (13.9-15)	12.7 (12.2-13.2)	11.2 (10.7-11.6)	10.2 (9.8-10.6)	9.5 (9.1-9.8)	8.6 (8.2-9)
Limit 18U	90.7 (88.6-92.9)	68.4 (65.8-70.9)	50.4 (48.4-52.4)	36.3 (34.9-37.8)	27.5 (26.3-28.8)	22.2 (21.2-23.2)	18.2 (17.5-18.9)	15.1 (14.5-15.8)	13.1 (12.5-13.7)	11.3 (10.8-11.8)	10 (9.6-10.4)	8.9 (8.4-9.3)	8.1 (7.7-8.5)	7.5 (7.1-7.8)	6.8 (6.5-7.1)
Limit 24U	91.9 (89.8-94)	68.3 (65.8-70.9)	49.8 (47.9-51.8)	35.8 (34.3-37.2)	27.1 (25.9-28.4)	21.9 (20.8-22.9)	17.9 (17.1-18.6)	14.8 (14.1-15.4)	13 (12.4-13.5)	11.1 (10.6-11.6)	9.8 (9.4-10.2)	8.8 (8.4-9.2)	8 (7.6-8.4)	7.3 (7-7.7)	6.7 (6.4-7)

For MCE magnitudes ranging from 20-300 casualties, the median (IQR) time in hours to exhaustion of type O PRBC with increasingly restricted individual casualty overall PRBC allowance (H_{6A})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
Limit 12U	* (*-*)	4 (2.5-5)	2 (1.6-2.5)	1.4 (1.2-1.7)	1.2 (1-1.3)	1 (0.9-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.8 (0.7-0.8)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)
Limit 18U	11.5 (5.7-*)	1.9 (1.5-3.1)	1.3 (1.1-1.7)	1 (0.9-1.3)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.4-0.5)
Limit 24U	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)

* = Supply not exhausted for 72 hour simulation duration.

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding P1 casualties treated in full within 1 hour of arrival with restriction of emergency type O PRBC provision to a maximum of 6U to P1s and denial of emergency type O to P2s in addition to an increasing overall PRBC provision restriction (H_{6B})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	64.6 (61.3-67.9)	39.8 (37.3-42.3)	27.8 (26.1-29.5)	20.5 (19.3-21.7)	16.1 (15.1-17.1)	13.6 (12.8-14.4)	11.6 (11-12.3)	10 (9.5-10.6)	8.8 (8.4-9.3)	7.7 (7.2-8.1)	7.2 (6.8-7.6)	6.5 (6.1-6.9)	5.9 (5.6-6.2)	5.6 (5.3-5.9)	5 (4.7-5.3)
Limit 12U	66.2 (62.9-69.4)	42.8 (40.2-45.3)	29.5 (27.8-31.3)	22.3 (21-23.6)	17.6 (16.6-18.6)	15.1 (14.3-16)	12.8 (12.1-13.5)	11 (10.4-11.6)	9.8 (9.4-10.3)	8.4 (8-8.9)	7.8 (7.4-8.1)	7 (6.6-7.4)	6.2 (5.8-6.5)	6.1 (5.8-6.5)	5.5 (5.2-5.8)
Limit 18U	66.2 (62.9-69.4)	42.9 (40.4-45.4)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.2 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.8 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)
Limit 24U	66.2 (62.9-69.4)	42.9 (40.4-45.4)	29.5 (27.8-31.3)	22.2 (20.9-23.5)	17.7 (16.7-18.6)	15.1 (14.3-16)	12.9 (12.2-13.6)	11.1 (10.5-11.6)	9.9 (9.4-10.3)	8.5 (8.1-9)	7.9 (7.5-8.2)	7.1 (6.6-7.5)	6.3 (6-6.6)	6.2 (5.9-6.6)	5.6 (5.3-5.9)

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding P2 casualties treated in full within 4 hours of arrival with restriction of emergency type O PRBC provision to a maximum of 6U to P1s and denial of emergency type O to P2s in addition to an increasing overall PRBC provision restriction (H_{6B})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	92.9 (89.6-96.2)	71.5 (67.6-75.3)	55.7 (52.3-59.1)	43.2 (40.5-46)	35.2 (32.9-37.5)	28.7 (26.3-31.1)	25.4 (23.6-27.2)	21.4 (19.9-23)	19.6 (18.1-21.1)	16.3 (15-17.5)	15.3 (14.1-16.5)	13.8 (12.7-15)	13.3 (12.3-14.3)	12 (11-13.1)	11.4 (10.6-12.2)
Limit 12U	93.1 (89.8-96.4)	68.8 (64.5-73.1)	52 (48.6-55.5)	37.7 (35.1-40.4)	30.8 (28.6-33)	23.4 (21-25.8)	20.1 (18.3-21.8)	16.8 (15.4-18.3)	14.5 (13.3-15.8)	12.3 (11.2-13.4)	11.4 (10.3-12.5)	10.5 (9.5-11.5)	9.9 (9-10.7)	8.9 (8-9.7)	8.2 (7.5-8.9)
Limit 18U	92.1 (88.3-95.8)	68.6 (64.3-72.9)	52 (48.6-55.4)	37.7 (35.1-40.4)	30.7 (28.5-32.9)	23.4 (21.1-25.8)	20 (18.3-21.7)	16.8 (15.4-18.2)	14.6 (13.3-15.8)	12.2 (11.1-13.3)	11.4 (10.3-12.5)	10.4 (9.4-11.4)	9.9 (9.1-10.7)	8.8 (8-9.6)	8.3 (7.5-9)
Limit 24U	92.1 (88.3-95.8)	68.6 (64.3-72.9)	52 (48.6-55.4)	37.7 (35.1-40.4)	30.7 (28.5-32.9)	23.4 (21.1-25.8)	20 (18.3-21.7)	16.8 (15.4-18.2)	14.6 (13.3-15.8)	12.2 (11.1-13.3)	11.4 (10.3-12.5)	10.4 (9.4-11.4)	9.9 (9.1-10.7)	8.8 (8-9.6)	8.3 (7.5-9)

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding casualties treated in full within 6 hours of arrival with restriction of emergency type O PRBC provision to a maximum of 6U to P1s and denial of emergency type O to P2s in addition to an increasing overall PRBC provision restriction (H_{6B})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	92.3 (90.4-94.1)	69.4 (67-71.8)	51.6 (49.6-53.6)	38 (36.5-39.5)	29.6 (28.4-30.8)	23.9 (22.7-25.1)	20 (19.2-20.8)	16.8 (16-17.5)	14.9 (14.4-15.5)	12.6 (12.1-13.1)	11.4 (11-11.8)	10.3 (9.9-10.7)	9.6 (9.2-10)	8.7 (8.3-9.1)	8 (7.7-8.4)
Limit 12U	93.6 (91.9-95.4)	70.2 (67.7-72.8)	50.6 (48.6-52.6)	36.7 (35.2-38.2)	28.6 (27.4-29.8)	22.9 (21.7-24)	18.9 (18.1-19.7)	15.8 (15.1-16.5)	13.9 (13.4-14.4)	11.7 (11.3-12.2)	10.6 (10.2-11)	9.6 (9.2-10)	8.5 (8.1-8.8)	8.1 (7.7-8.4)	7.4 (7.1-7.7)
Limit 18U	93.3 (91.5-95)	70.2 (67.7-72.8)	50.8 (48.8-52.8)	36.9 (35.4-38.3)	28.7 (27.5-29.9)	22.9 (21.8-24.1)	19 (18.2-19.8)	15.9 (15.2-16.5)	14 (13.5-14.5)	11.8 (11.3-12.3)	10.7 (10.3-11.1)	9.6 (9.2-10.1)	8.6 (8.2-8.9)	8.1 (7.8-8.5)	7.5 (7.2-7.8)
Limit 24U	93.3 (91.5-95)	70.2 (67.7-72.8)	50.8 (48.8-52.8)	36.8 (35.4-38.3)	28.7 (27.5-29.9)	22.9 (21.8-24.1)	19 (18.2-19.8)	15.9 (15.2-16.5)	14 (13.5-14.5)	11.8 (11.3-12.3)	10.7 (10.3-11.1)	9.6 (9.2-10.1)	8.6 (8.2-8.9)	8.1 (7.8-8.5)	7.5 (7.2-7.8)

For MCE magnitudes ranging from 20-300 casualties, the percentage of bleeding casualties treated in full within 12 hours of arrival with restriction of emergency type O PRBC provision to a maximum of 6U to P1s and denial of emergency type O to P2s in addition to an increasing overall PRBC provision restriction (H_{6B})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	92.4 (90.5-94.2)	69.4 (67-71.8)	51.6 (49.6-53.6)	38 (36.5-39.5)	29.6 (28.4-30.8)	23.9 (22.7-25.1)	20 (19.2-20.8)	16.8 (16-17.5)	14.9 (14.4-15.5)	12.6 (12.1-13.1)	11.4 (11-11.8)	10.3 (9.9-10.7)	9.6 (9.2-10)	8.7 (8.3-9.1)	8 (7.7-8.4)
Limit 12U	93.7 (92-95.5)	70.2 (67.7-72.8)	50.6 (48.6-52.6)	36.7 (35.2-38.2)	28.6 (27.4-29.8)	22.9 (21.7-24)	18.9 (18.1-19.7)	15.8 (15.1-16.5)	13.9 (13.4-14.4)	11.7 (11.3-12.2)	10.6 (10.2-11)	9.6 (9.2-10)	8.5 (8.1-8.8)	8.1 (7.7-8.4)	7.4 (7.1-7.7)
Limit 18U	93.4 (91.6-95.1)	70.2 (67.7-72.8)	50.8 (48.8-52.9)	36.9 (35.4-38.3)	28.7 (27.5-29.9)	22.9 (21.8-24.1)	19 (18.2-19.8)	15.9 (15.2-16.5)	14 (13.5-14.5)	11.8 (11.3-12.3)	10.7 (10.3-11.1)	9.6 (9.2-10.1)	8.6 (8.2-8.9)	8.1 (7.8-8.5)	7.5 (7.2-7.8)
Limit 24U	93.4 (91.6-95.1)	70.2 (67.7-72.8)	50.9 (48.8-52.9)	36.8 (35.4-38.3)	28.7 (27.5-29.9)	22.9 (21.8-24.1)	19 (18.2-19.8)	15.9 (15.2-16.5)	14 (13.5-14.5)	11.8 (11.3-12.3)	10.7 (10.3-11.1)	9.6 (9.2-10.1)	8.6 (8.2-8.9)	8.1 (7.8-8.5)	7.5 (7.2-7.8)

For MCE magnitudes ranging from 20-300 casualties, the median (IQR) time in hours to exhaustion of type O PRBC with restriction of emergency type O PRBC provision to a maximum of 6U to P1s and denial of emergency type O to P2s in addition to an increasing overall PRBC provision restriction (H_{6B})

Total PRBC Limit per Casualty (Units)	Casualty Load														
	20	40	60	80	100	120	140	160	180	200	220	240	260	280	300
Baseline	9.7 (5.4-*)	1.9 (1.5-3)	1.3 (1.1-1.7)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.7 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.5)	0.5 (0.4-0.5)
Limit 12U	* (8.1-*)	2.2 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (1-1.3)	1 (0.8-1.2)	0.9 (0.8-1)	0.8 (0.7-0.9)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
Limit 18U	13.6 (7.4-*)	2.1 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)
Limit 24U	12.6 (7.4-*)	2.1 (1.7-3.3)	1.5 (1.3-1.9)	1.1 (0.9-1.3)	1 (0.8-1.1)	0.9 (0.8-1)	0.8 (0.7-0.8)	0.8 (0.7-0.8)	0.7 (0.6-0.8)	0.6 (0.6-0.7)	0.6 (0.5-0.7)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.5-0.6)

* = Supply not exhausted for 72 hour simulation duration.