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TITLE: Exploitation of Bayesian Networks for Clinical Decision Support on the Battlefield

PRINCIPAL INVESTIGATOR: Col Nigel Tai

CONTRACTING ORGANIZATION: Queen Mary University London

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14. ABSTRACT: The purpose of this research is to optimize the care of battlefield trauma patients through the development of Bayesian-network (BN) machine learning-powered clinical decision-support (CDS) tools. Scope: The scope of the research encompasses the refinement of existing BNs, and development and prototyping of new BNs designed for pre-hospital, en-route, and deployed healthcare facility stages of care, such that CDS prototypes are available for piloting and assessment in future, real-world clinical studies. Major Findings â€œ Year 2 Data. Access to UK MoD, Queen Mary University of London and Londonâ€™s Air Ambulance data sets granted and Data Preparation, Linkage, Reconciliation, Merging and Cleaning undertaken. HRPO submission for Data exploitation submitted. Model generation. Novel Military Trauma Induced Coagulopathy Model produced using data from 678 military patients. Calibration was good (slope 1.3, intercept -0.023) with excellent discrimination (AUROC 0.95 (0.92-0.97)). Accuracy was 0.91 with Brier Score 0.06 and Brier skill score 0.5. Model Refinement. To ensure the model is fit for use in an austere environment, it needs to factor in clinician uncertainty in identifying and recognizing relevant clinical variables (such as the presence of particular injuries) that the model needs to work off. Retrospective study evaluating diagnostic performance of expert trauma clinicians in the prehospital setting, comparing with diagnoses identified in hospital. 921 patients were included in our study. Overall accuracy of prehospital was 92% (95% confidence interval (CI) 0.916 to 0.923), 93% (95% CI 0.930 to 0.936) when clinicians had high certainty of injuries, and 39% (0.368 to 0.406) when clinicians had low certainty of injuries. Military mortality model build methodology completed. Build will include modelling of late stage deaths from Acute Kidney Injury. Designed and updating server technology for integration of BN predictor capture and risk presentation, translation of underlying Server technology (from php to javascript) in order to allow for multiple Apps to interact with the same Server (ie improving future scalability), user log in system; admin upload of Agena Risk files to allow saving of Bayesian Network states (and readiness for input); tailoring functionality to allow admin users to specify user privileges; outputs can be displayed using bar charts, pie charts or icon arrays, and dynamic risk over time. Prototype digital interface for injury capture ("Body Map") designed. User evaluation methodology completed. Ethics proposal for user evaluation study submitted to Research Ethics Committee.9) Follow-on clinical impact protocol developed. Conclusion The project is proceeding well toward its endpoint of delivering a suite of validated clinical decision support tools that will enhance the care of injured service men and women.					
15. SUBJECT TERMS Trauma, Prediction, Coagulopathy, Mortality, Limb Salvage, Transfusion, Machine Learning, Transfusion, Machine Learning,					
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1. INTRODUCTION:

The research subject concerns optimizing the care of battlefield trauma patients through the purposeful development and validation of accurate, clinically credible prognostic tools that will support informed and personalized treatment decisions by quantifying clinically relevant risks. The scope of the research encompasses the development and prototyping of tools designed for pre-hospital, en-route, and deployed healthcare facility stages of care, such that these prototypes are available for piloting and assessment in a clinical context.

2. KEYWORDS:

Trauma, Prediction, Coagulopathy, Mortality, Limb Salvage, Transfusion, Machine Learning, Clinical Decision Support, Military Surgery

3. ACCOMPLISHMENTS:

The scope of this project is to use machine-learning techniques established by the funded research group (COMputer Battlefield Assistance in Trauma care and Injury Decision-support: COMBAT-AID) to enable military trauma clinicians to provide precision-medicine on the battlefield. The date of Project Start was 15 September 2019.

- Recruited Dr Chris Joyner PhD in to the allotted Software Dev role specified in the terms of the award. Responsibilities include development of User Interfaces for clinicians to capture injury data, to navigate the evidence browser, illustration and presentation of risk to clinicians to aid decision-making.
- Data. Access to UK MoD, Queen Mary University of London and London's Air Ambulance data sets granted and Data Preparation, Linkage, Reconciliation, Merging and Cleaning undertaken. HRPO submission for Data exploitation submitted and gained.
- Model generation. Novel Military Trauma Induced Coagulopathy Model produced using data from 678 military patients. Calibration was good (slope 1.3, intercept -0.023) with excellent discrimination (AUROC 0.95 (0.92-0.97)). Accuracy was 0.91 with Brier Score 0.06 and Brier skill score 0.5.
- Model Refinement. To ensure the model is fit for use in an austere environment, it needs to factor in clinician uncertainty in identifying and recognizing relevant clinical variables (such as the presence of particular injuries) that the model needs to work off. Retrospective study evaluating diagnostic performance of expert trauma clinicians in the prehospital setting undertaken. 921 patients were included in our study. Overall accuracy of prehospital diagnosis was 92% (95% confidence interval (CI) 0.916 to 0.923), 93% (95% CI 0.930 to 0.936) when clinicians had high certainty of injuries, and 39% (0.368 to 0.406) when clinicians had low certainty of injuries.
- Military mortality model build methodology completed. Build will include modelling of late stage deaths from Acute Kidney Injury.
- Designed and updating server technology for integration of BN predictor capture and risk presentation, translation of underlying Server technology (from php to javascript) in order to allow for multiple Apps to interact with the same Server (ie improving future scalability), user log in system; admin upload of Agena Risk files to allow saving of Bayesian Network states (and readiness for input); tailoring functionality to allow admin users to specify user privileges; outputs can be displayed using bar charts, pie charts or icon arrays, and dynamic risk over time.
- Prototype digital interface for injury capture ("Body Map") designed.
- User evaluation methodology completed. Ethics proposal for user evaluation study submitted to Research Ethics Committee.
- Follow-on clinical impact protocol developed.

What opportunities for training and professional development has the project provided?

3 PhD students who will be supervised by Col N Tai, Prof K Brohi, Dr William Marsh, Mr Zane Perkins, and Dr Evangelina Kyrimi. All 3 students will be registered to Queen Mary University London. Supervisors and students enrol in QMUL programmes to foster their continuing development https://www.qmul.ac.uk/doctorscollege/?page_id=49. These opportunities are a requirement for satisfactory study and supervision.

How were the results disseminated to communities of interest?

Stakeholders (Defence Medical Services, US JTS leadership) will be sent a copy of the annual report including links to relevant publications.

What do you plan to do during the next reporting period to accomplish the goals?

Gain REC ethics approval for use-ability studies and refine user interface (input, outputs) to ensure fitness for deployment. Build holistic interface.
Complete evidence browser.
Repurpose refined Mil TIC tool to produce blood consumption prediction tool
Continue mortality tool development, integrating organ failure (late stage) death model.

4. **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

Artificial intelligence and Machine Learning are part of the modern discourse when considering advances in improved medical care, yet many approaches lack the ability to integrate patient data, clinical expertise and evidence-derived knowledge in deriving prognoses that can support decision-making. Published results from our foundational work, contributing to the projects goals, confirm that accurate, Bayesian Network-powered models can be produced that, by incorporating expert knowledge and data-sets, out-perform standard prediction tools with regard to the prediction of traumatic coagulopathy and risk of limb loss in trauma. However, generation of accurate predictions means little if clinicians are reluctant to use the tool, if they do not trust the result or both. We have advanced the discipline by developing a user-configurable interface powered by a 6 level system architecture that marries inputs, computation, outputs and evidence. We have also learnt how the ability of a tool to explain its reasoning in making a prediction is or is not valued by clinicians, and how this influences trust in the model. We have used an novel approach to predicting mortality that incorporates dynamic variables, accounting for the effect of interventions, which provides predictions tailored to the stage of care across a combat area – one that outperforms established mortality prediction tools. And we have made significant in-roads in to the development of a system that predicts likely consumption of blood transfusion resource, based on what the individual patient requires rather than what the clinician is likely to prescribe.

What was the impact on other disciplines?

The research outputs will contribute to the development of clinical decision support tools applicable to non-trauma, non-military patients. The modelling techniques developed are impactful for other areas of human expert decision-making where support is required, as the approaches used are applicable in Law, Engineering, Defence and the Financial sector.

What was the impact on technology transfer?

Nothing to report – technology transfer options will be considered/developed during year 3.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Nothing to report.

5. **CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, “Nothing to Report,” if applicable:*

Changes in approach and reasons for change

Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing significant to report – project goals and direction remain extant.

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nil Significant to Report

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

All figures USD based on DoD agreed budget											
PRECOVID						POSTCOVID					
	Sep-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Total Y1		Sep-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Total Y1
Pis	9,609	13,982	13,982	13,982	51,555	Pis	9,609	13,982	13,982	13,982	51,555
PDRA	0	0	16,092	16,092	32,184	PDRA	0	0	10,797	16,195	26,992
CRFs	0	0	36,959	36,959	73,918	CRFs	0	0	0	23,814	23,814
Prog	0	0	18,140	18,140	36,280	Prog	0	0	0	0	0
PM	0	1,918	3,837	3,837	9,592	PM	0	1,420	4,257	4,298	9,974
Travel	0	0	0	22,700	22,700	Travel	0	0	0	0	0
Fees	0	0	6,802	6,802	13,604	Fees	0	0	0	0	0
Stipend	0	0	5,688	5,688	11,376	Stipend	0	0	0	948	948
M&S	0	0	4,909	0	4,909	M&S	0	0	0	0	0
Computer	0	0	7,979	0	7,979	Computer	0	0	0	1,050	1,050
Subcont (RCDM)	1,906	1,906	1,906	1,906	7,624	Subcont (RCDM)	1,906	1,906	1,906	1,906	7,624
Infra	8,259	8,259	8,259	8,259	33,036	Infra	8,259	8,259	8,259	8,259	33,036
Total	19,774	26,065	124,553	134,365	304,757	Total	19,774	25,567	39,201	70,453	154,994

As illustrated the Year One spend is diminished from £304K to £154K due to delays in staff start dates. This does not translate in to a reduction in the anticipated total spend over the lifetime of the project.; original cost profile remains extant. PI, Principle Investigator. PDRA, Postdoctoral Research Assistant. CRF, Clinical Research Fellow. Prog, Software Programmer. PM, Project Manager. M&S, Materials and Supplies. Subcontractor (RCDM); Royal Centre for Defence Medicine.

YEAR TWO COSTS – No major deviances. Yr 2 costs (USD506K) higher than Yr 1 (USD 157K) due to planned hiring of staff (not recruited during year 1).

	2019	2020	2020	2020	YEAR 1	2020	2021	2021	2021	YEAR 2
	Sep-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Total Y1	Oct-Dec	Jan-Marc	April-Jun	Jul-Sep	Total Y2
Pis	9,609	13,982	13,982	13,982	51,555	13,982	13,982	13,982	13,982	55,928
PDRA	0	0	10,797	16,195	26,992	16,195	16,195	16,805	17,287	66,482
CRFs	0	0	0	23,814	23,814	46,654	46,540	58,620	58,620	210,433
Prog	0	0	0	0	0	9,220	10,854	10,852	11,170	42,095
PM	0	1,420	4,257	4,298	9,974	4,379	4,379	4,379	4,508	17,645
Travel	0	0	0	0	0	0	0	0	0	0
Fees	0	0	0	0	0	0	0	0	27,235	27,235
Stipend	0	0	0	948	948	5,688	5,688	5,688	5,688	22,750
M&S	0	0	0	0	0	0	0	0	0	0
Computer	0	0	0	3,505	3,505	135	0	774	0	908
Subcont (RCDM)	1,906	1,906	1,906	1,906	7,624	1,906	1,906	1,906	1,906	7,624
Infra	8,259	8,259	8,259	8,259	33,036	13,738	13,738	13,738	13,738	54,951
Total	19,774	25,567	39,201	72,907	157,448	111,895	113,281	126,743	154,132	506,051

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nil Significant to report

Significant changes in use or care of vertebrate animals

Nil Significant to report

Significant changes in use of biohazards and/or select agents

Nil Significant to report

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

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Books or other non-periodical, one-time publications.

Nil significant to report

Other publications, conference papers and presentations.

ACCEPTED BY MILITARY HEALTH SYSTEMS RESEARCH SYMPOSIUM 23-26 JUL 2021

Predicting Trauma Induced Coagulopathy in combat casualties: updating a civilian AI risk prediction model for use in a military population – ORAL PRESENTATION

Rebecca S Stoner MBChB , Evangelia Kyrimi PhD, Jared M Wohlgemut MBChB, Erhan Pisirir MSc, Rory Rickard PhD, Jennifer M Gurney MD, William Marsh PhD, Zane B Perkins PhD, Nigel RM Tai MD

Accuracy of clinical identification of life- and limb-threatening injuries by expert

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nil significant to Report

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Bayesian networks as described in Appendix.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nil significant to report

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nil significant to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name	Principle Role	Project time	Contribution	Other funding support	Notes
Nigel Tai	PI	On project for 24 mths at 13.3%	Overall leadership functions; review meetings, hiring and staff establishment	MoD employee	Honorary QMUL and NHS contracts
William Marsh	CI	On project for 24 mths at 13.3%	Leadership esp wrt Computer Science aspects; review meetings and staff establishment.	QMUL employee	
Zane Perkins	Investigator	On project for 6 mths at 20%	Project supervision and academic management of Clinical PhD students; review meetings; hiring and staff establishment	NHS employee	Part funded by DoD grant
Evangelina Kyrimi	Post-Doctoral Research Assistant	On project for 16 mths at 100%	Model development and supervision of Computer Science PhD Student; review meetings.	Nil	Fully funded by DoD grant
Rebecca Stoner	QMUL PhD Candidate Clinical Fellow	On project for 13 mth at 100%	Model development & refinement	Nil	COVID 19 prevented earlier start
Jared Wohlgemut	QMUL PhD Candidate Clinical Fellow	On project for 13 mth at 100%	Clinical Decision Support system Interface development, assessment and workflow integration	Nil	COVID 19 prevented earlier start
Javier Sandin Llorente	Operations manager Centre for Trauma Sciences QMUL	On project for 18 mths at 20%	Liaison with funder, QMUL Research Office, financial oversight and contractual management	QMUL employee supported by multiple C4TS awards	
Prof Karim Brohi	CI	On project for 18 months at 2.67%	Critical analysis, leadership, authority for Centre 4 trauma science data resources.	Full time QMUL academic	
Dr Chris Joyner	QMUL Comp Science Lecturer	On project for 13 months at 60%	Software and System Developer	Full time QMUL academic	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nil significant to report

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

- *Other.*

Nil significant to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: *For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.*

QUAD CHARTS: *If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.*

- 9. APPENDICES:** *Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.*

ANNUAL REPORT TECHNICAL NARRATIVE W81XWH-19-2-0047 – YR 1 AND 2

**EXPLOITATION OF BAYESIAN NETWORKS FOR CLINICAL DECISION SUPPORT ON
THE BATTLEFIELD**

AUTHOR COL NIGEL TAI (PRINCIPLE INVESTIGATOR)

REPORT DATE 14 SEPT 2021

ABSTRACT

Purpose: The purpose of this research is to optimize the care of battlefield trauma patients through the development of Bayesian-network (BN) machine learning-powered clinical decision-support (CDS) tools.

Scope: The scope of the research encompasses the refinement of existing BNs, and development and prototyping of new BNs designed for pre-hospital, en-route, and deployed healthcare facility stages of operational patient care, such that CDS prototypes are available for piloting and assessment in future, real-world clinical studies.

Major Findings (Yr 2):

1. Secured requisite better labelled data in order to complete model building.
2. Model generation. Novel Military Trauma Induced Coagulopathy Model produced using data from 678 military patients. Calibration was good (slope 1.3, intercept -0.023) with excellent discrimination (AUROC 0.95 (0.92-0.97)). Accuracy was 0.91 with Brier Score 0.06 and Brier skill score 0.5.
3. Model Refinement. To ensure the model is fit for use in an austere environment, it needs to factor in clinician uncertainty in identifying and recognizing relevant clinical variables (such as the presence of particular injuries) that the model needs to work off. Retrospective study evaluating diagnostic performance of expert trauma clinicians in the prehospital setting, comparing with diagnoses identified in hospital. 921 patients were included in our study. Overall accuracy of prehospital was 92% (95% confidence interval (CI) 0.916 to 0.923), 93% (95% CI 0.930 to 0.936) when clinicians had high certainty of injuries, and 39% (0.368 to 0.406) when clinicians had low certainty of injuries.
4. Military mortality model build methodology completed. Build will include modelling of late stage deaths from Acute Kidney Injury.
5. Designed and updating server technology for integration of BN predictor capture and risk presentation, translation of underlying Server technology (from php to javascript) in order to allow for multiple Apps to interact with the same Server (ie improving future scalability), user log in system; admin upload of Agena Risk files to allow saving of Bayesian Network states (and readiness for input); tailoring functionality to allow admin users to specify user privileges; outputs can be displayed using bar charts, pie charts or icon arrays, and dynamic risk over time.
6. Prototype digital interface for injury capture ("Body Map") designed.
7. User evaluation methodology completed. Ethics proposal for user evaluation study submitted to Research Ethics Committee.
8. Follow-on clinical impact protocol developed.

Conclusion: An evidenced BN-powered CDS tool suite for combat trauma patients is being developed. The project is proceeding well toward its endpoint of delivering a suite of validated clinical decision support tools that will enhance the care of injured service men and women.

1. AIMS

1.1. The aim of this narrative report is to supplement the Annual Report submitted in regard to the above project in order to provide additional context and supplementary information. Paragraphs related to last year's report are in grey.

2. PROJECT SCOPE

2.1. The scope of this project is to use machine-learning techniques established by the funded research group (COMputer Battlefield Assistance in Trauma care and Injury Decision-support: COMBAT-AID) to enable military trauma clinicians to provide precision-medicine on the battlefield. The date of Project Start was 15 September 2019.

3. GENERAL COMMENTS

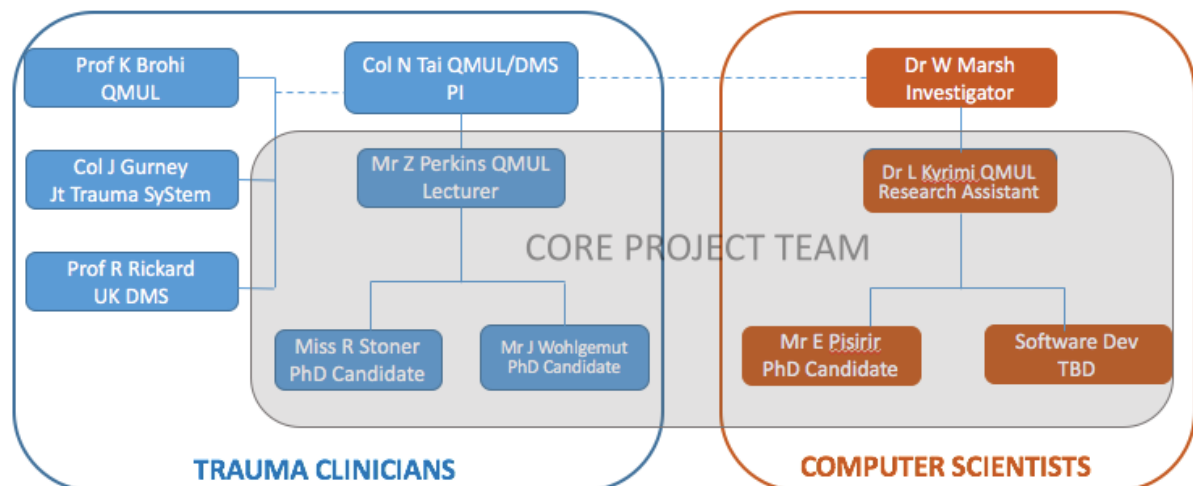
3.1. The first year of the project has been characterized by consolidation of both preparatory and substantive work pertaining to the deliverables, with the highlights being a number of foundational publications that underwrite the science and performance of our Machine-Learning networks used to prognosticate in major trauma. The recruitment of the core project team is more than 80% complete, though disruptions due to COVID19 have impacted on start-times for three of these appointments. Access to UK data for refining models and training has not been problematic and efforts to add important labels to UK JTTR datasets will mature in Year 2, allowing military-specific TIC and blood prediction models to be developed. Interface development has been proceeding satisfactorily.

3.2 Outputs have been moderately affected by Covid 19 but not to an extent that threatens delivery. The option of a one-time 12-month extension has been considered but not enacted ¹.

4. TEAM RECRUITMENT AND STRUCTURE

4.1. The diagram below portrays the individuals comprising the research team:

¹ DoD guide for funded investigators. "The recipient may initiate, without prior approval, a one-time extension without funds to the expiration date of the award for a period of up to 12 months, as long as the extension without funds does not involve a change in the approved objectives or scope of the project. The recipient shall notify the USAMRAA Grants Officer in writing at least 30 calendar days prior to the expiration date of the award. The notification shall state the additional time needed, the reasons for the extension, and the work to be completed during the extension period."



COMBAT-AID DEVELOPMENT TEAM
COMPUTER BATTLEFIELD ASSISTANCE IN TRAUMA CARE & INJURY DECISION SUPPORT

SUPPORTED BY US DOD W81XWH-19-2-0047 - Exploitation of Bayesian Networks for Clinical Decision Support on the Battlefield

4.2. The hiring plan of the Core Project Team is 100% completed. COVID 19 and the Requirement for clinical staff to undertake re-deployment in support of the NHS response delayed the on-boarding of two clinical PhD appointments. Restrictions on international travel also delayed the start of the PhD Computer Scientist. The software developer position remains unfilled (Aug 2020).

Role	Principle Function	Interview	Appointment	Start Date	Notes
Lecturer	Project supervision and academic management of Clinical PhD students	24 Jan 2020	Mr Zane Perkins	1 March 2020	Academic role combined with Clinical role as Consultant Trauma Surgeon
QMUL Post-Doctoral Research Assistant	Model development and supervision of Computer Science PhD Student	30 Jan 2020	Dr E Kyrimi	1 May 2020	
QMUL PhD Candidate Clinical	Model development & refinement	24 Feb 2020	Ms R Stoner	3 Aug 2020	COVID 19 prevented earlier start
QMUL PhD Candidate Clinical	Clinical Decision Support system Interface assessment and Integration	24 Feb 2020	Mr J Wohlgemut	3 Aug 2020	COVID 19 prevented earlier start
QMUL PhD Candidate Computer Science	Model development & refinement	April 2020	Mr E Pisiri	14 Sept 2020	COVID 19 prevented earlier start

QMUL Software Development	Interface development & refinement	Oct 2020	Dr C Joyner		
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5. YEAR ONE AND TWO PROJECT MILESTONES

5.1. Major Task. Application for Local IRB and US HRPO study approval

“In progress (40%)”

5.1.1. Approvals are split over two national settings – UK and US. For the UK setting, approvals pertain to the use of JTTR (UK Defence Medical Services Trauma Registry), and to a lesser degree, the QMUL Centre For Trauma Sciences ACIT (Acute Coagulopathy in Trauma) data registry. The PI has had authority to utilize JTTR in respect of UK DMS research conducted in the field of Clinical Decision Support for the past 8 years. ACIT data registry access is granted under the terms that the ACIT PI (Co-Investigator Professor Karim Brohi) convened. These permissions have enabled foundational and pre-project ground work during 2019 and 2020. A set of specific UK JTTR permissions is being sought; Professor (Surgeon Captain) Smith of the UK DMS Academic Department of Military Emergency Medicine has granted JTTR use in anticipation of formal approval³ and the generation of a data sharing agreement between QMUL and Defence Medical Services. There is no requirement for Research Ethics Committee application for model build activity; REC will be approached regarding whether the clinician interview/scenario case studies anticipated in year two will require formal approval.

5.1.2. Co-Investigator Colonel Jennifer Gurney occupies a senior leadership position within US Joint Theatre Trauma System and will aid the progress of IRB approval for access to, and data abstraction from the JTS trauma registry. This process will be necessary in order to perform external validation on the MIL TIC model, the MIL Blood Prediction Model and to train and validate the Mortality Prediction Model and Overflight models in Year 3. The LIMB Mil Model was trained and validated on an exclusively military population and does not require JTS data.

5.1.2 YEAR TWO UPDATE: Permissions gained from UK MoD for use of JTTR and other relevant UK DMS datasets; from Queen Mary University of London Centre for Trauma Science Patient Datasets, and from London's Air Ambulance for London's Air Ambulance Patient Datasets. A data handling policy was written to set out how this data would be used. Submission was made for data use and build was made to US DoD HRPO and granted (28 Sept 2021, E00655.1a. Local Research Ethics Committee Approval is being made for studies of human use-ability testing. US DoD IRB approval will be sought for US DoD JTS data pertaining to other components of this work. Further HRPO submissions will be made covering these two areas. HRPO terms as below:

1. *The U.S. Army Medical Research and Development Command, Office of Research Protections (ORP), Human Research Protection Office (HRPO) reviewed protocol for applicability of human subjects protection regulations.*
2. *The research involves the use of de-identified data to develop a suite of accurate and clinically credible prognostic models and clinical decision support tools to assist clinicians providing prehospital, en route, or hospital care for individuals who have sustained battlefield injury.*

³ Email received 3 Sept 2020

3. The HRPO determined this protocol comprises research not involving human subjects as it does not involve a living individual about whom an investigator (whether professional or student) conducting research obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens (32 CFR 219.102). The project may proceed with no further requirement for review by the HRPO. The HRPO protocol file will be closed.

If additional projects under this award involve non-exempt research, documents must be submitted to HRPO for review and approval.

4. In the event that there is a change to the subject research or statement of work (SOW), the Principal Investigator must notify the Contracting Officer's Representative (COR) or Grant Officer's Representative (GOR) and send a description of the change to the HRPO at usarmy.detrick.medcom-usamrmc.other.hrpo@mail.mil referencing both the proposal log number and the HRPO log number listed in the "SUBJECT" line above. The HRPO will re-open the protocol file if necessary.

Any changes to the SOW that the COR or GOR determines could involve research with human subjects (as defined above) must be reviewed by the HRPO prior to approval by the Contracting Officer/Grants Officer.

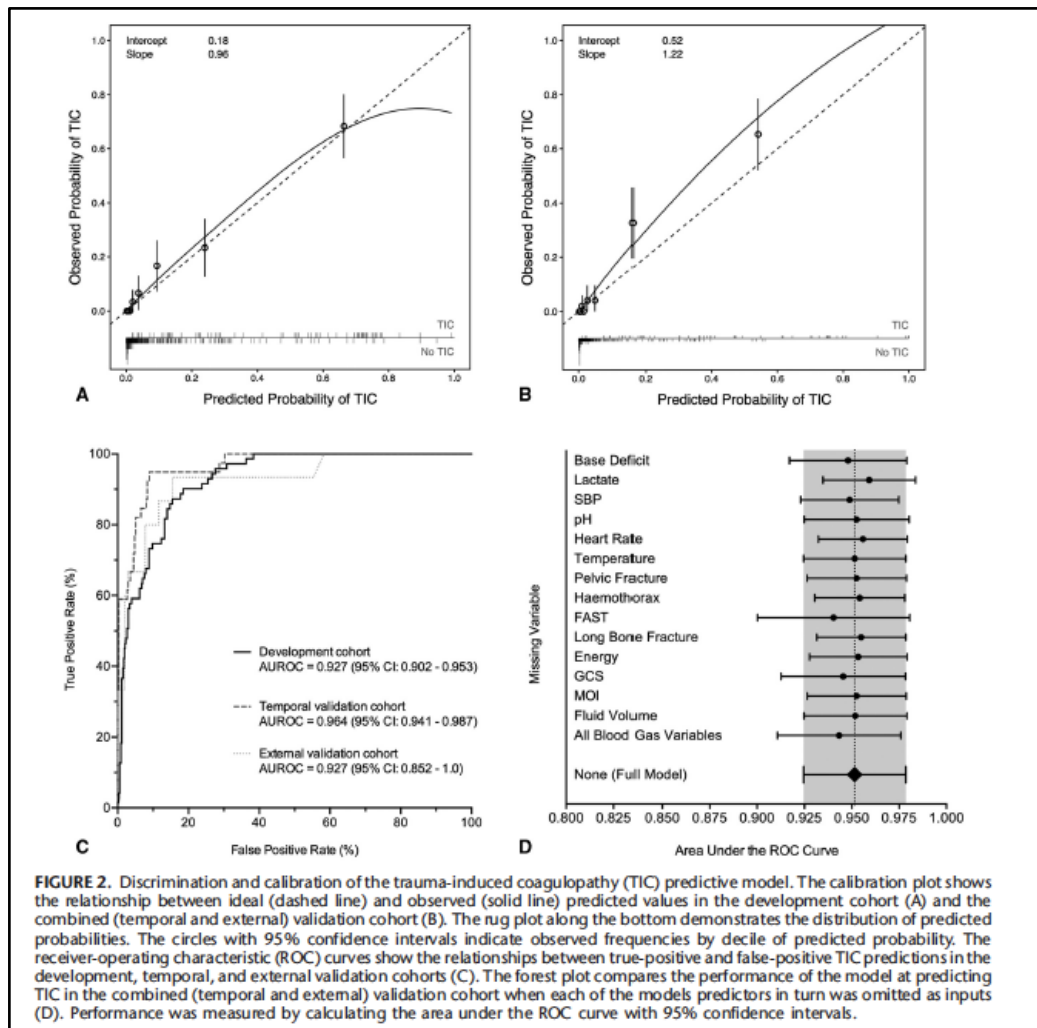
5. Do not construe this correspondence as approval for any contract or grant/cooperative agreement funding. Only the Contracting Officer/Grants Officer can authorize expenditure of funds by notice of official award documentation. It is recommended that you contact the appropriate contract/grants specialist or Contracting/Grants Officer regarding the expenditure of funds for your project.

5.2. Major Task: Develop and validate a prognostic model for Trauma Induced Coagulopathy (TIC)

- a. "Development Complete (100%)**
- b. Civilian Validation Complete (100%)**
- c. Military Validation (100%) and Military Re-development (80%)**

5.2.1. The background to this task is that TIC exacerbates hemorrhage and is associated with higher morbidity and mortality in trauma patients. Early and aggressive treatment of TIC (balanced transfusion with blood products and early surgical control of haemorrhage) improves patient outcome. However, injured patients that develop TIC can be difficult to identify, which may compromise effective treatment. Our group's solution to this problem - an over-arching prognostic model of TIC - powered by knowledge-driven machine learning using Bayesian Networks - was published in *Annals of Surgery* in January 2020⁴. This paper described how the prediction model was developed using domain knowledge of the causal mechanisms of TIC⁵, and trained using data from 600 major trauma patients. Rates of TIC in the derivation and validation cohorts were 11.8% and 11.0%, respectively, and patients who developed TIC were significantly more likely to die (54.0% vs 5.5%, $P < 0.0001$), require a massive blood transfusion (43.5% vs 1.1%, $P < 0.0001$), or require damage control surgery (55.8% vs 3.4%, $P < 0.0001$), than those with normal coagulation. In the development dataset, the 14-predictor BN accurately predicted this high-risk patient group: area under the receiver operating characteristic curve (AUROC) 0.93, calibration slope (CS) 0.96, brier score (BS) 0.06, and brier skill score (BSS) 0.40 as portrayed below:

⁴ Perkins et al. Early Identification of Trauma-Induced Coagulopathy. Development and Validation of a Multivariable Risk Prediction Model. *Ann Surg*. 2020 Jan 14. doi: 10.1097/SLA.0000000000003771.



Encouragingly, the model maintained excellent performance in the validation population: AUROC 0.927 and 0.964 respectively for the validation cohorts (Figure 2 reproduced as above). We therefore concluded that the BN could accurately predict the risk of TIC in an individual patient from standard admission clinical variables and that this model could optimize the early, accurate, and efficient activation of hemostatic resuscitation protocols.

5.2.2. We synchronously undertook preliminary work to understand the performance of this model in a military population⁶. Sourcing a group of military trauma patients where there was accessible data containing both the features and inputs required by the model and the laboratory markers of coagulopathy (prothrombin time - PT, international normalized ratio - INR, rotational thromboelastometry - ROTEM) to allow us to verify the model's prediction proved challenging. Eventually, a data cohort of 106 such patients – selected for another study – was identified and permission obtained to use their data for this study. A further challenge was how to incorporate Blast mechanism in a model where Mechanism of Injury was dichotomized into Blunt and Penetrating.

⁵ PhD thesis. Major Max Marsden. Queen Mary University London. 2020. Supervisor Col N Tai. In Composition.

⁶ Mossadegh S. Chapter 3. Predictive accuracy of the TIC-BN in military patients. In: Mossadegh S. Application and development of Bayesian Networks for predictive modelling of coagulopathy and mortality in trauma patients. PhD Thesis. Queen Mary University London. 2020. Pp 110-138. Supervisor: Col Nigel Tai

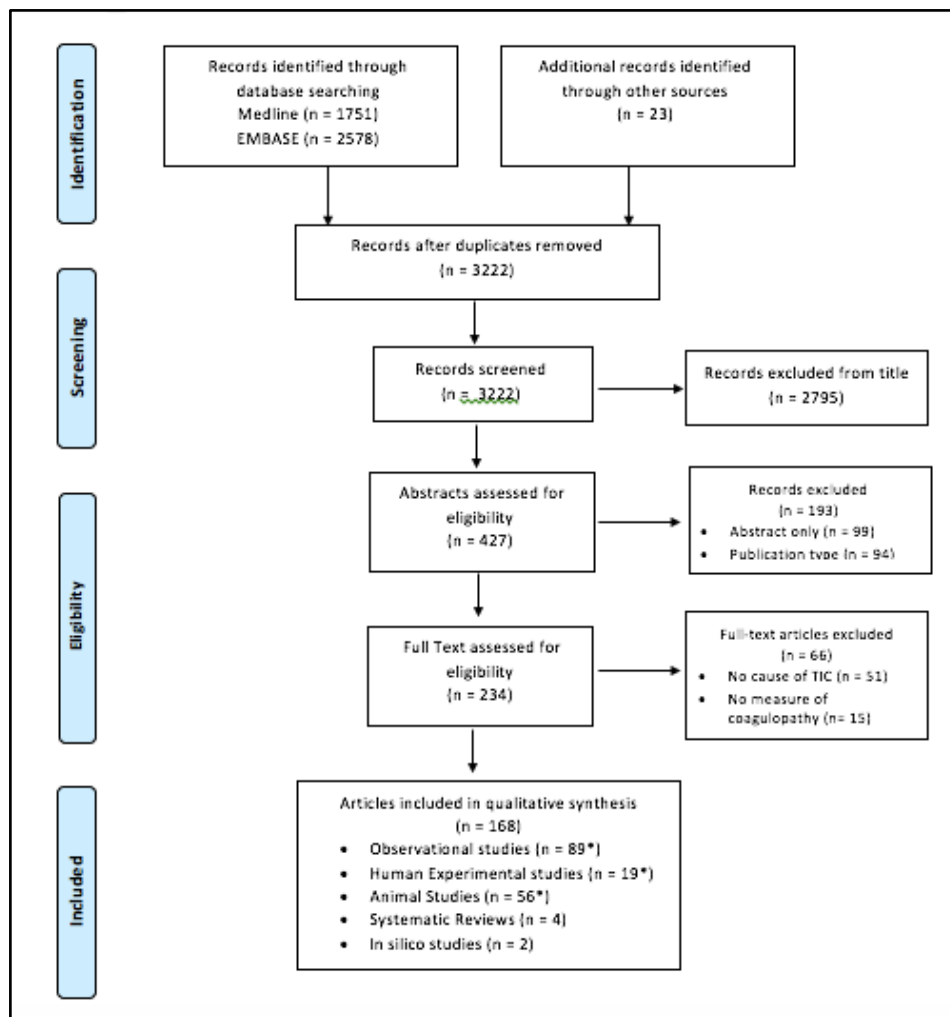
TIC-BN Prediction Based on:	AUROC	Specificity at 0.90 Sensitivity	Specificity at 0.80 Sensitivity
Exclude MOI	0.66 [0.54 – 0.77]	0.15	0.31
Exclude MOI and Physiology	0.63 [0.51 – 0.74]	0.16	0.43
Blunt MOI Substituted for Blast	0.67 [0.56 – 0.78]	0.24	0.29
Exclude Physiology (Blunt as Blast)	0.64 [0.53 – 0.76]	0.18	0.41
Penetrating MOI Substituted for Blast	0.66 [0.54 – 0.77]	0.20	0.31
Exclude Physiology (Pen. as Blast)	0.63 [0.52 – 0.74]	0.26	0.45
<i>TIC-BN – Trauma Induced Coagulopathy Bayesian Network, AUROC – Area Under Receiver Operator Curve, MOI – Mechanism of Injury, Phys. – Physiology, Pen. – Penetrating.</i>			

5.2.3. The results of this study revealed that for military patients the TIC BN performed worse than the civilian patient groups used for its development. Potential reasons for underperformance include the military population differing significantly from the development cohort (age, physiology, injury severity). The presence of Blast was not a define-able input feature for this model and this may also have contributed to lack of performance.

5.2.4 To understand and improve this model, our group is collaborating with the UK Centre for Defence Pathology in order to take the dataset of UK JTTR-documented casualties and linking this to existing laboratory data held on the UK Defence Medical Services Laboratory Information Management System, so that a more representative population can be used to develop and train an augmented, military specific version of the model.

5.2.5. This work will be addressed by Dr Rebecca Stoner, W81XWH-19-2-0047- funded PhD candidate (Trauma & Orthopaedic trainee) working with Mr Erhan Pisirir, W81XWH-19-2-0047- funded PhD candidate (Computer Science), supervised by Dr Lina Kyrimi W81XWH-19-2-0047- funded post-Doctoral Research Assistant (Computer Science).

5.2.6. As part of the preparatory work to refine the model in favour of a military specific variant, we have undertaken a systematic review of the causes of trauma induced coagulopathy. We searched the MEDLINE and EMBASE databases using a combination of the terms “trauma” and “coagulopathy” from inception of the databases to 01 January 2017. Original articles were included that provide evidence of a causal relationship between a given factor and TIC. Data was extracted and summarised in a narrative form. The evidence presented in each study was assessed with a modified Bradford Hill’s criteria for causation and the study’s risk of bias. The protocol was registered with PROSPERO; RD42017057482



5.2.7. One hundred and sixty-eight articles were included in this review. Two articles described more than one study. Causal evidence was provided from three main categories of study: human observational (89 studies), human experimental (19 studies) and animal experimental (56 studies). There is evidence to support seven causes of coagulopathy: hypoperfusion, tissue injury, acidaemia, hypothermia, dilution, brain injury and choice of resuscitation fluid. We concluded that multiple study designs provide casual evidence for a combination of endogenous and iatrogenic drivers of Trauma induced coagulopathy. ⁵

5.2.8 YEAR TWO UPDATE Specific Aim 1: Develop and validate a prognostic model for TIC in injured military personnel (TIC-MIL)

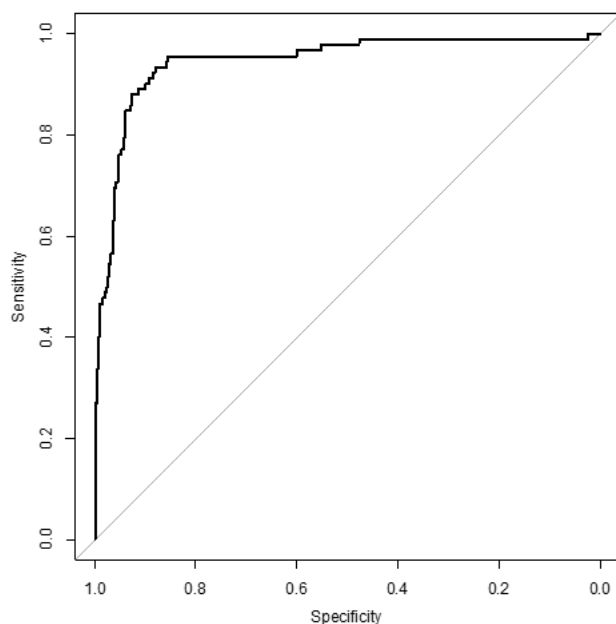
5.2.9. Major Task 1: Develop a prognostic model for TIC

Methods: Data was obtained from the UK Joint Theatre Trauma Registry, comprising UK military personnel injured in Iraq and Afghanistan between 2009-2014 with laboratory testing of coagulation on arrival at a Medical Treatment Facility. The model structure was updated from the civilian TIC-BN to incorporate blast mechanism, injuries characteristic of military trauma, and estimated blood loss per injury. The two latent variables with unknown states in the training dataset, perfusion and TIC, were labelled in several ways through a combination of rules-based classification and data clustering, followed by expert review of discrepancies. Internal 10-fold cross validation was conducted to test the model's performance in terms of discrimination, calibration, and accuracy.

Progress: Model developed and internally validated. Initial results subset presented at Blast Injury Conference 2021, full initial results accepted for oral presentation at MHSRS 2021 (cancelled due to COVID). Full final results submitted to European Congress of Trauma and Emergency Surgery 2022.

Results: Our development cohort included 678 combat casualties with median age 24 (18-55) years. 675/678 (99.6%) were male, with a median Injury Severity Score of 9 (Interquartile range 4-20). Overall mortality was 2.9%. The rate of TIC was 12.6%. Calibration was good (slope 1.3, intercept -0.023) with excellent discrimination (AUROC 0.95 (0.92-0.97)). Accuracy was 0.91 with Brier Score 0.06 and Brier skill score 0.5.

Figures/Tables: 10-fold cross validation



Next Steps: This work leads to Major Task 2: External validation, for which the data request is in progress. It also relates to Specific Aim 5, Major Task 2: Develop a prognostic model for blood product requirements. We also plan to incorporate the diagnostic accuracy data to simulate model use in Role 1 thereby extending model/Decision Support application for far-forward personnel.

5.2.10. Accuracy and uncertainty of prehospital clinical assessment of injury

[SOW: Specific Aim 1, major task 1, subtask 1, to help develop structure of TIC-MIL BN]

Aims: 1) Determine the diagnostic accuracy of prehospital clinical assessment in identifying life- or limb-threatening injuries. 2) Determine the effect of clinician uncertainty on diagnostic inaccuracy of prehospital clinical assessment in identifying life- or limb-threatening injuries. 3) Analyse factors affecting diagnostic inaccuracy of prehospital clinical assessment in identifying life- or limb-threatening injuries, including missed injuries.

Methods: Retrospective study evaluating diagnostic performance of expert trauma clinicians in the prehospital setting, comparing with diagnoses identified in hospital. All adult (≥ 16 years of age) injured patients who were conveyed to the regional major trauma centre between 01/01/2019 and 31/12/2020, who were assessed by expert trauma clinicians in an urban helicopter emergency medical service were included.

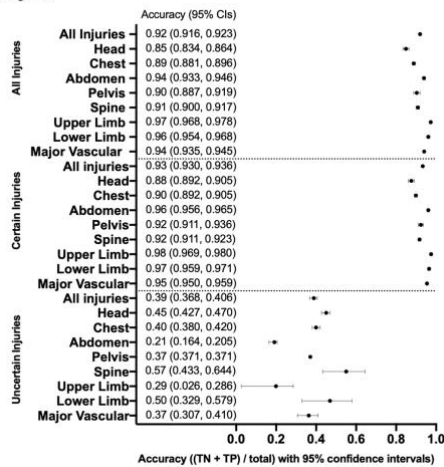
Progress: Completed data collection, analysis, and write up. Preparing for submission to journal.

Results: 921 patients were included in our study. Overall accuracy of prehospital was 92% (95% confidence interval (CI) 0.916 to 0.923), 93% (95% CI 0.930 to 0.936) when clinicians

had high certainty of injuries, and 39% (0.368 to 0.406) when clinicians had low certainty of injuries.

Figures/Tables:

Figure 2: Accuracy of prehospital identification of life and limb-threatening injury AIS categories.



Next Steps: Incorporate accuracy and uncertainty information of injury predictors into TIC-MIL and TIC-CIV models, then validate using my database, including prognostic performance with and without accuracy/uncertainty information.

5.3. Major Task. Develop and validate adaptation of a LIMB-MIL prognostic model that can predict projected viability of an injured limb/outcome of limb reperfusion

- “Development Complete (100%)”
- Military Validation Complete (100%)”

5.3.1 The background to this task is that estimating the likely success of limb revascularization in patients with lower-extremity arterial trauma is challenging. However, such judgements are central to decisions made by trauma clinicians weighing up whether to attempt limb salvage or perform amputation. The reason why such decisions are difficult is that there are a variety of factors that need to be considered, accompanied by different weights, which may interact with each other to influence the anticipated outcome. A prediction model that can quantify an individual patient’s risk of failed revascularization may prevent futile attempts at limb salvage or un-necessary ablation in an otherwise viable limb. This work was chosen for presentation at the annual meeting of the American Surgical Association and published in Annals of Surgery in July 2020⁷.

⁷ Perkins et al. Predicting the outcome of limb revascularization in patients with lower-extremity trauma. Development and external validation of a supervised machine-learning algorithm to support surgical decisions. Ann Surg. 2020 Jul 9. doi: 10.1097/SLA.0000000000004132

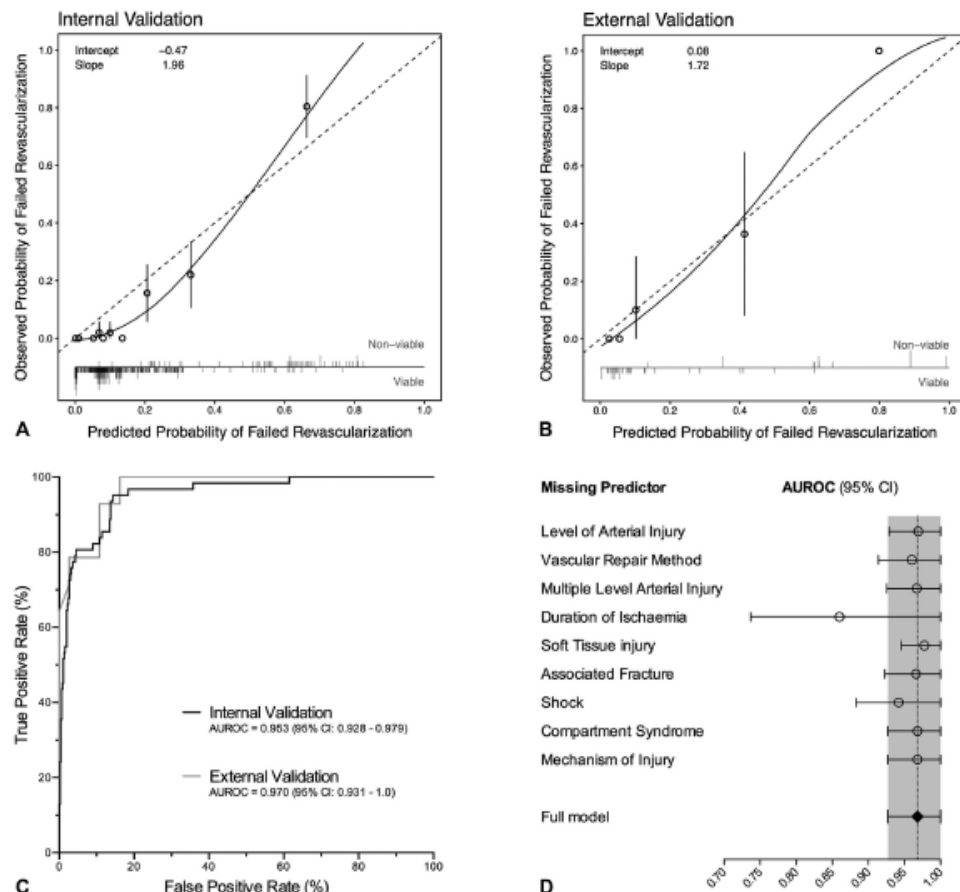


FIGURE 2. Performance of the Bayesian network prognostic model. The calibration plot shows the relationship between ideal (dashed line) and observed (solid line) predicted values in the internal (A) and external (B) validation cohorts. The rug plot along the bottom demonstrates the distribution of predicted probabilities. The circles with 95% confidence intervals indicate observed frequencies by decile (internal validation) and quintile (external validation) of predicted probability. The receiver-operating-characteristic curves show the relationships between true positive and false positive predictions in the internal and external validation cohorts (C). The forest plot compares the performance of the model at predicting revascularization failure in the external validation cohort when each of the models predictors in turn was omitted as inputs (D). Performance was measured by calculating the area under the receiver-operating-characteristic curve (AUROC) with 95% confidence intervals.

5.3.2. Performance was compared to the mangled extremity severity score on a population of 508 US military and 51 UK military casualties with major extremity trauma. Rates of amputation performed because of nonviable limb tissue were 12.2% and 19.6% respectively. A 10-predictor BN accurately predicted failed revascularization: area under the receiver operating characteristic curve (AUROC) 0.95, calibration slope 1.96, Brier score (BS) 0.05, and Brier skill score 0.50. The model maintained excellent performance in an external validation population: AUROC 0.97, calibration slope 1.72, Brier score 0.08, Brier skill score 0.58, and had significantly better performance than mangled extremity severity score at predicting the need for amputation [AUROC 0.95 (0.92–0.98) vs 0.74 (0.67–0.80); $P < 0.0001$]. We concluded that the prediction model can accurately predict the outcome of limb revascularization at the time of initial wound evaluation.

5.3.3. Next Steps: This work leads to Major Task 2: External validation, for which the data request is in progress. It also relates to Specific Aim 5, Major Task 2: Develop a prognostic model for blood product requirements. We also plan to incorporate the diagnostic accuracy data to simulate model use in Role 1.

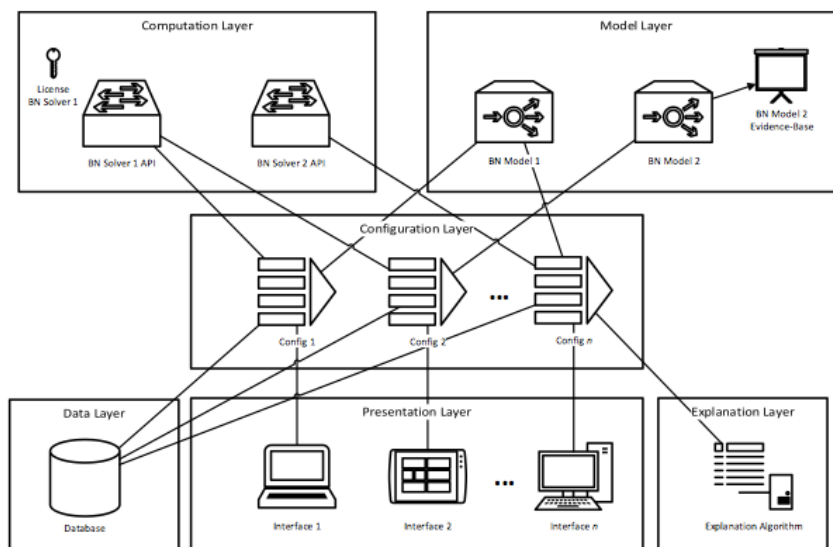
5.4. Major Task. Develop a prototype Clinical Decision Support tool for use of the TIC-MIL and LIMB-MIL prognostic models.

- a. “Interface (90%)
- b. Evidence Browser/Library (80%)”

5.4.1. The background to this is that, whilst prognostic tools may produce accurate predictions, technical barriers regarding implementation and the user-experience related to these models slows-down their adoption in clinical care. Clinicians prefer prediction models that are easy-to-use, have a clear evidence-base and an interpretable reasoning mechanism. Although technologies that separately provide these features are available, their integration and delivery to clinicians is a complex task. Work has been carried out regarding integration of Predictive Model and Clinical Decision support. The proposed framework integrates technologies for data-handling and user interfaces with model computation and explanation. It offers a simple interface for system-administrators, model developers and clinical end users, enabling each of these actors to focus on their tasks while implementing and using a predictive model.

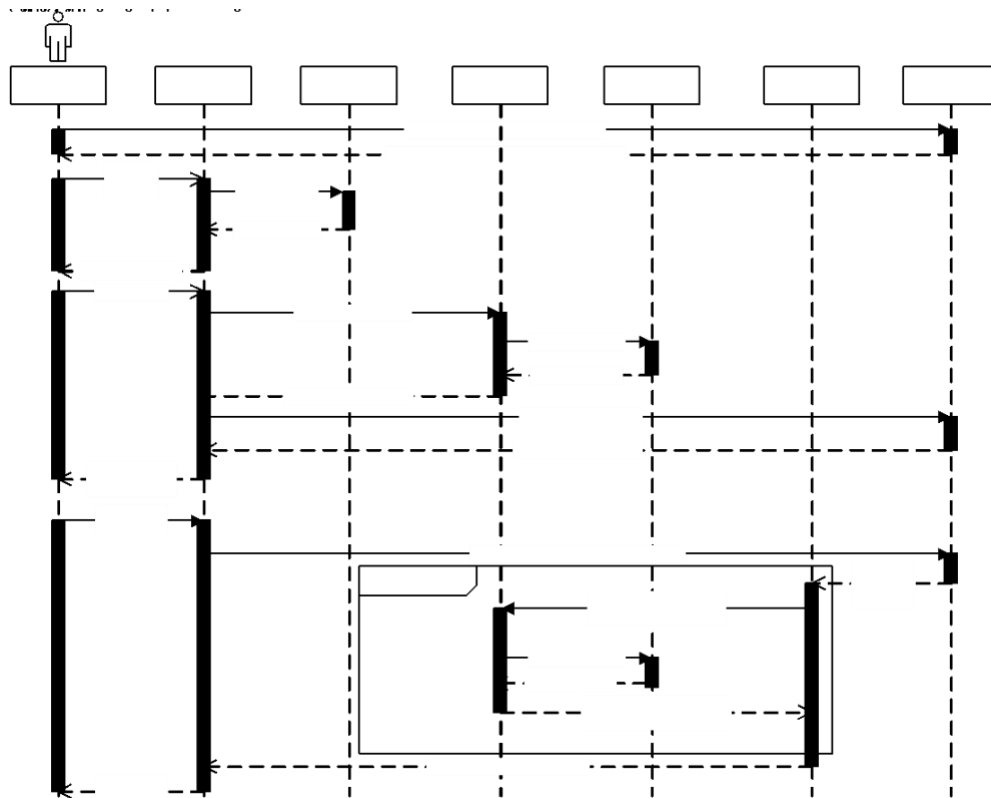
5.4.2. The framework enables the integration of modelling software, database, explanation and evidence infrastructure, and user interface. Clinical models computed by different modelling software can be implemented to a variety of user interfaces by using simple configuration files (CFs). The framework is based on probabilistic graphical models, (Bayesian Networks) in particular. The system is sufficiently flexible to be expanded with other types of interfaces, software and modelling technologies as communication between database, user interface and modelling software is handled by standardized forms.

5.4.3. The approach to this work required the identification of six layers needed to compose the interface and supportive functions. These layers consist of a presentation layer (that prepares the user input and output interfaces), a computation layer (that contains the BN inference software), and a model layer that contains the BN models and, if available, their evidence-bases). The configuration layer defines the design of the user interfaces, and the model and BN software that will be used for them. User information and privileges, and the data about past predictions are kept in the data layer. The explanation layer includes algorithms that can provide a detailed explanation of the reasoning mechanism of specific predictions as illustrated below.

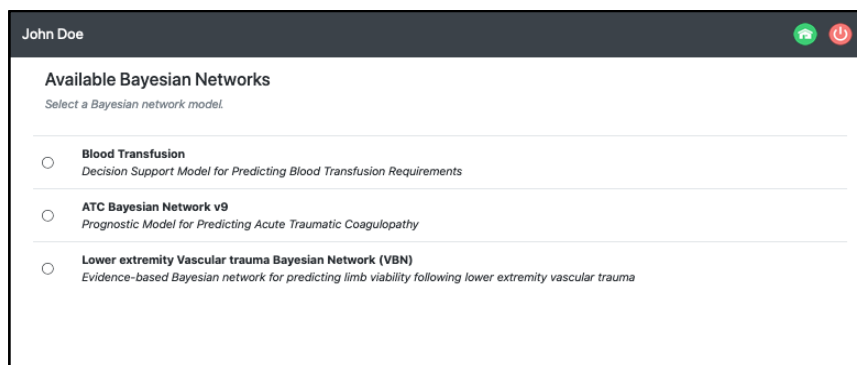


5.4.4 The engineered solution to combine these layers is represented below. When an end user enters the system, the framework checks the access privileges of the end user in the Data Layer and shows the available interfaces for this end user. The end user then selects

an interface, and the interface is built in the Presentation Layer based on its settings as defined in the Configuration Layer. Next, the end user enters inputs on the interface. The Presentation Layer prepares the input Java Script Object Notation (JSON) in the format based on these inputs and passes it to the Computation Layer. The software and BN model defined in CF are used by the Computation Layer to compute the posteriors of the output variables requested. The posteriors are encoded into the output JSON format and sent back to the Presentation Layer. Afterwards, the Presentation Layer prepares the graphs for displaying the outputs and records both the input and the output, in other words the prediction, as JSON strings in the Data Layer.



5.4.5 Screenshots from the User Interface are portrayed below to demonstrate the progress made in delivering the solution:



- Initial User Interface with presentation of different BNs to User

John Doe

ATC Bayesian Network v9

To create a new patient, click the button below.

[Create a new patient](#)

Previous patients

To review and make new predictions for existing patients click a patient below.

DoA: 2020-06-24
Created by: byet

DoA: 2020-08-31
Created by: johndoe

Prediction generated: 2020-08-31 at 07:27:32 (johndoe) [View](#) [Revise](#) [Delete](#)

[New prediction for this patient](#) [Delete patient](#)

DoA: 2020-06-26, Sex: Female, Age: L65, Mechanism: Blunt, Energy: Low
Created by: lina

DoA: 2020-06-22, Age: L65, Mechanism: Blunt, Energy: High
Created by: william

- Patient record selection or creation of record

John Doe

ATC Bayesian Network v9

Prognostic Model for Predicting Acute Traumatic Coagulopathy

[Patient Info](#) [Background Information](#) [Primary Survey](#) [Vitals](#) [Arterial Blood Gass](#)

8/18. Haemothorax

☒ Yes
☐ No
☐ Unknown

10/18. Unstable Pelvis

☐ Yes
☐ No
☒ Unknown

9/18. Long Bone Injury

☐ Yes
☐ No
☒ Unknown

11/18. FAST Scan

☐ Positive
☒ Negative
☐ Unknown

[Home Page](#) [Calculate ATC Risk](#)

- Initial Input of variables – note that coagulopathy risk (ATC) can be calculated without proceeding to next page

John Doe

ATC Bayesian Network v9

Prognostic Model for Predicting Acute Traumatic Coagulopathy

[Patient Info](#) [Background Information](#) [Primary Survey](#) [Vitals](#) [Arterial Blood Gass](#)

12/18. Heart Rate

BPM

14/18. Temperature

°C

13/18. Systolic Blood Pressure

90

15/18. Glasgow Coma Score

e.g. 13

[Home Page](#) [Calculate ATC Risk](#)

Further input screens for variables

John Doe

ATC Bayesian Network v9

Prognostic Model for Predicting Acute Traumatic Coagulopathy

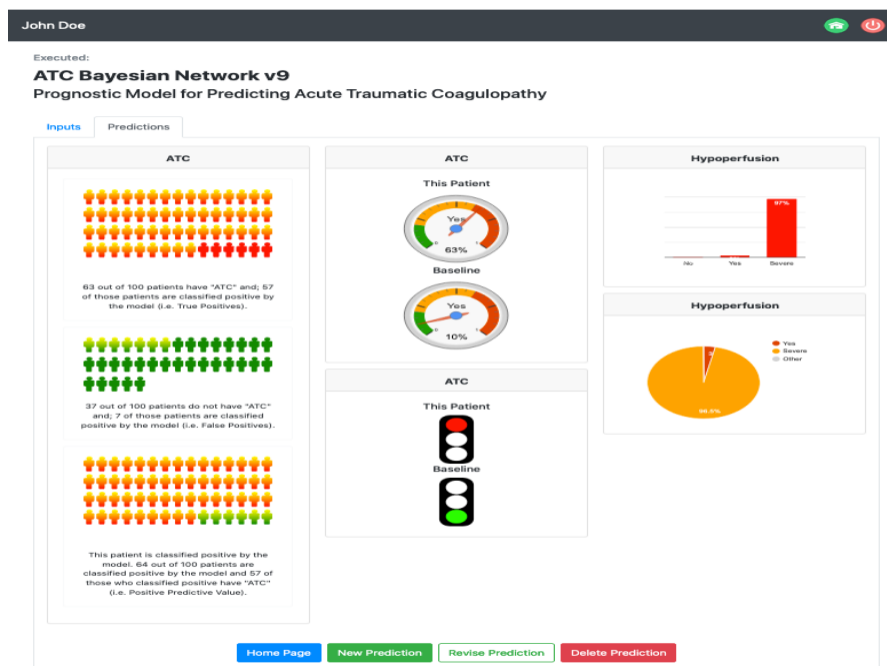
Patient Info Background Information Primary Survey Vitals Arterial Blood Gass

16/18. **Lactate**
mmol/L

18/18. **pH**
6.9

17/18. **Base Excess**
mmol

Home Page Calculate ATC Risk



Risk calculated and portrayed in a number of different figurative formats

5.4.6. This system/framework is near completion. The next stage is to a) expose the User Interface to a range of users and refine according to user feedback and b) develop a more intuitive data input segment that allows variables to be inputted in a more facile manner (touch screen, tablet-oriented, anatomic representations of injury).

5.4.7. The background to the evidence library is that, as well as a facile user interface (that encourages clinicians to use the tool), and an accurate portrayal of outcome (that conveys the prognostic information in a clinically meaningful way), the proposed system will generate trust if it can deliver an *explanation* as to the result. We have developed two approaches to this problem.

5.4.8. The first approach is to link the published evidence that the model has relied upon to generate its prediction. This curated list of pubmed listed papers – or Evidence Browser – has previously been compiled for the TIC model. An online evidence browser for the MIL LIMB BN has also been progressed. The model variables are described, and the model

structure presented to explain the relationships between variables. Additionally, the evidence browser defines the states that each variable can take. The browser allows the user to distinguish between predictors, causal factors and latent variables in the model. The evidence for variable types, relationships and states come from several sources, including: primary research, meta-analysis of primary research, expert opinion, and data-driven statistical inference techniques. The browser provides definitions and references to the original sources of information, including: datasets, academic articles, and expert opinions. The remaining work related to the LIMB BN evidence browser, is to complete the links connecting the original sources of evidence used to informed model development and the evidence browser interface

Main Page
Variables
Relations
Fragments
Data
Experts
Publications

Evidence Browser: Relation: Hypoperfusion → ATC

Relation: **Hypoperfusion** → ATC

Evidence:

- Hypoperfusion appears to be a primary driver of trauma coagulopathy. Acute traumatic coagulopathy is only evident in the presence of tissue hypoperfusion
[References]
Brohi2009
BrohiEtAl2007a
BrohiEtAl2007b
BrohiEtAl2008
CohenEtAl2013
FrithEtAl2010
HessEtAl2008
SimmonsEtAl2011
SpahnEtAl2013
WafaisadeEtAl2010
- Coagulopathy is associated with combination of tissue hypoperfusion and tissue injury in a mice model
[References]
CheseboroEtAl2009
- Coagulopathy developed in rats subjected to haemorrhagic shock and tissue perfusion.
[References]
FrithEtAl2010
- Patients with severe tissue injury but no physiologic derangement rarely present with a coagulopathy. Tissue trauma is, therefore, an initiator of coagulation, but in isolation is rarely responsible for clinical coagulopathy.
[References]
Brohi2009
BrohiEtAl2007a
SpahnEtAl2013

The screenshot above shows the evidence regarding a relation included in the BN, and its references. When an end user clicks one of the references, they are directed to its PubMed link. An evidence-base could enable better understanding of the model and build trust with end-users as it can clarify the clinical knowledge-base of the model. Whilst the TIC BN Browser is 100% complete (and will be utilizable by the military variant), the evidence browser for the MIL LIMB BN is in development (80% compiled) and should be completed within the next three months.

5.4.9. The second approach is to use a tiered explanatory function that will allow the user to configure the degree of detail that the CDS portrays in explaining why a given result has been generated. Such functionality permits the end-user to tailor the amount of detail to her personal circumstances and the time that she has to drill in to the explanation. Our method can be used in hybrid networks that have both continuous and discrete nodes and requires no user input. In addition, we simplify the process of identifying the most important evidence and chains of reasoning, so we can rapidly produce a good and concise explanation, but not

necessarily the most complete one. The method produces an incremental explanation that has three successive levels of detail, as illustrated thus:

Prediction	
The probability of <u>TIC</u> is 11%. This patient has a 14% increase in probability of having <u>TIC</u> compared to an average trauma call patient	
Explanation: Level 1	
Factors supporting the <u>TIC</u> prediction	Factors not supporting the <u>TIC</u> prediction
Pre-hospital fluids > 500ml** GCS: 5** Haemothorax: Yes** Energy High	Systolic Blood Pressure: 168 Long bone fracture: No Lactate: 0.9
Explanation: Level 2	
26% increase in probability of having a <u>Normal 'Tissue Perfusion'</u> , compared to an average trauma call patient 230% increase in probability of having a <u>Severe 'Tissue Injury'</u> compared to an average trauma call patient	
Explanation: Level 3	
Factors supporting the <u>Severe 'Tissue Injury'</u> prediction	Factors not supporting the <u>Severe 'Tissue Injury'</u> prediction
GCS: 5 Haemothorax: Yes Energy High	Long Bone Fracture: No
Factors supporting the <u>Normal 'Tissue Perfusion'</u> prediction	Factors not supporting the <u>Normal 'Tissue Perfusion'</u> prediction
Systolic Blood Pressure: 168 Lactate: 0.9 Long Bone Fracture: No	Haemothorax: Yes

5.4.10. The relationship between Trust and Explanation has been studied by our group and published in 2020 in *Artificial Intelligence in Medicine* (Impact Factor 4.47) ⁸. In this study, 10 trauma case scenarios were presented to 16 senior and 16 junior clinicians, who were asked to predict the likelihood of coagulopathy and exposed to the results of the CDS prediction, with and without an accompanying, tiered explanation. The primary objectives of the evaluation were to assess: (i) similarity between clinicians' reasoning and that supplied in the model's explanation and (ii) an assessment of any increase in trust associated with the provision of an explanation. The secondary objectives were to assess: (i) potential benefit to the clinicians' assessment and decision making given an explanation and (ii) clarity of the explanation. The study showed that an explanation is meaningful and similar to clinicians' own reasoning for their native (un-augmented) predictions. Clinicians liked the explanation function as it gave them an insight into the model's reasoning, but they would prefer the explanation output to be graphically enhanced, and felt that the second tier of explanation was too detailed to be used in an acute clinical setting.

5.4.11. YEAR TWO UPDATE. Designing/updating server technology for integration of BN predictor capture and risk presentation

[SOW: Specific Aim 3, subtask 1]

Aims: Translation of underlying Server technology (from php to javascript) in order to allow for multiple Apps to interact with the same Server (ie improving future scalability).

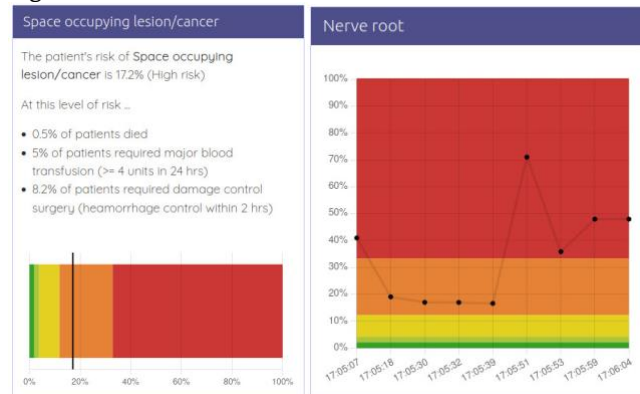
⁸ Kyrimi et al. An incremental explanation of inference in Bayesian networks for increasing model trustworthiness and supporting clinical decision making. *Artif Intell Med E pub* 2020 Jan 31. doi: 10.1016/j.artmed.2020.101812

Methods: Implementation of new features including: user log in system; admin upload of Agena Risk files to allow saving of Bayesian Network states (and readiness for input); tailoring functionality to allow admin users to specify user privileges; outputs can be displayed using bar charts, pie charts or icon arrays, and dynamic risk over time.

Progress: Server running well, and individual Bayesian Network risk models able to be uploaded, and configured using widgets (Javascript). Writing up dynamic risk presentation review.

Results: NA

Figures/Tables:



(Note- please ignore wording of “space occupying lesion/cancer” and “nerve root” - these are widgets being used for another project, which are being adapted for prediction of TIC)

Collaborators: Chris Joyner, Erhan Pisirir

5.4.12. Prototype digital interface for injury capture ('Body Map')

[SOW: Specific Aim 3, subtask 2]

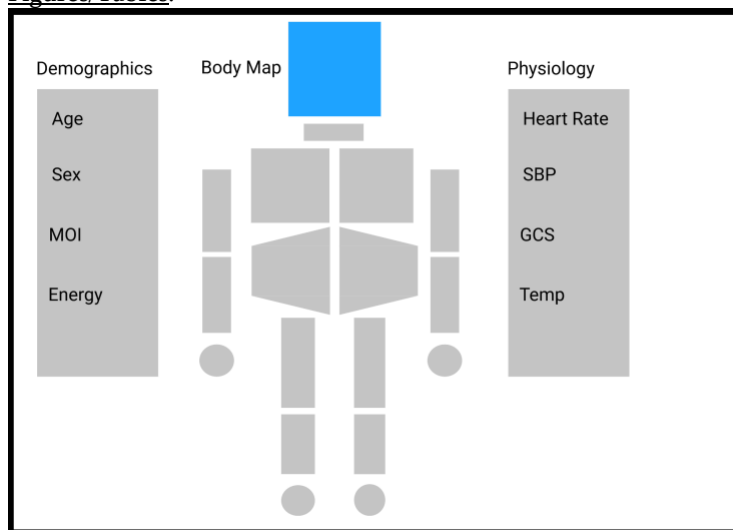
Aim: Develop a prototype digital interface for injury capture, capable of recording injury information and capturing for BN risk prediction.

Methods: Identifying the injury information which must be entered into the Bayesian Network (BN) models currently developed or under development. Then, utilising the Figma.com prototyping website, create a prototype body map which captures only necessary injury information.

Progress: In mid-stages of developing a basic prototype body map on Figma.com prototyping website, capable of selecting key injury predictors which fuel the model. Need to add uncertainty toggle (probably/high certainty or possibly/low certainty), and improve design.

Results: NA

Figures/Tables:



Collaborators: Chris Joyner, Evangelia Kyrimi, Rebecca Stoner, Erhan Pisirir

5.4.13. **Visual aids for interpreting predictive probability distributions obtained from Bayesian Network models and overcoming cognitive biases**

[SOW: Specific Aim 3, subtask 1]

Aims: Interpreting predictive probability distributions obtained from Bayesian Network (BN) models and for overcoming the associated biases via visual aids.

Methods: Various visual aids for risk prediction and model performance will be shown to participants on an online questionnaire study, and the effectiveness of these visualizations will be evaluated.

Progress: Submitted to ethics, awaiting approval before inviting participants.

Results: NA

Figure/Tables: NA

6. **YEAR TWO PROJECT MILESTONES**

Research Phase 2 - Months 13-24

“Major Task 1 – User simulation experiments and user interviews

Major Task 2 – Develop a prognostic model for blood product requirements – 40% complete

Major Task 3 – External validation of prognostic performance

Major Task 4 – Develop a prognostic model of mortality in injured military personnel - 40%

Major Task 5 – External validation of prognostic performance”

6.1. **Major Tasks 2-3. Develop a prognostic model for blood product requirements**

6.1.1. A large amount of foundational work, and significant substantive work, has been completed ahead of schedule. The background is that, during the development of the TIC BN model it became apparent that prediction of blood product requirement was a derivable function of the model, as TIC and major bleeding are inter-related. Whilst there are over 40 published models to identify patients with major bleeding such decision support models are not in regular clinical practice. In the UK, the National Institute for Health and Care Excellence guidelines specifically warn against using these models ^{9,6}. In the USA, the ABC score is the most widely cited and endorsed for the prediction of massive haemorrhage.

6.1.2. We have made a preliminary assessment of the extent to which the TIC BN could be used to predict patients at risk of bleeding and to understand whether it would have superior accuracy to native predictions. Using a retrospective study design, we compared the real-world predictive accuracy of clinicians to a hypothetical decision made by the TIC BN, employing a civilian research trauma database. The study population was 858 patients of whom 697 received 0-3 units of blood, 112 received 4-9 units and 49 received 10 or more. We found the sensitivity and specificity of the TIC BN to be 84% and 89% respectively when predicting that a patient would need 4 or more units of blood (Packed Red Blood Cells; PRBC) for trauma resuscitation, and 96% and 86% when predicting that a patient would need 10 or more units. Concerning prediction of 4 units PRBC need or more, and at the default TIC BN operating threshold of 10%, there was no statistical difference between the TIC BN and native clinical judgement in sensitivity (74% vs 75%, $p = 0.87$). However, clinicians were more specific (95% vs 92%, $p = 0.002$). For a prediction of 10 units or more, model sensitivity improved but did not reach statistical significance (86% vs 96% $p = 0.13$).

⁹ Major trauma: assessment and initial management (NICE guideline 39). 2016. at www.nice.org.uk/guidance/ng39.

At the second definition clinicians remained more specific than the model (86% vs 85%, $p = 0.02$). The TIC BN model was superior to the ABC score.

	≥ 4 PRBCs			≥ 10 PRBCs		
	Clinicians	ED TIC BN ¹	ABC Score	Clinicians	ED TIC BN ¹	ABC Score ²
Sensitivity, %	74	84	40	86	96	59
Specificity, %	95	89	94	86	86	90
Positive Predictive Value, %	78	63	55	28	29	21
Negative Predictive Value, %	94	96	89	98	100	98
Accuracy, %	91	88	85	86	86	89

The impact of these findings is that the native model seems to perform as well or as near well as clinicians, and much better than the most reported alternative prediction tool.

6.1.3. We then looked at the use of the model in a pre-hospital environment and undertook a prospective external validation ($n=135$) of the pre-hospital use of a TIC BN and its ability to predict whether *any* blood would be transfused in civilian patients with a discrimination AUROC = 0.89 (95% CI 0.83 – 0.95). This was not significantly different to expert clinicians' predictions (clinical judgement = AUROC = 0.89 (0.84 – 0.95), $p = 0.874$). Continuous blood volume prediction was unfeasible and instead clinically relevant categories of blood transfusion were used. Using information taken immediately after a pre-hospital primary survey the TIC BN was able to predict blood volume transfused within 4 hours of injury in categories of 0, 1-4, >4 units of PRBCs with an accuracy of 67% and Cohen's $\kappa = 0.420$ (95% CI 0.305 – 0.534). When clinicians were given information from the TIC BN model their classification accuracy improved from 61% to 70% and Cohen's $\kappa = 0.521$ (95% CI 0.395 - 0.647).

6.1.4. The TIC model, with minimal reconfiguration, appears to offer useful and meaningful predictive functionality regarding likely blood product requirement. These predictions could be made immediately after the pre-hospital primary survey and within 15 minutes of arrival in the ED. However, the model is configured for civilian and not military trauma patients, and thus a specific military model was developed, recognizing the importance of predicting blood transfusion directly (rather than by conversion of a patient's risk of TIC). Models were iteratively developed, first trained in a civilian patient cohort and then later in a military cohort, that predicted both the likelihood of blood transfusion pre-hospital and the volume of blood transfused in-hospital within 4 hours of injury. These models contained the same basic structure as the TIC models but were also able to predict 4 outcomes directly: 1) the likelihood of any prehospital blood, 2) the likelihood of >4units of blood within 4 hours of injury, 3) the risk of TIC from pre-hospital information and 4) the risk of TIC from ED information. The model was developed and internally validated on 2555 patients from the UK JTTR. JTTR data provided information from the pre-hospital (Role 1) phase of care and ED (Role 3) care.

6.1.5 The military model structure (page 32) was largely unchanged from the civilian model with the inclusion of blast as a mechanism of injury and increased granularity on amputation injuries. Some parameters (priors) for this model were learnt from data and some were lifted directly from the civilian model where military data was not available. In internal cross validation the military BN was able to predict pre-hospital blood transfusion with AUROC of 0.77 (0.73-0.80) and patients that would receive more than 4 units of blood within 4 hours of injury with an AUROC of 0.91 (0.89-0.93). Further work will be undertaken to refine this model and externally validate it on suitable populations.

6.1.6. User experiments testing usability of CDSS predictor capture, CDSS risk presentation, explanation generator, and knowledge browser

[SOW: Specific aim 4, 8, and 9]

Aims: 1) Evaluate the usability of a user interface for electronic capture of predictors in trauma. 2) Determine the advantages, disadvantages, barriers to workflow and clinical credibility of a user interface for electronic capture of predictors. 3) Evaluate the usability of a user interface for risk presentation in trauma. 4) Determine the effect of a user interface for dynamic risk presentation in trauma on clinician situational awareness, decision making and credibility. 5) Evaluate the usability of the explanation page of the CDSS. 6) Determine the effect of explanations of the model and reasoning on end user understanding of, trust in, and decision confidence before and after using a CDSS. 7) Evaluate the usability of the medical evidence browser of the CDSS. 8) Determine the effect of a knowledge browser on end user understanding of, trust in, and decision confidence after using a CDSS.

Methods: Prospective iterative, observational mixed methods study evaluating a CDSS designed for use by prehospital trauma clinicians.

Progress: Designing the protocol and preparing for submission to QMUL for sponsorship and HRA for approval. Aim to submit in October 2021.

Results: NA

Figures/Tables: NA

Collaborators: Erhan Pisirir

6.1.7. YEAR 2 UPDATE. Specific Aim 5: Develop and validate a prognostic model for blood product requirements

Methods: This work will use the dataset from the UK JTTR, plus additional data from Prof Tom Woolley/DSTL. The structure of the developed TIC-MIL model will be used as a basis for the transfusion model structure, since it now incorporates measures of blood loss per injury.

Progress: Ongoing

6.1.8. Accuracy of prehospital clinical assessment of major bleeding

[SOW: background work for Specific Aim 5, major task 2, subtask 1]

Aims: 1) Determine the diagnostic accuracy of prehospital clinical assessment of major bleeding. 2) Analyse factors affecting diagnostic inaccuracy of prehospital clinical assessment of major bleeding.

Methods: Retrospective study evaluating diagnostic performance of expert trauma clinicians in the prehospital setting, comparing with in-hospital indicators of major bleeding. Major bleeding will be defined as a composite of biochemical (raised lactate/BE), clinical (≥ 4 blood transfusions given) and surgical outcomes (damage control surgery). All adult (≥ 16 years of age) injured patients who were conveyed to the regional major trauma centre between 01/01/2019 and 30/06/2021, who were assessed by expert trauma clinicians in an urban helicopter emergency medical service were included.

Progress: Data collection ongoing.

Results: NA

Figures/Tables: NA

6.2. Major Task 2-4. Develop a prognostic model of mortality.

6.2.1. Exploratory work has allowed us to understand the performance of the civilian TIC model in predicting military mortality, using the highly selected JTTR population (used to explore prediction of TIC in military cohorts (section 5.2.2)). In this population of 322

severely injured patients, the model performed reasonably (AUROC 0.76-0.78) although it did not outperform other established models of trauma mortality:

Trauma Score	AUROC	Specificity at 0.90 Sensitivity	Specificity at 0.80 Sensitivity
TIC-BN (Penetrating)	0.76 [0.68 – 0.85]	0.46	0.62
TIC-BN (Blunt)	0.78 [0.69 – 0.86]	0.50	0.66
ISS	0.89 [0.82 – 0.95]	0.60	0.90
NISS	0.86 [0.79 – 0.93]	0.64	0.77
TRISS	0.80 [0.72 – 0.88]	0.48	0.81
RTS	0.74 [0.65 – 0.83]	0.44	0.50
<i>TIC-BN – Trauma Induced Coagulopathy Bayesian Network, AUROC – Area Under Receiver Operator Curve, ISS – Injury Severity Score, NISS – New ISS, TRISS – Trauma ISS, RTS – Revised Trauma Score</i>			

6.2.2. Further sensitivity studies showed that, counter-intuitively, mechanism of injury and physiology inputs contributed little to model performance which led us to the conclusion that a novel model should be progressed. Furthermore, we wished to understand whether the incorporation of clinical interventions (resuscitative treatments), as a further tier of model features, would be feasible and allow refined performance. This approach is novel and has not been described before for BN-based CDS tools.

6.2.3. Prior to this, a systematic literature review was conducted to identify factors important in the prognostication of combat death and to provide a resource for later evidence browser generation¹⁰. Eight literature databases were searched from 2000 to 2016 and 640 papers were reviewed. 46 of these were deemed of sufficient quality and utility to be applicable to model development. Four themes were consistently reported: 1) combat death is most likely to occur in the pre-hospital domain 2) Haemorrhage is the leading cause of death, of which 80% of mortality is potentially survivable 3) Airway Compromise and Tension Pneumothorax is the second most common domain of potentially survivable death 4) Traumatic Brain Injury is the primary reason for un-survivable injury. Factors influence and compound one another and deriving weighted variables from the literature is challenging. The literature review also proved useful in that it allowed the identification and categorization of causes of death Mechanism of Injury, Anatomy, Physiology, Interventions and Time) and grouping by whether the variables were static or dynamic for model exploitation.

6.2.4. The approach to model development was to create separate BNs for Role 1 care (most forward echelon of medical care) and *en-route* medical evacuation (Medical Emergency Response Team). The network was trained on 1227 military trauma patients using 10-fold cross validation. The performance was good – AUROC 0.89 (95% Confidence Intervals 0.83-0.95) and 0.86 (95% CI 0.79 -0.94) and compared well to established prognostic models. The model required less anatomic data to generate predictions.

¹⁰ Mossadegh S. Chapter 4. Combat Mortality Systematic Literature Review. In: Application and development of Bayesian Networks for predictive modelling of coagulopathy and mortality in trauma patients. PhD Thesis. Queen Mary University London. 2020. Pp 140-168. Supervisor: Col Nigel Tai.

Model	MIL-BN-T1 AUROC	MIL-BN-T2 AUROC
MIL-BN	0.89 (0.83 – 0.95)	0.86 (0.79 – 0.94)
ISS	0.84 (0.75 – 0.92)	0.91 (0.82 – 1.0)
NISS	0.81 (0.71 – 0.91)	0.92 (0.86 – 0.99)
TRISS	0.89 (0.87 – 0.91)	0.91 (0.87 – 0.96)
<i>MIL-BN – Military Bayesian Network, ISS – Injury Severity Score, NISS – New ISS, TRISS – Trauma ISS</i>		

6.2.5. Mortality was 1.1% at Role 1 and 1.55% for en-route care, and small numbers of deaths in the UK JTTR database emphasizes the requirement for external validation in order to assess for bias. However, this work holds considerable promise as a novel means of predicting combat death, that will allow retrospective postulation of the effect of different treatments on that death. In other words the tool may not only offer clinical decision support functionality but also Mortality Review utility for system governance. The model now needs to be refined to include Role 2 and Role 3 care phases in order to make it applicable to the system as a whole¹¹.

6.2.6. YEAR TWO UPDATE **Specific Aim 6, Major Task 4: Develop prognostic model for mortality in injured military personnel (SURVIVAL-MIL)**

Project: Development of a prognostic model for trauma induced acute kidney injury, to form part of the mortality model

Methods: Model structure has been developed from expert knowledge and literature.

Parameters are learned from data. Initial data is from the UK civilian Activation of Coagulation and Inflammation in Trauma observational study dataset, obtained from Barts Health NHS Trust and Queen Mary University of London.

Progress: Structure developed. Dataset obtained. Parameter learning in progress.

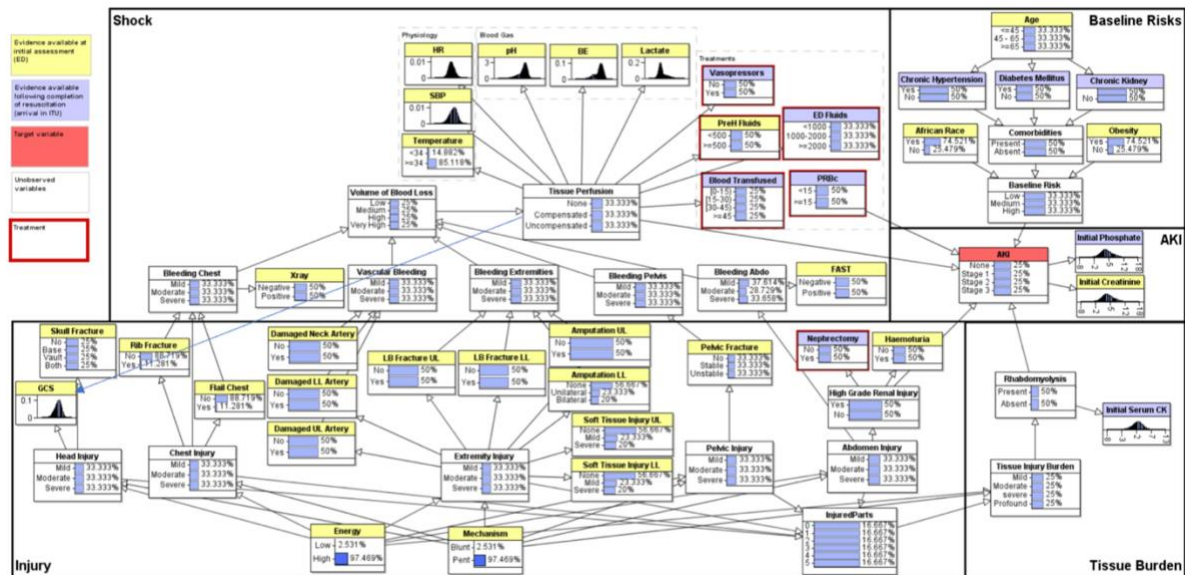
6.2.7. **Major Task 4 – Develop prognostic model for mortality in injured military personnel (from second year)**

We have proposed a methodology for developing this type of graphical probabilistic models. Our methodology has been submitted for publication in the journal of expert systems with applications (Impact Factor: 6.954). A subset of this model, capturing acute kidney injury has been developed. The training dataset is 90% complete. The model's internal validation will be completed in the following days.

¹¹ Mossadegh S. Chapter 5. Development and internal validation of a military mortality governance tool using Bayesian Networks. In: Application and development of Bayesian Networks for predictive modelling of coagulopathy and mortality in trauma patients. PhD Thesis. Queen Mary University London. 2020. Pp 169-216. Supervisor: Col Nigel Tai.

Results: Pending
Figures/Tables:

Trauma-AKI BN structure: (not trained yet)



Next steps: Internal validation of the TAKI model. External validation with UK military (JTTR) data. Combining this model with the TIC-MIL model and another for head injury to capture the main causes of trauma related mortality to develop SURVIVAL-MIL.

6.3. YEAR 3 PROJECT MILESTONES –

6.3.1. **Specific Aim 9** - Evaluate the clinical usability of the prototype CDS tool and validate the effect the tool has on the clinical credibility of the suite of prognostic models.

6.3.2. **User experiments testing usability of CDSS predictor capture, CDSS risk presentation, explanation generator, and knowledge browser**

[SOW: Specific aim 4, 8, and 9]

Aims: 1) Evaluate the usability of a user interface for electronic capture of predictors in trauma. 2) Determine the advantages, disadvantages, barriers to workflow and clinical credibility of a user interface for electronic capture of predictors. 3) Evaluate the usability of a user interface for risk presentation in trauma. 4) Determine the effect of a user interface for dynamic risk presentation in trauma on clinician situational awareness, decision making and credibility. 5) Evaluate the usability of the explanation page of the CDSS. 6) Determine the effect of explanations of the model and reasoning on end user understanding of, trust in, and decision confidence before and after using a CDSS. 7) Evaluate the usability of the medical evidence browser of the CDSS. 8) Determine the effect of a knowledge browser on end user understanding of, trust in, and decision confidence after using a CDSS.

Methods: Prospective iterative, observational mixed methods study evaluating a CDSS designed for use by prehospital trauma clinicians.

Progress: Designing the protocol and preparing for submission to QMUL for sponsorship and HRA for approval. Aim to submit in October 2021.

Results: NA

Figures/Tables: NA

Collaborators: Erhan Pisirir

6.3.3. Subtask 3: Develop a protocol for a clinical impact study of the CDS tool. The following study methodology has been developed.

6.3.4. Study Proposal

Title: Effect of an Artificial Intelligence (AI) Risk Prediction System on clinician situational awareness and decision-making during the prehospital care of trauma patients.

Research Question: During the prehospital management of trauma patients, is an AI risk prediction system able to augment a treating clinicians' perception of an individual patient's risk of adverse outcomes (situational awareness) and subsequent clinical decisions, compared to standard unassisted clinician performance?

Background: Good judgement and sound decision-making are essential to safe and effective clinical practice. However, clinical decisions are often made under challenging conditions, and these conditions may impair considered judgement. This is especially true in trauma care, where inadequate information, high degrees of uncertainty, critical time constraints, and high levels of risk, are common. Naturalistic Decision-Making (NDM) is the science of studying how experts make decisions in these demanding, real-world situations. Using NDM concepts, two critical stages in decision-making have been identified. These are 1) situational awareness and 2) choosing a course of action. In the clinical domain, *situational awareness* is defined as a cognitive process that involves continuous perception and comprehension of a patient's condition, and the ability to anticipate its future state. This involves recognizing potential problems and assessing the level of risk these problems pose. Situational awareness drives decision-making, and ultimately the actions performed. Misinterpreting a situation during this early stage of decision-making may compromise the delivery of safe and effective care, and is the most common cause of clinical error. High quality, accurate and validated risk prediction models already exist for the majority of important outcomes following injury. However, they are rarely adopted into clinical practice, and clinicians are reluctant to trust such tools to support treatment decisions.

Brief trial description:

- a) *Study design.* Pragmatic controlled before-and-after trial. Participants will be randomly allocated (4:1) to the intervention or control arms of the study.
- b) *Population/participants.* Study participants are the clinical decision-makers involved in the prehospital assessment and management of trauma patients. The secondary study population is adult trauma patients attended by clinicians enrolled in the study.
- c) *Intervention.* The Artificial Intelligence (AI) risk prediction and decision support system. The AI system is designed to help healthcare professionals assess an individual patient's risk of an adverse outcome (death or serious complication) following injury. By providing clinician users with accurate risk estimates at the point of care, the AI system aims to improve their situational awareness and thereby support earlier, better informed and personalized treatment decisions. The system consists of a suite of validated risk prediction algorithms for adverse outcomes, including (1) Mortality (early and overall) and (2) serious complications that impact clinical management, such as Trauma-Induced Coagulopathy (TIC) and Acute Kidney Injury (AKI). In addition, the system provides the user with an explanation of the reasoning behind the predictions produced and allows the user to browse the knowledge and evidence on which the predictions are based.
- d) *Outcomes.* Primary outcome measures are the accuracy of clinical judgement of the patient's risk of:

- 1) Early (within 24 hours of injury) mortality,
- 2) 30-day mortality,
- 3) Early (within 24 hours of injury) Trauma Induced Coagulopathy (TIC) – defined as a laboratory Prothrombin time ratio (PTR) > 1.2, and
- 4) Acute Kidney Injury (AKI) – defined according to the KDIGO criteria. Primary outcomes will be measured as the likelihood/probability (scored using a 0 to 100% confidence scale) of the event occurring and will be measured immediately after hand-over of the patient to the hospital trauma team.

Secondary outcome measures will include:

- 1) The proportion of patients that die (early and 30-day mortality) or develop a serious complication (TIC or AKI),
 - 2) Clinical outcomes including prehospital scene times, blood transfusion requirements in the first 24 hours, time to Major Haemorrhage Protocol (MHP) activation and time to surgical intervention in patients with active haemorrhage,
 - 3) The appropriateness of key clinical decisions (MHP activation, initiation of blood transfusion)
 - 4) The degree of cognitive load associated with key clinical decisions (MHP activation, initiation of blood transfusion).
- e) *Analysis.* Primary outcomes: The performance of naïve (before) and augmented (after) clinicians in the intervention arm of the study will be assessed in terms of discrimination (Area Under the Receiver Operating Characteristic Curve, AUROC), calibration (calibration plot, intercept and slope) and accuracy (Brier Score and Brier Skill Score). Performance will be compared using unpaired test designs and visually (for calibration plots). Graphical trend interpretation will be used to compare the intervention and control arms of the study. Secondary outcomes: Secondary outcomes in the before and after groups will be compared using conventional statistical methods.

Feasibility:

- a) *Sample size.* For the purpose of sample size calculation, the measure of effect is the AUROC. The baseline ability of clinicians to predict mortality or serious complications following trauma is largely unknown. We have estimated the performance of expert trauma clinicians to predict TIC as an AUROC of 0.83. An improvement of 0.05 would be regarded a clinically relevant. We determined that a sample size of 1296 patients, 648 in each group, would provide the study with 80% power to detect an effect size of 0.05 with 95% confidence. We allowed for a maximum of 20% ineligibility or loss to follow-up, and thus the estimated sample size is 1555.
- b) *Identification of potential trial participants?* Clinicians working for London's Air Ambulance will be approached to participate in the trial.
- c) *How many potential participants will be treated in the centre?* London's Air Ambulance has 16 substantive consultants and six registrars. Each registrar does a six-month secondment (twelve registrars/year). The service treats approximately 1600 patients per year, with each registrar treating approximately 150 patients per secondment. Secondary outcome data will be collected at the four Major Trauma Centres in the London Trauma System – The Royal London Hospital, St Mary's Hospital, Kings College Hospital, and St Georges Hospital.

6.4. SUMMARY OF YR 2

The team is now complete and significant progress has been made with regard to completion of Year One, Year Two and Year Three milestones. Base layer system improvements have been made for better user experience and interface. The military TIC

model has been developed. User assessment methodology has been developed. HRPO permissions have been secured for all model build activities and research.



