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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
327 Mile End Road London E1 4NS
UK

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Colonel Nigel RM Tai

E-Mail: nigel.tai@nhs.net

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Queen Mary University London
327 Mile End Road London
E1 4NS
UK

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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.

15. SUBJECT TERMS

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

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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.

Research Phase 1 – Months 1-12

1. Apply for Local IRB and US HRPO study approval
    a. In progress (35%) – UK data permissions agreed in principle
2. Develop and validate a prognostic model for TIC
    a. Development Complete (100%)
    b. Civilian Validation Complete (100%)
    c. Military Validation (20%)
3. Develop and validate adaptation of a LIMB-MIL prognostic model that can predict projected viability of an injured limb/outcome of limb reperfusion
    a. Development Complete (100%)
    b. Military Validation Complete (100%)
4. Develop a prototype Clinical Decision Support tool for use of the TIC-MIL and LIMB-MIL prognostic models.
    a. Interface (75%)
    b. Evidence Browser/Library (80%) – Update further work on the browser has occurred

Research Phase 2 - Months 13-24

5. Evaluate clinical usability of prototype CDS tool
6. Develop and validate a prognostic model for blood product requirements – 40%
7. Develop and validate a prognostic model for mortality in injured military personnel - 40%

Research Phase 3 – Months 25-36

8. Develop and validate prognostic model that can quantify patient-specific risks related to right place and right time care (OVERFLIGHT)

A detailed narrative of activity and accomplishments is provided in the appendix to this report.

The first year of the project has been characterized by consolidation of both preparatory and substantive work pertaining to the deliverables of both Year One and Year Two, 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. Approvals for access to US datasets is pending.

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

The project team includes 3 PhD students who will be supervised by Col N Tai, Prof K Brohi, Dr William Marsh, Mr Zane Perkins, and Dr Evangalina 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/doctoralcollege/?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, Uniformed Services University of Health Services, US JTS leadership) will be sent a copy of the annual report including links to relevant publications.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

1. Complete permissions for data extraction. The route to UK permissions is made facile by legacy permissions granted in work undertaken prior to grant application in 2017 and award in 2019, with recent correspondence between UK DMS data gate-holders and the research team supporting continued data access on these terms (Appendix 5.1.1)
2. Refine the current TIC model so that it is applicable to military populations (Appendix 5.2.4). Work with UK DMS pathology contacts to secure more labelled data to accomplish this.
3. Complete Interface/Evidence-Browser development (Appendix 5.3-5.4 p 23-30) through continuation of work done to date.
4. Continue CDS user experience, workflow integration and use-ability surveys.
5. Continue blood product prediction tool development (Appendix 6.1. p 30-31) and mortality tool development (Appendix 6.2 p 32-33) by progressing substantial work done to date.
6. Set conditions for OVERFLIGHT tool through preliminary study of potential refinements to existing models to acquire understanding of whether new or refined model is required.

4. **IMPACT:** D*escribe 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.

The largest area of delay to achievement has been with regard to staff hire, which was affected by two factors. Firstly, permission to recruit individuals in to research positions was contingent upon the Award, which meant a delay due to the time between provision of the Award (Sept 15 2019) and start date of researchers (due to requirement to write job descriptions, obtain institutional permission to recruit, advertise, short-list, interview, offer employment, and negotiate release from current employment and on-board). The second factor was COVID19, which meant that clinical researchers could not begin their research duties because of an imposed NHS requirement to contribute to prioritise care for COVID patients (Appendix section 3 and 4). A minor amount of delay was caused by an Operational Deployment that affected the PI's (Col Tai's) personal ability to contribute to the project over Apr-June, 2020 although Dr Marsh and Mr Perkins mitigated this. These factors have in turn impinged on the US IRB approval progression (less so for UK approvals due to extant permissions from legacy or foundational work).

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

All figures USD based on DoD agreed budget

PRECOVID

	Sep-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Total Y1
Pis	9,609	13,982	13,982	13,982	51,555
PDRA	0	0	16,092	16,092	32,184
CRFs	0	0	36,959	36,959	73,918
Prog	0	0	18,140	18,140	36,280
PM	0	1,918	3,837	3,837	9,592
Travel	0	0	0	22,700	22,700
Fees	0	0	6,802	6,802	13,604
Stipend	0	0	5,688	5,688	11,376
M&S	0	0	4,909	0	4,909
Computer	0	0	7,979	0	7,979
Subcont (RCDM)	1,906	1,906	1,906	1,906	7,624
Infra	8,259	8,259	8,259	8,259	33,036
Total	**19,774**	**26,065**	**124,553**	**134,365**	**304,757**

POSTCOVID

	Sep-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Total Y1
Pis	9,609	13,982	13,982	13,982	51,555
PDRA	0	0	10,797	16,195	26,992
CRFs	0	0	0	23,814	23,814
Prog	0	0	0	0	0
PM	0	1,420	4,257	4,298	9,974
Travel	0	0	0	0	0
Fees	0	0	0	0	0
Stipend	0	0	0	948	948
M&S	0	0	0	0	0
Computer	0	0	0	1,050	1,050
Subcont (RCDM)	1,906	1,906	1,906	1,906	7,624
Infra	8,259	8,259	8,259	8,259	33,036
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.

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.

Development and Validation of a Multivariable Risk Prediction Model: Early Identification of Trauma-induced Coagulopathy: Perkins ZB, Yet B, Marsden M, Glasgow S, Marsh W, Davenport R, Brohi K, Tai NRM. Published as Ann Surg. 2020 Jan 14. doi: 10.1097/SLA.000000000000377. Link

Predicting the Outcome of Limb Revascularization in Patients With Lower-extremity Arterial Trauma: Development and External Validation of a Supervised Machine-learning Algorithm to Support Surgical Decisions. Perkins ZB, Yet B, Sharrock A, Rickard R, Marsh W, Rasmussen TE, Tai NRM Ann Surg. 2020 July 09. Doi: 10.1097/SLA.0000000000004132. Link

Accepted for presentation at the 140th ASA Annual Meeting being held April 16-18, 2020, at Grand Hyatt Washington in Washington, D.C – Latter Cancelled due to COVID19

An incremental explanation of inference in Bayesian networks for increasing model trustworthiness and supporting clinical decision making. Kyrimi E, Mossadegh S, Tai N, Marsh W. Artif Intell Med. 2020 Mar;103:101812. doi: 10.1016/j.artmed.2020.101812. Epub 2020 Jan 31. Link

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

Nil significant to report

Other publications, conference papers and presentations.

Nil significant to report

- **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 12 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 12 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 4 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 1 mth at 100%	Model development & refinement	Nil	COVID 19 prevented earlier start
Jared Wohlgemut	QMUL PhD Candidate Clinical Fellow	On project for 1 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 6 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 12 months at 2.67%	Critical analysis, leadership, authority for Centre 4 trauma science data resources.	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

EXPLOITATION OF BAYESIAN NETWORKS FOR CLINICAL DECISION SUPPORT ON THE BATTLEFIELD

AUTHOR COL NIGEL TAI (PRINCIPLE INVESTIGATOR)

REPORT DATE 14 SEPT 2020

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:

1. We have published a model and prognostic tool for civilian trauma-induced coagulopathy (TIC) and have studied how it can be refined for military application using a military data-set. Whilst it performs reasonably, it requires further development; we are securing access to more and better-labelled training data in order to complete this.
2. We have published a model of traumatic limb-loss trained and validated on military populations; model development is completed and superior to any existing CDS tool.
3. We have developed a range of functions within the clinical decision-support tool to enhance use-ability, including configurable portrayal of prediction (i.e.: risk of predicted outcome) and search-able evidence browsers (i.e.: explanation of model reasoning and underlying evidence). Systematic reviews have been undertaken to support the evidence array and an early understanding of the value of explanation to “clinician trust” has been obtained.
4. The civilian TIC model has been modified to allow prediction of military trauma patient transfusion requirement in both pre-hospital (PH) and in-hospital (IH) settings. The model was moderately accurate for PH use (Area Under the Receiver-Operator Curve - AUROC - of 0.77) and highly accurate for IH patients (AUROC 0.91). We also explored how modification of the model could allow prediction of death in military trauma patients with good accuracy (AUROC 0.89 and 0.86 for PH and IH settings respectively). This involved using a novel way to utilize dynamic variables that take account of the effect of advanced trauma life support treatments on the likelihood of bad outcomes.

Conclusion: Whilst establishment of the research team has taken longer than expected (due to COVID19), the programme is making substantial progress on Year One and Year Two deliverables. An evidenced BN-powered CDS tool suite for combat trauma patients is feasible. By building on the findings and insights generated from this year’s work we are confident that the programme will deliver its designated outputs.

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.

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

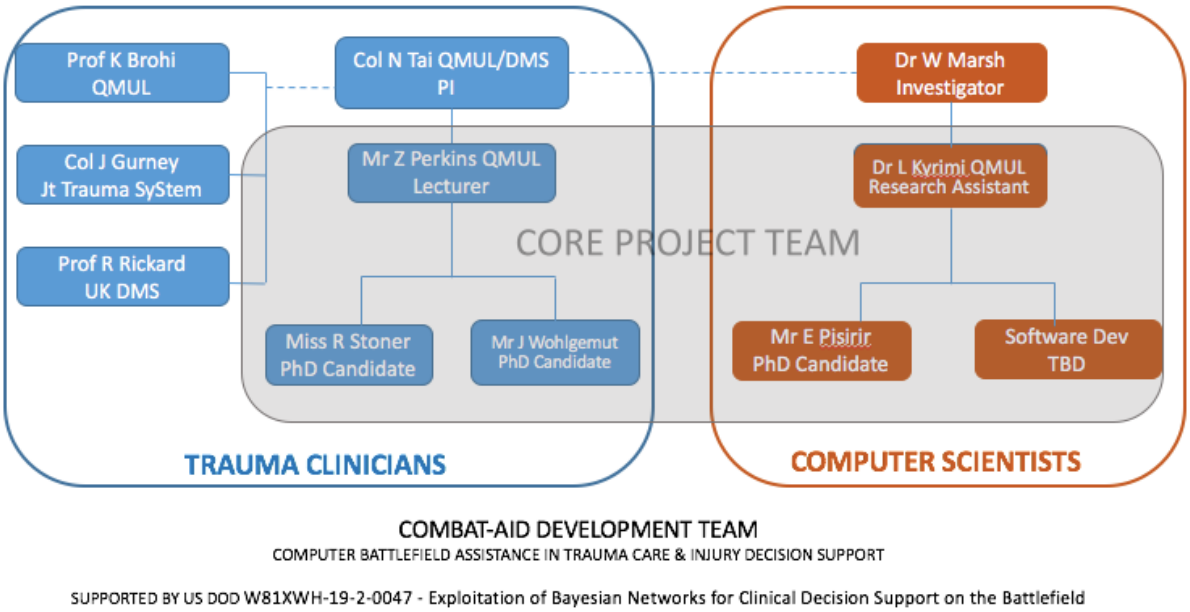
3.1. The first year of the project has been characterized by consolidation of both preparatory and substantive work pertaining to the deliverables, with the highlights being a number of foundational publications that underwrite the science and performance of our Machine-Learning networks used to prognosticate 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, though this is anticipated in order to permit completion. There is no requirement to review or change the agreed funding envelope for the project [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 85% completed. COVID 19 and the requirement for clinical staff to undertake re-deployment in support of the UK National Health Service 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	TBD	TBD	TBD	Recruitment process on-going

4.3. Dr Javier Sandin Llorente replaced Dr Tom Simpson as Operations Manager for the Centre for Trauma Sciences, Blizard Institute, Queen Mary University London in February 2020. Dr Llorente is responsible for the operational liaison between the QMUL Joint Research Management Office and our Funders as well as general project management.

4.4. Additional support to the aims of the project has come from the doctoral studies of three QMUL-registered researchers, funded from other sources, supervised by Colonel Tai and Dr Marsh.[2]

5. YEAR ONE PROJECT MILESTONES

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

"In progress (35%)"

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 approval [3] and the generation of a data sharing agreement between QMUL and Defence Medical Services. There is no requirement for Research Ethics Committee (REC) application for model build activity; REC will be approached for a determination as to 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 BN Mil Model was trained and validated on an exclusively military population and does not require further JTS data.

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 (20%)"

5.2.1. The background to this task is that trauma-induced coagulopathy (TIC) exacerbates hemorrhage and is associated with higher morbidity and mortality in trauma patients. Early

[2] Dr Barbaros Yet, Miss Sommeyah Mossadegh, Major Max Marsden.

[3] Email received 3 Sept 2020

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 2020 [4]. This paper described how the prediction model was developed using domain knowledge of the causal mechanisms of TIC [5], 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: with Area Under the Receiver Operating Characteristic curve (AUROC) of 0.93, calibration slope (CS) 0.96, brier score (BS) 0.06, and brier skill score (BSS) 0.40 as portrayed below:

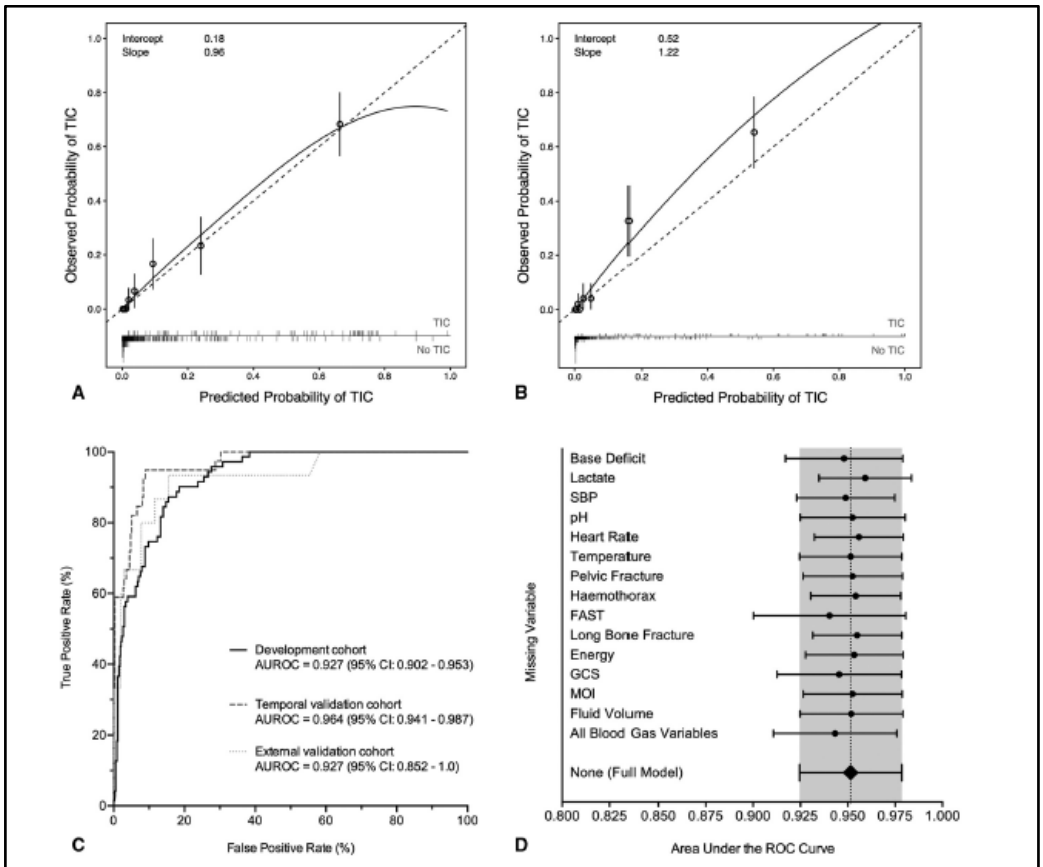


FIGURE 2. Discrimination and calibration of the trauma-induced coagulopathy (TIC) predictive model. The calibration plot shows the relationship between ideal (dashed line) and observed (solid line) predicted values in the development cohort (A) and the combined (temporal and external) validation cohort (B). The rug plot along the bottom demonstrates the distribution of predicted probabilities. The circles with 95% confidence intervals indicate observed frequencies by decile of predicted probability. The receiver-operating characteristic (ROC) curves show the relationships between true-positive and false-positive TIC predictions in the development, temporal, and external validation cohorts (C). The forest plot compares the performance of the model at predicting TIC in the combined (temporal and 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 ROC curve with 95% confidence intervals.[5]

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

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

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

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 population [6]. 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) needed to benchmark model predictions proved challenging. Eventually, a data cohort of 106 such patients was identified and permission obtained to use their data for this study. A further challenge was how to incorporate Blast mechanism – an important mechanism of injury in combat settings - within the model when this feature had not been part of the original model design. This was explored by sensitivity analyses where model accuracy was studied without Mechanism of Injury and physiology inputs, and when Blast MOI was treated by the model as either Penetrating or Blunt injury:

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

TIC-BN – Trauma Induced Coagulopathy Bayesian Network, AUROC – Area Under Receiver Operator Curve, MOI – Mechanism of Injury, Phys. – Physiology, Pen. – Penetrating.

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. AUROC figures ranged from 0.63 to 0.67 and relabeling blast injured patients as either penetrating or bluntly injured did not materially affect the prediction. 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 discrete, define-able input feature for this model and this may also have contributed to lack of performance.

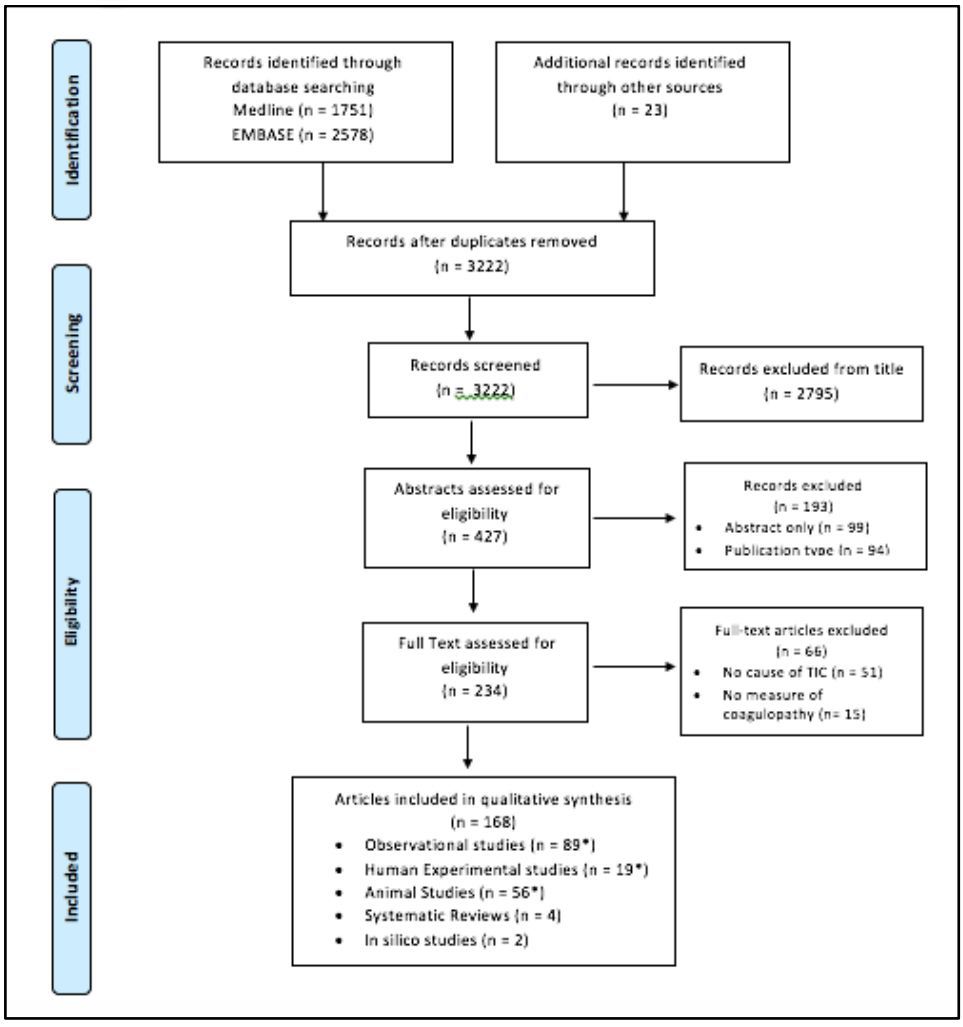
5.2.4 To better understand and improve the model, our group is collaborating with the UK Centre for Defence Pathology in order to take the dataset of UK JTTR-documented casualties and link this to existing laboratory data held on the UK Defence Medical Services Laboratory Information Management System, 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-

[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

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]

5.3. 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

a. "Development Complete (100%)
b. 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 2020[7].

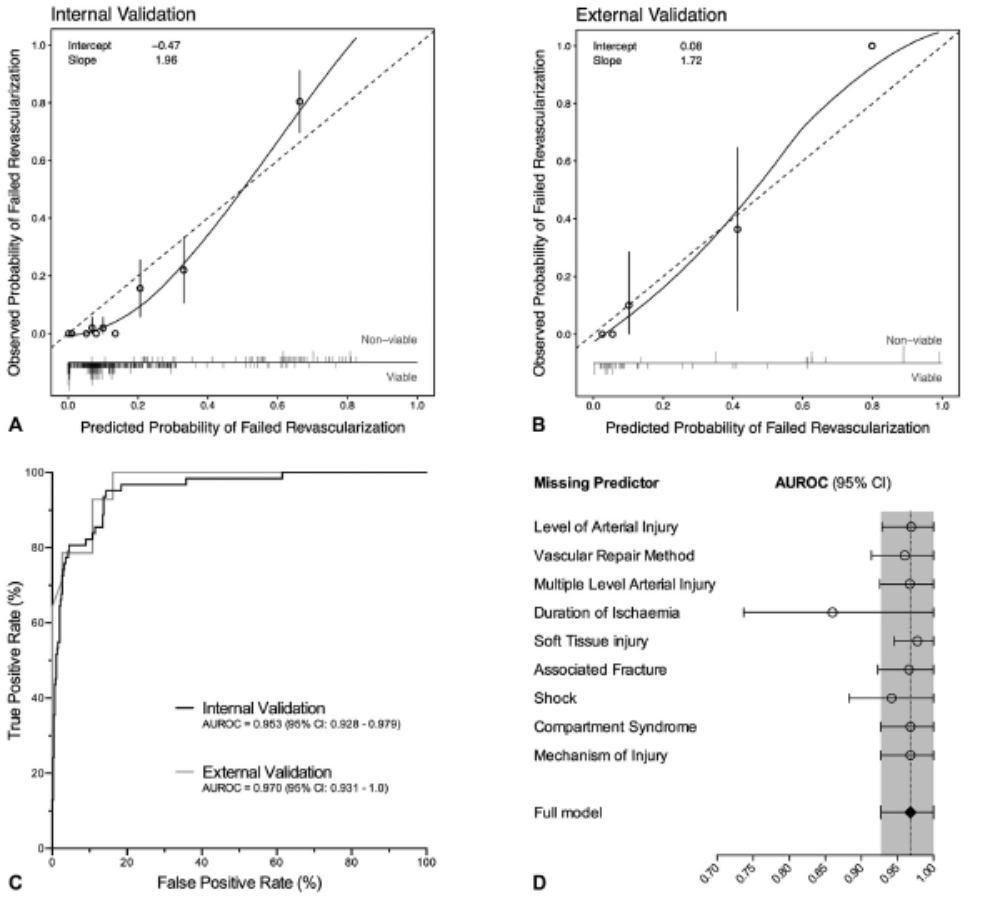


FIGURE 2. Performance of the Bayesian network prognostic model. The calibration plot shows the relationship between ideal (dashed line) and observed (solid line) predicted values in the internal (A) and external (B) validation cohorts. The rug plot along the bottom demonstrates the distribution of predicted 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.

[7] Perkins et al. Predicting the outcome of limb revascularization in patients with lower-extermity 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

5.3.2. Performance of this model was compared to a well known limb salvage score (the mangled extremity severity score - MESS) 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: AUROC 0.95, calibration slope 1.96, Brier score 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 (95% CI 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.

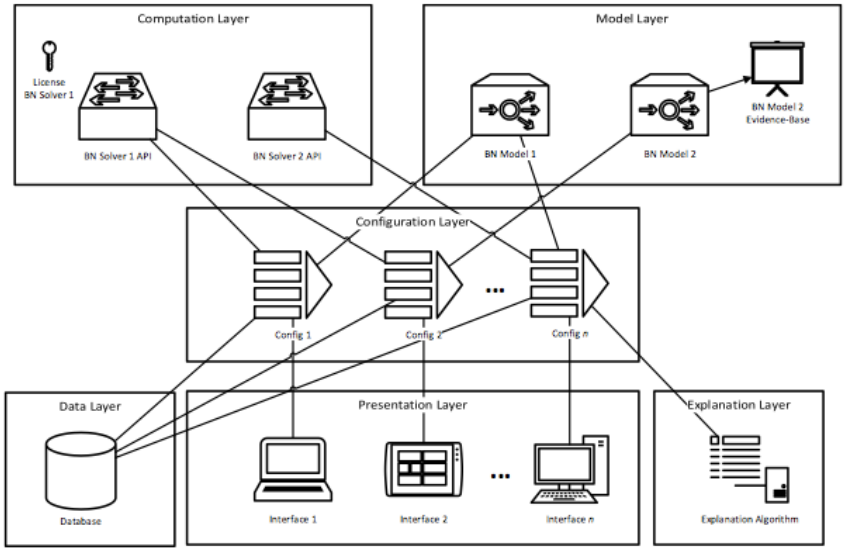
5.4. Major Task. Develop a prototype Clinical Decision Support tool for use of the TIC-MIL and LIMB-MIL prognostic models.

a. "Interface (75%)
b. Evidence Browser/Library (80%)"

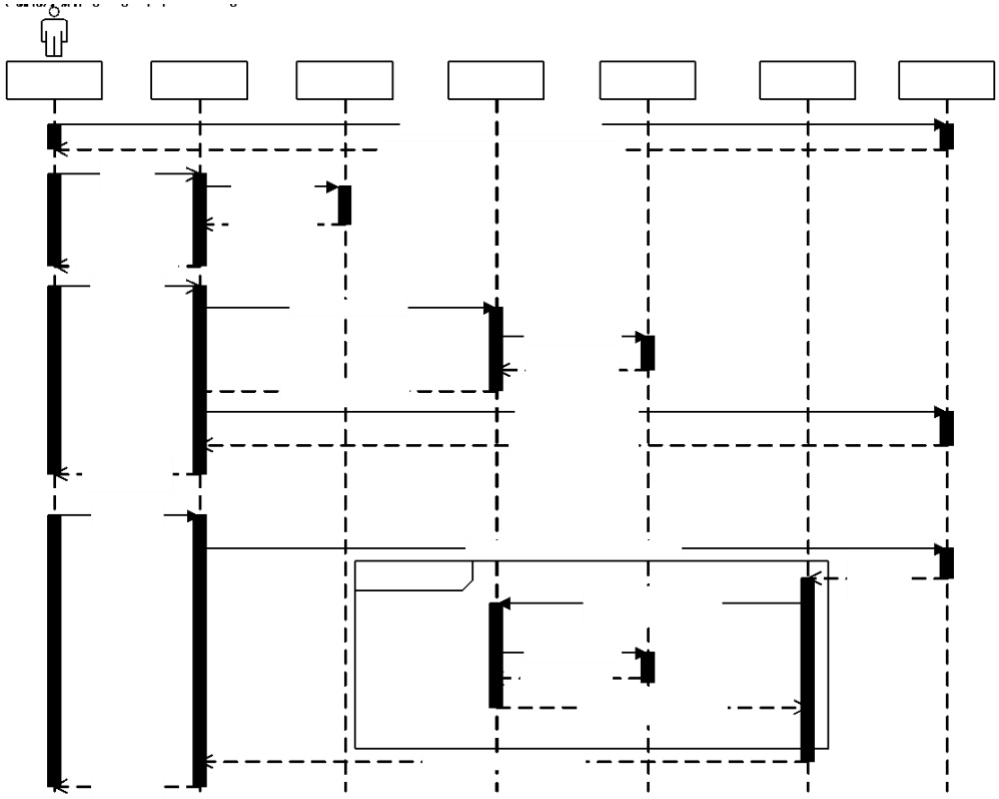
5.4.1. The background to this is that, whilst prognostic tools may produce accurate predictions, technical barriers regarding implementation and the user-experience related to these models slows-down their adoption in clinical care. Clinicians prefer prediction models that are easy-to-use, have a clear 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 a 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). 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.

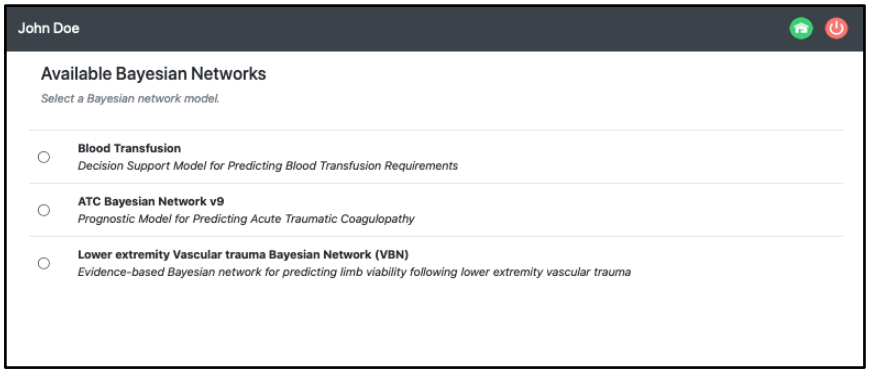
5.4.3. The approach to this work required the identification of six layers needed to compose the interface and supportive functions. These layers consist of a presentation layer (that prepares the user input and output interfaces), a computation layer (that contains the BN inference software), and a 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:



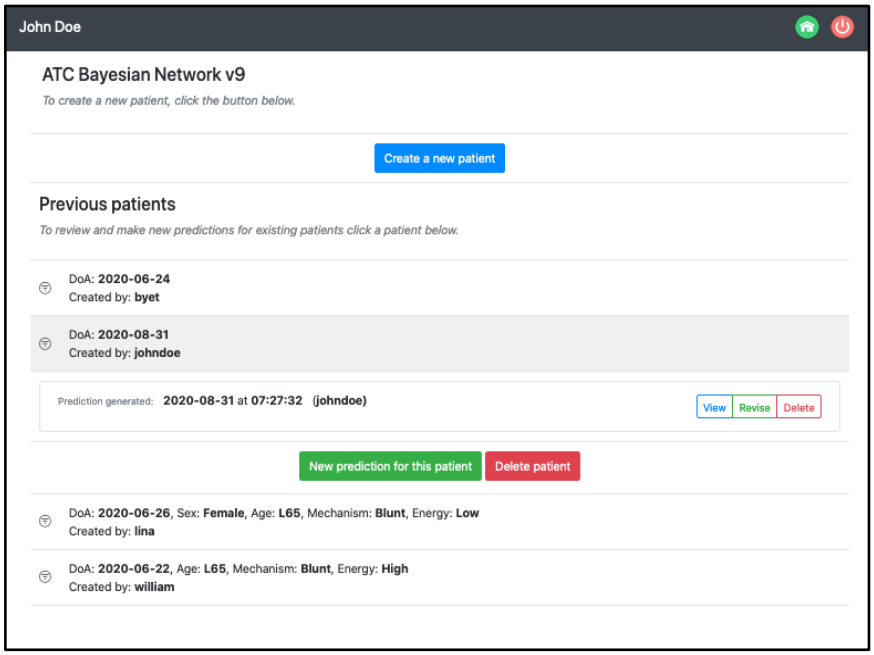
5.4.4 The engineered solution to combine these layers is represented below. When an end user enters the system, the framework checks the access privileges of the end user in the Data Layer and shows the available interfaces for this end user. The end user then selects an interface, and the interface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



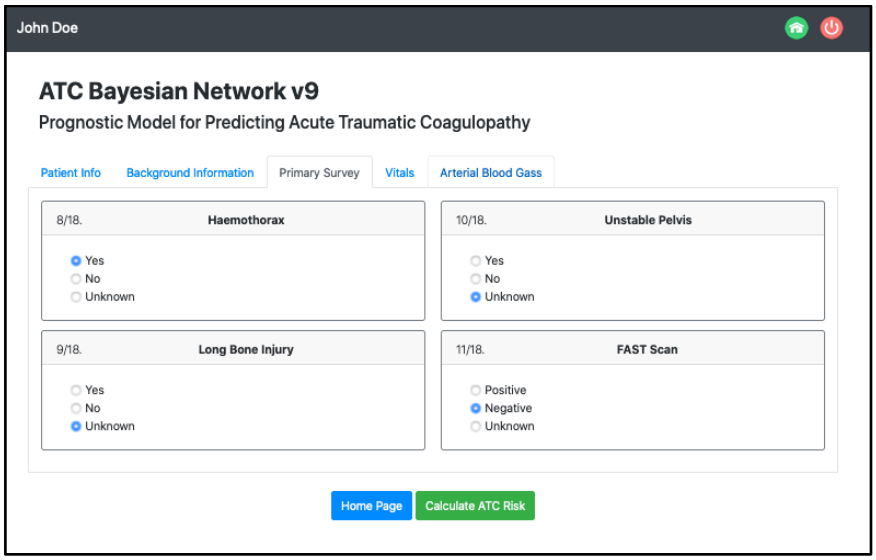
5.4.5 Screenshots from the User Interface are portrayed below to demonstrate the progress made in delivering the solution:



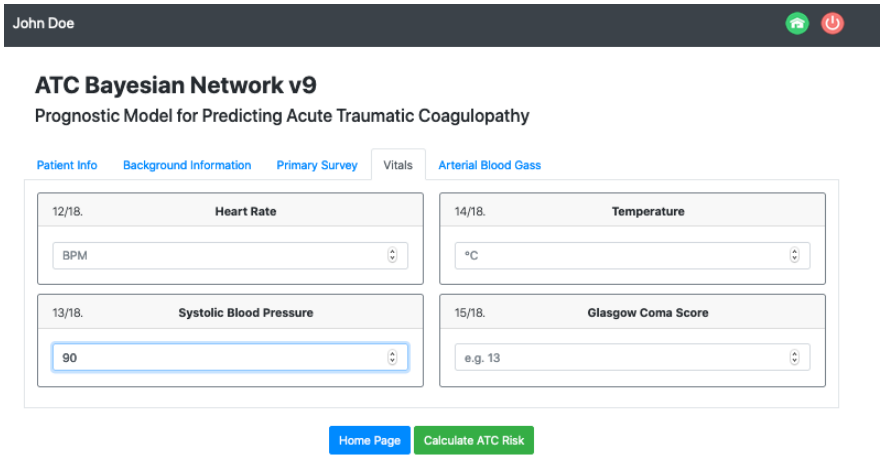
- Initial User Interface with presentation of different BNs to User



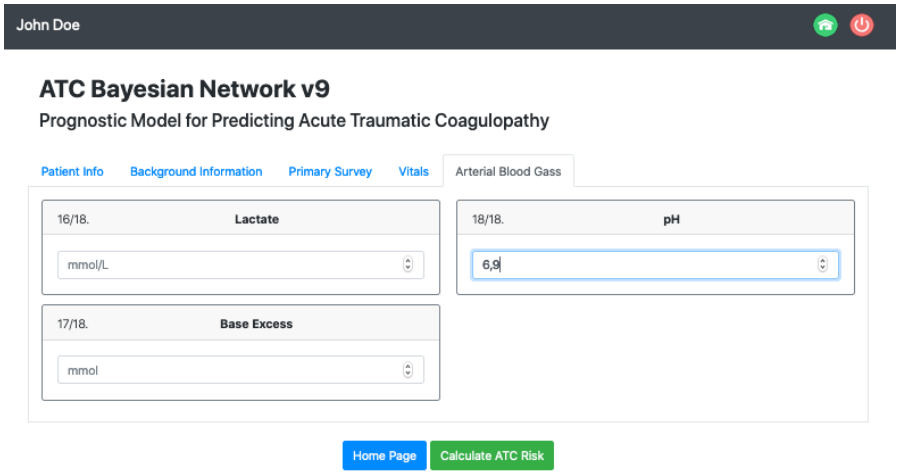
- Patient record selection or creation of record

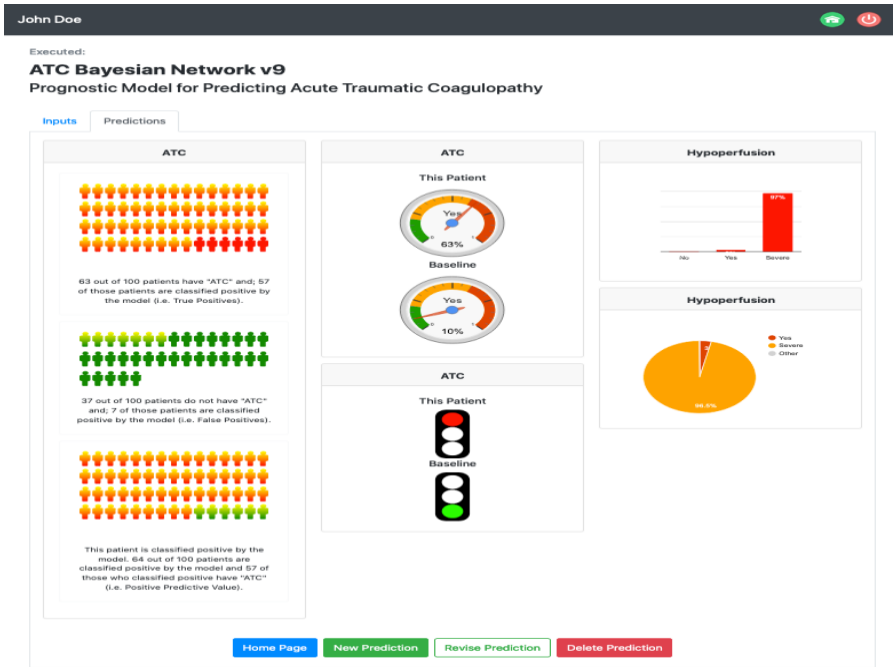


- Initial Input of variables – note that coagulopathy risk (ATC) can be calculated without proceeding to next page



Further input screens for variables



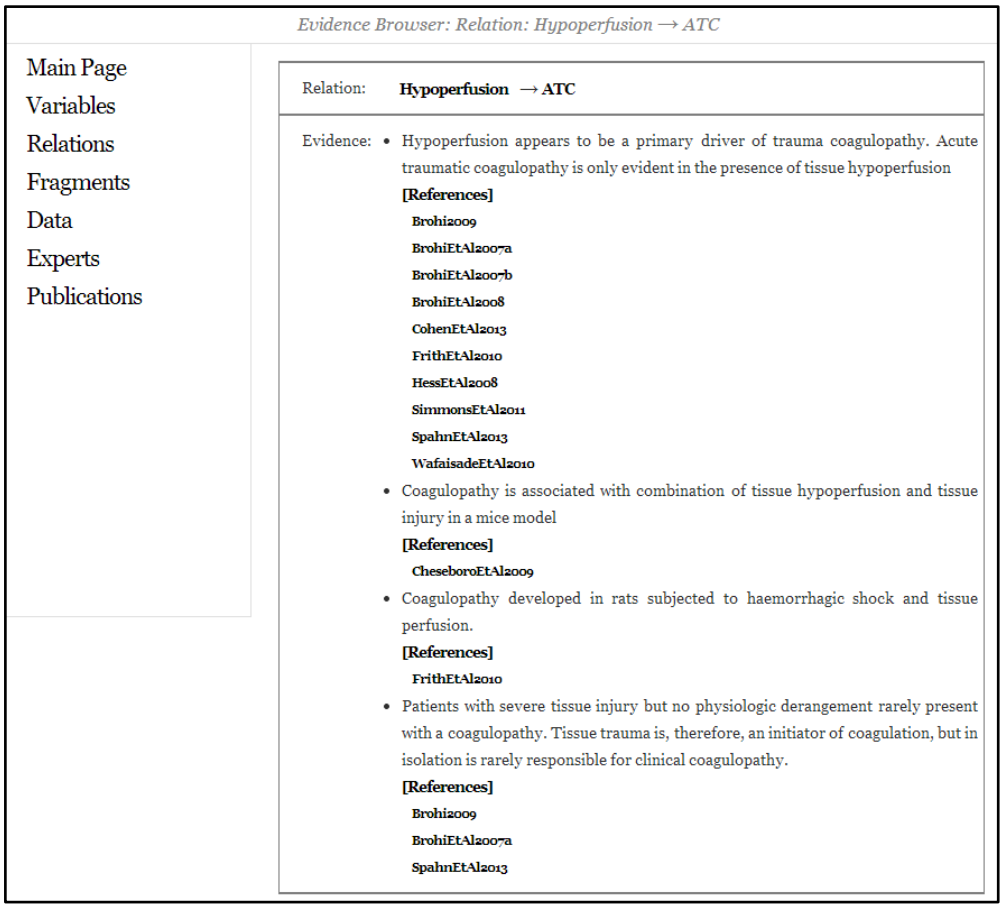


Risk calculated and portrayed in a number of different figurative formats

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



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 tool 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 understand and digest the explanation. Our method can be used in hybrid networks that use both continuous and discrete data and requires no user input. In addition, we have simplified the process of identifying the most important evidence and chains of reasoning, so the model can rapidly produce a good and concise explanation, but not necessarily the most complete one. As such, this method produces an incremental explanation that has three successive levels of detail, as illustrated thus:

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

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

[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

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 can be perceived as similar to that of clinicians' own reasoning when they are making un-augmented predictions. Interestingly, clinicians liked the explanation function (as it gave them an insight into the model's reasoning) but would prefer the explanation output to be graphically enhanced, and expressed that a second tier of explanation was too detailed to be used in an acute clinical setting.

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 to this task 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 help clinical end-users 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]. 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% $p = 0.13$). 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.

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

	≥4 PRBCs			≥10PRBCs		
	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 | = 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 | = 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 form 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.

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

5.3.1. 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

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

5.3.2. Further sensitivity studies showed that, counter-intuitively, mechanism of injury and physiology inputs contributed little to model performance (as per 5.2.3), 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 an additional 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.

5.3.3. 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 generation[10]. 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 (by Mechanism of Injury, Anatomy, Physiology, Therapeutic Interventions and Time) and grouping according to whether the variables were static or dynamic (for model exploitation).

5.3.4. The approach to model development was to create separate BNs for Role 1 care (i.e. the 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)

MIL-BN – Military Bayesian Network, ISS – Injury Severity Score, NISS – New ISS, TRISS – Trauma ISS

5.3.5. Mortality was 1.1% at Role 1 and 1.55% for en-route care, and small numbers of deaths in the UK JTTR database emphasized the requirement for external validation in order to assess for bias. This work holds considerable promise as a novel means of predicting combat death - one that will allow retrospective postulation of the effect of different treatments on likelihood of death. In other words the tool may not only offer clinical decision support functionality but also Mortality Review utility in order to augment system governance. The model now needs to be refined to include Role 2 (small field hospital) and Role 3 (large field hospital) phases of care in order to make it applicable to the deployed trauma system as a whole [11].

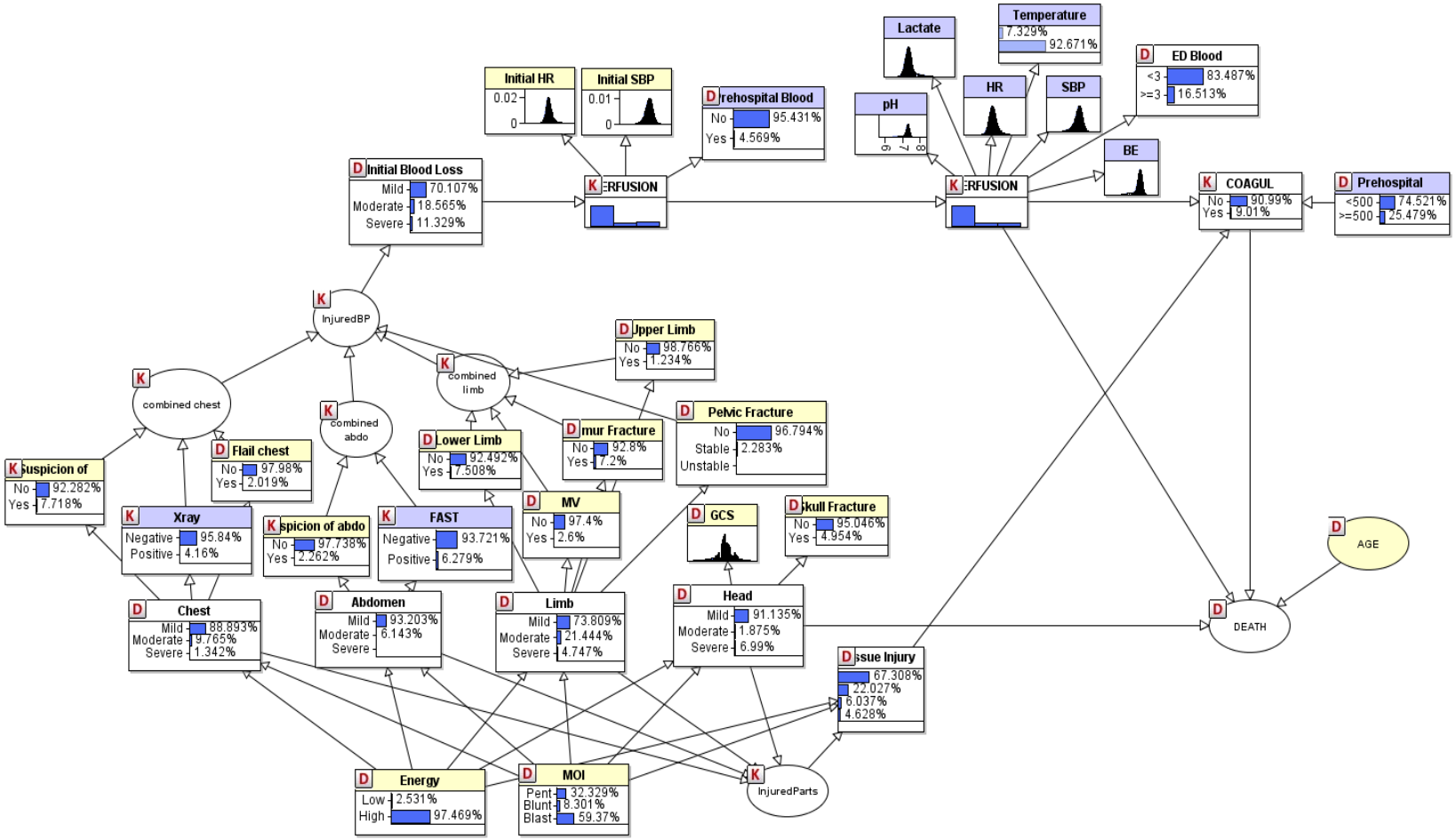
5.4. YEAR 3 PROJECT MILESTONES - Nil significant to report.

5.5. SUMMARY

The project award and start date was 15 September 2019, but establishing the core team has only recently been permissible given the constraints on start-dates imposed by the effect of COVID19 on the UK. The team is now extant bar the hiring of a software programmer. Spend for Year One is reflective of this lower cost burden. Despite this constraint, significant progress has been made with regard to Year One milestones as to development of the TIC model (published); performance in a military population (poorer than in a civilian cohort – therefore novel model required; systematic review conducted in support of latter); the effective conclusion of the MIL LIMB MIL BN model development (save for completion of the evidence browser and explanation functionality); and considerable development of the input and output interfaces. Furthermore, significant work has been done on the Year Two goal of establishing a prognostic tool for likely blood product requirement for injured troops with the development of a prototype military-specific model.

Nigel Tai
Principle Investigator and COMBAT-AID lead.

[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.



A Directed Acyclic Graph depicting the latent variables, conditional dependencies, nodes and associated probability functions that comprise the Bayesian Network developed to enable prediction of likelihood of requiring blood transfusion in military trauma.