Imperial College London

Research Governance and Integrity Team

Imperial College Healthcare NHS Trust

AI Clinician XP1

Passive evaluation in operational environment of the AI Clinician decision support system for sepsis treatment

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Name & Role	Date	Signature

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Study Management: Elizabeth Fagbodun & Farah Al-Beidh

Clinical Queries

Clinical queries should be directed to Matthieu Komorowski who will direct the query to the appropriate person

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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This protocol describes the AI Clinician study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS/DEFINITIONS

Human evaluators	ICU doctors (any level) assessing the AI in the background, without informing clinical practice
ICU	Intensive Care Unit
Sepsis-3	The current international definition of sepsis. Requires the presence of a suspected infection (administration of antibiotics and sampling of bodily fluids for bacteriological culture) and some degree of organ failure (an increase in SOFA score of 2 points or more)
SOFA	Sequential Organ Failure Assessment – an organ failure score

KEYWORDS

Sepsis, decision support system, artificial intelligence, machine learning, electronic health record

STUDY SUMMARY

TITLE	Passive evaluation in operational environment of the AI Clinician decision support system for sepsis treatment
DESIGN	Prospective multi-centre observational study in 4 ICUs from 2 different NHS Trusts.
AIMS	Confirm operational robustness and technical reliability of the AI Clinician software when operating in real-time in an operational ICU environment.
OUTCOME MEASURES	System / usability data; anonymised patient time series data; doses of treatment chosen by clinicians; assessment data by human evaluators.
POPULATION	Patients: adult patients in intensive care; human evaluators: ICU doctors of any grade.
ELIGIBILITY	Adult patients with sepsis in intensive care
DURATION	Up to 24 months.

1. INTRODUCTION

1.1. BACKGROUND

Sepsis is life-threatening organ dysfunction due to severe infection and affects 250,000 patients annually in the UK (pre-COVID-19), of whom 48,000 die. In addition, virtually all COVID-19 intensive care unit (ICU) deaths had sepsis. It is a leading cause of death and the most expensive condition treated in hospitals. It was recognised as a top research priority by the James Lind Alliance, a partnership of patients and clinicians to prioritise the most pressing unanswered questions facing the NHS.

The cornerstone of sepsis resuscitation is the administration of intravenous fluids and/or vasopressors (drugs that squeeze the blood vessels to increase blood pressure) to maintain blood flow to prevent organ failure. However, there is huge uncertainty around the individual dosing of these drugs in an individual patient, partially due to high sepsis heterogeneity. The current guidelines provide recommendations at a population-level but fail to individualise the decisions. Wrong decisions lead to poorer outcomes and increased ICU-resource use. A tool to personalise these medications could improve patient survival.

We have developed a new method to automatically and continuously review and recommend the correct dose of these medications to doctors, which was created using artificial intelligence (AI) techniques applied to large medical databases. The method we used is called reinforcement learning. In this framework, we model patients with sepsis in the ICU as belonging to a large number of possible disease states, and we analyse what interventions are likely to help them transition to healthier states, and

eventually to survival. We demonstrated in our initial publication that the value of the AI selected strategy was on average reliably higher than human clinicians. In a large validation cohort independent from the training data, mortality was lowest in patients where clinicians' actual doses matched the AI decisions: mortality rates rose, in a dose dependent manner, as the clinicians' actual decisions diverged from the AI decisions. We have estimated that our AI algorithm could reduce mortality by 10% (in relative terms), which represents over 1,000 lives saved annually in the UK and would scale to hundreds of thousands of lives worldwide. Now, we intend to start clinical testing of this AI technology in the UK.

The envisioned end-product will be a piece of software that will be accessible by clinicians (ICU doctors initially, then eventually to ICU nurses as well) at the bedside in intensive care. This software will be connected to the electronic patient record, which will be fed to the AI algorithm. In return, the AI will identify where the patient sits in the array of possible disease states, and which actions (a dose of intravenous fluids and vasopressors) are most likely to be beneficial.

First, we will develop this software tool, capable of processing patient data within the electronic patient record of NHS hospitals in real-time to suggest a course of action. We will start by evaluating and refining this tool in simulation studies. We will then test the AI tool in two NHS Trusts in a "shadow mode" when the result is **not** provided to duty clinicians in charge of patient care (**the purpose of this application**). This will allow comparison of actual decisions made and recommended decisions from the AI system. Later on (**this is not the purpose of this application**), in the second stage of the clinical evaluation, we will display the recommendations to clinicians to assess the acceptability of the tool to clinicians and also confirm the technical feasibility to inform future large scale clinical trials.

The long-term expected benefits of this project are numerous: improved patient survival, reduced use of precious intensive care resources and reduction in healthcare costs.

1.2. RATIONALE FOR CURRENT STUDY

Research question:
How well does our real-time AI-based system for fluid and vasopressor therapy for sepsis in the ICU perform in an operational clinical environment?

Hypotheses:

- We are able to run the system with high availability, reliability and acceptable lag (near real-time) at the bedside.
- The quality of AI suggestions, assessed by off-duty clinicians, is appropriate.
- Patients' outcomes are better when actual doctors' decisions match the suggested AI decisions (which remain hidden from on duty doctors).

2. STUDY OBJECTIVES

Primary objective:

- Confirm operational robustness and technical reliability of the software when operating in real-time in an operational ICU environment. We will measure indicators of system reliability and availability (e.g. what percentage of time is the system available, at different times of the day and night, on weekdays versus weekends, etc.) and the lag of the system (e.g. delay between data recorded at the bedside and model producing an output).

Secondary objectives:

- In the shadow mode study, human evaluators will assess the AI decisions: off-duty clinicians will evaluate the clinical correctness/appropriateness of AI suggested decisions. The evaluators will classify the AI suggested actions in different categories, such as “likely safe”, “likely inappropriate”, “possible too low”, or “possibly too high”.
- We will document learning points and develop standard operating procedures for deploying the tool in various hospital systems
- Finally, we will estimate patients’ outcomes (organ failure, ICU mortality and hospital mortality) if the AI decisions were followed and compare them to actual outcomes (which were linked with human decisions).

3. STUDY DESIGN

This study is a prospective multi-centre observational study that will include four intensive care units from two different NHS Trusts.

The duration of the study will be up to 24 months.
We will include 100 to 300 adult patients with early sepsis in ICU (within 24h of ICU admission). This number is a pragmatic, realistic estimate of how many patients will satisfy the inclusion criteria in the study period (assuming a conservative 60 admissions per month on each unit (reality is closer to 80-100 pre-COVID-19), and 20% sepsis at admission), and will allow us to deliver on the study objectives.

With regards to human assessors, we will include 6 to 15 ICU doctors, mixing senior registrars, ICU fellows and consultants.

The “system” will be a purpose built webapp accessed from a dedicated laptop, connected to an NHS ICT server, with secure login. It will be linked to a duplicate of the Philips ICCA database (Imperial College Healthcare NHS Trust) or the EPIC EHR (UCLH) which contains ICU patient data in near real time (estimated lag of 5 to 15

minutes). The system will be running the AI Clinician algorithm, which processes ICU patient data and outputs a suggested dose of intravenous fluids and vasopressors. Four times a day (every 6 hours), the system analyses newly admitted ICU patients and identify those who fulfil the sepsis-3 criteria. If they do, they will be added to a list of patients for potential inclusion that will be accessible from within the software (and assessed by human evaluator for enrolment).

The system will contain several tabs:

1- **Patient screening.** It displays a list of patients screened and highlighted by the system as fulfilling sepsis-3 criteria. The user (human evaluator) has the option to include them into the study, after verification of the inclusion/exclusion criteria (see sections 4.2 and 4.3 for these criteria).
2- **Individual patient data**. This screen contains a drop-down list of patients included in the study. After selecting one, the data time series of this individual patient are displayed here, along with the doses of fluids and vasopressors actually given by human "on-duty" doctors and nurses.
3- **Evaluation tab**. This is where the evaluation of the AI and human doctors' decisions takes place. The option to scroll through the various previous time points is provided. The evaluation by the human evaluator takes place in several subsequent steps: First, the human evaluator makes a recommendation based on patient data alone (data point #1). Then, the human evaluator is presented with the AI recommendation (data point #2), along with other information (confidence in the suggested decision, explanation of why this action was recommended). They "rate" the AI decisions, by classifying the AI suggested actions in different categories, such as "likely safe", "likely inappropriate", "possible too low", or "possibly too high". Finally, the human evaluator is presented with the actual decision (made by human clinicians, data point #3) and the subsequent patient evolution (at least a few hours, but the final outcome of ICU death or survival will be presented if available). The human evaluators rate the actual decisions using the same scale, e.g. "likely safe", "likely inappropriate", etc. There will be a free-text box to enable the user to provide feedback on their decisions.

The software will be accessed on the dedicated laptop from within the NHS hospitals by off-duty clinicians enrolled in the study, whom we call "human evaluators". To explore system's usability around the clock, there will be no restrictions with regards to timing of the research, so the human evaluators will be able to conduct the research at any time and on any day of the week.

We intend to conduct the study during 1-hour sessions, during which the users will conduct these 2 actions:
1) Identify new patients for inclusion from a pre-screened list
2) Assess multiple decisions made on multiple included patients. Based on a conservative number of 5 patients with sepsis on each unit at any point in time, and between 4 - 10 sessions per user, we will gather a maximum of 600 to 1,500 data points (100 data points per user for 6 to 15 users). We expect to include an estimated

100 to 300 separate patients across 4 sites (based on 20 patients per month per unit and 27 months of total study period over the 4 units, which gives 540 potential eligible patients). This will enable to complete the study objectives.

Data about the system's operational reliability will be automatically collected:

- Time elapsed between a clinical event (e.g., administration of a fluid bolus) and the record appearing in the database. This exploits the property of some clinical events to be time-stamped to quantify the lag in the system.
- Date and time of all system accesses
- Server status, down-time events, planned and unplanned outages. These events can be monitored remotely and logged by the ICT team.

An independent online form (survey-type) will be created to log all technical issues that the users may encounter (e.g., system unavailable, login issues etc). This survey will be kept separate from the system, so it can't be affected by server outage for example.

The data about the system's operational reliability and the technical issues reports do not contain patient sensitive information and will be available to researchers at Imperial College London, in the research groups of Prof Anthony Gordon and Prof Aldo Faisal.

After running the study for 3 months on each study site, an interim analysis will be performed to test the data quality. A pseudo-anonymised dataset including the fields described in section 3.1 "study outcome measures" of all patients included so far in the study will be created. All patient identifiable information will be removed, patient NHS number will be replaced by an ad-hoc random number, and the mapping between the patients' true identity and identifiers will be kept on the NHS server. No patient health records will leave NHS systems.

The final analysis will occur at the end of the study period (after month 18, in August 2022), once all data has been collected. The pseudo-anonymised dataset will be transferred encrypted to an Imperial College London secured server, within the Faisal Lab. Researchers in Anthony Gordon and Aldo Faisal groups will then conduct various modelling and analyses to assess the AI suggested decisions.

This trial will be conducted across four intensive care units: Imperial College Healthcare Trust - Charing Cross Hospital, Hammersmith Hospital, St Marys Hospital and University College London Hospital. All four units are capable of treating critically ill patients.

Routine clinical data (demographics, diagnosis, severity of illness, presence and duration of mechanical ventilation, ICU and hospital length of stay and hospital mortality, see appendix for more specific information) will be collected until hospital discharge from the recruiting centre. All outcome data will be collected from hospital databases including microbiology results.

To determine how the tool was implemented at each site, a trained researcher will accompany all site initiation visits to make observations and take field notes regarding discussions of planning and implementation at site.

3.1. STUDY OUTCOME MEASURES

Data of interest	Study outcome measures
System / usability data	Data availability: what percentage of essential and optional data fields are available 24/7. System availability: delay in generating response 24/7. Number and nature of technical issues (drop-outs, freezes).
Anonymised patients' data	Patient demographics (age in years, gender, primary diagnosis) Outcomes: organ function (hourly SOFA), ICU and hospital mortality
Bedside physicians' data	Doses administered to patients of intravenous fluids and vasopressors, which are action chosen by on-duty clinicians
Evaluators' data (the doctors assessing the AI in the background)	Evaluator's grade and seniority A custom-made interface linked to a database will capture and record the following: - What dose they would recommend, before and after seeing the AI suggested dose. - Agreement with AI suggested dose: does it appear appropriate, too high or too low?

4. PARTICIPANT ENTRY

4.1. INCLUSION CRITERIA

For patients:
Adult patient > 18 years old
Admitted to an intensive care unit
Likely or confirmed diagnosis of sepsis as per sepsis-3 definition (as defined in the glossary)
ICU length of stay > 24h

For evaluators:

ICU doctors at the senior registrar, ICU fellow or consultant level

4.2. EXCLUSION CRITERIA

For patients:
Not for full active care, e.g. not for vasopressors
Not expected to survive more than 24h
Elective surgical admission (these patients are regularly on antibiotics but given as a prophylaxis, with no sepsis)
Opted-out for use of their data for research (NHS and NHS-X website)

For both patients and evaluators:
Declined participation
No patient consent is required

4.3. WITHDRAWAL CRITERIA

For evaluators:
Requested withdrawal from study. Human evaluators may request withdrawal by contacting the study coordinators. In the event that an evaluators request withdrawal from the study, no further data will be collected from them.

5. ADVERSE EVENTS

It is an observational study, so there is no direct risk for patients or the human evaluators. Adverse events involve data security questions, in particular data breach and loss of personal identifiable information. These aspects are addressed in section 8.3 “confidentiality”.

6. ASSESSMENT AND FOLLOW-UP

There will be no follow-up. The study ends at each participating site, at the time of hospital discharge of the last recruited patient.

7. STATISTICS AND DATA ANALYSIS

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

Data of interest	Statistical analyses

System / usability data	Simple descriptive statistics (e.g. average system lag, number of technical issues per week…)
Anonymised patients' data	Simple descriptive statistics of the patient characteristics. Comparison of the training and prospective cohorts (simple parametric and non-parametric tests comparing demographics, severity of illness, etc).
Evaluators' data (the doctors assessing the AI in the background)	Descriptive statistics from evaluators data: Agreement between initial human evaluator doses (data point #1) and AI decisions (data point #2), and between AI decisions (data point #2) and actual doses given to patients (data point #3). Proportion of AI decisions (data point #2) classified as appropriate / possibly too low / possibly too high Proportion of human decisions (data point #3) classified as appropriate / possibly too low / possibly too high
AI decisions evaluation	Quantitative analyses of AI decisions: estimate patients' outcomes if the AI decisions were followed and compare them to actual outcomes (which were linked with human decisions). We will use 2 methods: 1) compare short-term outcomes between model-concordant treatment and model-non-concordant treatment, with confounder adjustment; 2) off-policy policy evaluation of the AI policy in the prospective ICHT cohort.

8. REGULATORY ISSUES

8.1. ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Health Regulatory Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2. CONSENT

Consent will be sought from participating clinicians. A full explanation will be provided in the form of a written explanation covering the details of the study, their role and any potential risks of participating. Any remaining questions that participants have after reviewing the written documentation will be answered by the investigator team.

All clinician participants are free to withdraw from the study at any stage upon written request to the investigator team without giving reasons. Their data will remain in the study unless they request for it to be removed.

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Potential patients will only be identified by local NHS staff at the recruiting site and they will maintain the same duty of confidentiality owed to all patients by medical and nursing staff. All personal identifiable data will be kept within the NHS hospital and routine NHS databases. Pseudonymisation of patient data will be completed by the trusts research informatics team who form a part of the extended care team. Because of all of the above we will not seek specific patient consent for this phase of the study.

Approval from the sponsor (Imperial College London / NHS Healthcare Trust) data controller has also been sought.

8.3. CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study as per the Data Protection Act.

The General Data Protection Regulation (2016/679) broadly defines personal data breaches as a security incident that leads to the confidentiality, integrity or availability of personal data being affected. There will be a personal data breach whenever any personal data is lost, destroyed, corrupted or disclosed; if someone accesses the data or passes it on without proper authorisation; or if the data is made unavailable, for example, when it has been encrypted by ransomware, or accidentally lost or destroyed. Personal data breaches will be immediately reported to the Sponsor, the Data Protection Officer, and RGIT. Any breaches will be documented in the TMF/ISFs, and will follow Sponsor/Data Controller reporting processes.

We have put measures in place to limit the risk of data confidentiality breach. Identifiable data will not leave trust servers. The study will only use pseudo-anonymised data so confidentiality of patients and clinician participants will be maintained, however the Principal Investigator will ensure to preserve the confidentiality of participants and fulfil transparency requirements under the General Data Protection Regulation (GDPR).

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study. Private health information such as patient identity, date of birth and date of death are not required. The lookup table mapping new patient identifiers and their initial identity will only be kept within trust systems. Identifiable information of clinician participants will likewise only be kept within trust systems.

Data will be kept encrypted in a secured lab accessible only (via swipe and pin code access) to members of the Imperial College Critical Care Research lab (under Prof. Anthony Gordon). The computer itself where the data will be kept is password protected, and its hard drives are encrypted.

8.4. INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5. SPONSOR

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6. FUNDING

NIHR-NHS X are funding this study. Participants will be remunerated up to £100 for time spent in the study.

8.7. AUDITS

The study may be subject to audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Matthieu Komorowski.

10. PUBLICATION POLICY

The results of the project will be published in a peer-reviewed, high impact, and ideally fully open access journal.

11. REFERENCES

M. Komorowski, L. A. Celi, O. Badawi, A. C. Gordon, and A. A. Faisal, “The Artificial Intelligence Clinician learns optimal treatment strategies for sepsis in intensive care,” Nature Medicine, vol. 24, no. 11, p. 1716, Nov. 2018.

G Kennedy, B Gallego,Clinical prediction rules: A systematic review of healthcare provider opinions and preferences, International Journal of Medical Informatics, Volume 123, 2019, Pages 1-10, ISSN 1386-5056, https://doi.org/10.1016/j.ijmedinf.2018.12.003.

Appendix 1. Summary of investigations, treatment and assessments

Investigations / Assessments		
	Screening	At each assessment session
System Set-Up		
Medical History	X	
Clinical Evaluation	X	X
Operational Reliability checks		X
Informed consent (Clinician)	X	

Appendix 2. Summary of required data fields.

Category	Items	Format	Unit	Comment
Cohort selection	Patient unique identifier	Integer/code	-	
Cohort selection	Date and time of administration of antibiotics	Date	-	Any oral of IV antibiotic (no topical, e.g. cream or eye drops)
Cohort selection	Date and time any blood or urine culture sent for MCS	Date	-	

Demographics	Age	Continuous	days or years	
Demographics	Gender	Binary	-	
Demographics	Weight at the time of ICU admission	Continuous	kg	
Demographics	Readmission to intensive care	Binary	-	Has this patient already been admitted to ICU during this hospital stay ?
Demographics	Comorbidities/past medical history (ICD codes)	Free text	-	if possible!
Demographics	Delay between hospital admission and ICU admission	Date	hours	
Demographics	ICU and hospital mortality	Binary	-	
Vital signs	Glasgow coma scale	Continuous	-	
Vital signs	Heart rate	Continuous	bpm	
Vital signs	Systolic blood pressure	Continuous	mmHg	
Vital signs	Mean blood pressure	Continuous	mmHg	
Vital signs	Diastolic blood pressure	Continuous	mmHg	
Vital signs	Respiratory rate	Continuous	bpm	
Vital signs	SpO2 = pulse oxymetry	Continuous	%	
Vital signs	Temperature	Continuous	Celsius	
Lab values	Potassium	Continuous	meq/L	
Lab values	Sodium	Continuous	meq/L	
Lab values	Chloride	Continuous	meq/L	
Lab values	Glucose	Continuous	mg/dL	
Lab values	BUN = Blood Urea Nitrogen = Urea	Continuous	mg/dL	
Lab values	Creatinine	Continuous	mg/dL	
Lab values	Magnesium	Continuous	mg/dL	
Lab values	Calcium	Continuous	mg/dL	
Lab values	Ionised Calcium	Continuous	mg/dL	
Lab values	CO2 : total CO2	Continuous	meq/L	
Lab values	SGOT	Continuous	u/L	
Lab values	SGPT	Continuous	u/L	
Lab values	Total_bilirubin	Continuous	mg/dL	
Lab values	Albumin	Continuous	g/dL	
Lab values	Hb = Haemogobin	Continuous	g/dL	
Lab values	WBC count	Continuous	E9/L	

Lab values	Platelets count	Continuous	E9/L	
Lab values	PTT = Partial Thromboplastin Time	Continuous	s	
Lab values	PT = prothrombin time	Continuous	s	
Lab values	INR = International Standardized Ratio	Continuous	-	
Blood gas	Arterial_pH	Continuous	-	
Blood gas	paO2	Continuous	mmHg	
Blood gas	paCO2	Continuous	mmHg	
Blood gas	Arterial base excess	Continuous	meq/L	
Blood gas	Arterial lactate	Continuous	mmol/L	
Blood gas	HCO3 = bicarbonate	Continuous	meq/L	
Ventilation parameters	Mechanical Ventilation	Binary	-	Is the patient mechanically ventilated?
Ventilation parameters	Interface for oxygen administration	categorical	-	E.g. face mask, nasal cannulae…
Ventilation parameters	Flow of oxygen	Continuous	L/min	Helps estimating the effective FiO2
Ventilation parameters	FiO_2 = inspired fraction of oxygen	Continuous	-	May not be documented if there is a flow of O2 in L/min
Medications and fluid balance	Intravenous Fluid intake	Continuous	mL	IV crystalloids given for resuscitation
Medications and fluid balance	Vasopressor	Continuous	mcg/kg/min	Includes infusions of noradrenaline, adrenaline, phenylephrine, vasopressin, metaraminol, dopamine
Other interventions	Renal replacement therapy	Categorical	-	any indication that the patient is undergoing acute dialysis for acute renal failure
Other interventions	Sedation	Continuous	-	any continuous infusion of propofol, midazolam, fentanyl, remifentanil, thiopental, atracurium, rocuronium

Medications and fluid balance	Urine output	Continuous	mL	Includes items such as -- "Foley" -- "Void -- "Condom Cath" -- "Ileoconduit" -- "Suprapubic" -- "Nephrostomy" -- "Ureteral Stent"
Medications and fluid balance	Cumulated fluid balance since ICU admission	Continuous	mL	
Preadmission data	Total IV fluid intake prior to ICU admission	Continuous	mL	
Preadmission data	Total urine output prior to ICU admission	Continuous	mL	