Study Title: Digital alerting to improve sepsis detection and patient outcomes in NHS Trusts
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Funder:	NIHR HS&DR
Version:	**3.1** – to reflect changes in sponsor for HRA approval and inclusion of qualitative protocol
	3.2 – to reflect change in funding statement and version control
	3.3 – addition of HRA Amendment approval

Version Control Table

Date	Version	Description of changes
11/03/22	3.1	Format changes and reflection of changes in sponsor and inclusion of details qualitative protocol. Wording of Aim and Objectives for WS3 improved.
28/03/22	3.2	Version control table added. Funding statement amended. Year on p32 changed from 2020 to 2021.
12/05/22	3.3	Recording of date of HRA Amendment Approval for change of sponsor.
12/01/23	3.4	Addition of date of WP3 REC reference and HRA approval date

TABLE OF CONTENTS

1. KEY STUDY CONTACTS

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Sponsor	Institute of Cancer Research Clinical Research & Development, The Royal Marsden NHS Foundation Trust, Downs Rd, Sutton SM2 5P rdccr@rmh.nhs.uk 020 8661 3903
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Funder(s)	National Institute for Health Research Health and Social Care Delivery Research (NIHR HS&DR) HS&DR Project: NIHR129082

2. LAY SUMMARY

Sepsis is a serious disease, most often caused by a bacterial infection and can be treated with antibiotics. Identifying patients with sepsis as early as possible means treatment with antibiotics can be started earlier. To identify patients who may have sepsis, measurements such as high or low temperature and fast breathing rate are used to create a score showing the possibility of sepsis. Electronic Health Records (EHR) in hospitals contain the information needed to create a score and can alert a doctor or nurse that a patient may have sepsis. Research has shown that more patients get antibiotics earlier because of hospitals using this type of digital alert. Different hospitals have used different methods to create a score and use different types of digital alerts. This research wants to find out

a) What scores and systems are in use in different NHS Trusts in England and Wales.
b) What impact the alerts have had on patients
c) What hospital doctors, nurses and patients think about digital alerts for sepsis and how they use them in hospitals.
d) How digital alerts are used and how they affect patient care can help us to see how they could be used better so patients can benefit.

3. SYNOPSIS & ETHICAL APPROVALS

Study Title (short title)	Digital alerting to improve sepsis detection and patient outcomes in NHS Trusts. (DiAlS)
Sponsors	Institute of Cancer Research Clinical Research & Development, The Royal Marsden NHS Foundation Trust, Downs Rd, Sutton SM2 5P University of Oxford Research Governance, Ethics & Assurance Team, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB.
Funder	National Institute for Health Research Health and Social Care Delivery Research (NIHR HS&DR).
Study Design, including methodology	Quantitative study treating the introduction of alerts as a natural experiment Qualitative study including observation of healthcare professionals working in hospitals, one-on-one interviews with healthcare professionals and focus groups with patients/carers.
Study Participants, including sampling strategy - Quantitative	Adult patients within the scope of the alert in six NHS Trusts
Study Participants, including sampling strategy - Qualitative	Hospital healthcare professionals who use, or help implement, sepsis alerts in NHS trusts. Patients/carers recruited from NHS trusts, who have previously had sepsis or are carers or family members of patients who have had sepsis. Approximately 25-30 healthcare professionals

	Approximately 20 patients/carers, 3-4 focus groups each with around 6 patients/carers.

This project has two key parts which require ethics approval – quantitative analysis (WorkStream 2) and qualitative analysis (WorkStream 3)

	Quantitative Analysis	Qualitative Analysis
Lead Investigator	Dr Kate Honeyford	Dr Sarah Tonkin-Crine
Sponsor	Institute of Cancer Research (ICR)	University of Oxford Research Governance, Ethics & Assurance Team, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB.
IRAS Project ID	288328	313699
REC reference	NA	22/PR/1020
HRA Approval	15th Jan 2021	4th Nov 2022
Amendments	The original sponsor of this project was Imperial College. As of 1st Dec 2022 Dr Kate Honeyford no longer worked at Imperial College and all data extraction ceased. We now have approval from ICR and are in the process of submitting an amendment to HRA	
Amendment approved	12 May 2022	
Amendment No./Sponsor Ref:	AM2203-39	

4. ABBREVIATIONS

A&E	Accident and Emergency
AWARE	Access, Watch, and Reserve
CDI	Clostridium difficile infections
CI	Chief Investigator
CQUIN	Commissioning for Quality and Innovation
EWS	Early Warning Score
FoI	Freedom of Information
HCP	Healthcare Professional
HRA	Health Research Authority
ICF	Informed Consent Form
MRC	Medical Research Council
NEWS	National Early Warning Score
NHS	National Health Service
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RGEA	Research Governance, Ethics & Assurance Team
SOP	Standard Operating Procedure
SoS	Suspicion of Sepsis
WS	Work Stream

5. BACKGROUND AND RATIONALE

Sepsis is a common cause of serious illness and death with an estimated 123,000 cases and 46,000 deaths in the UK each year.[1] Similarly, high levels of sepsis have been reported internationally[2,3] and sepsis is recognised by World Health Organisation as a global health priority.[4] Many countries have nationwide sepsis action plans and all UK hospitals have set targets to rapidly diagnose and treat patients with sepsis. Timely appropriately targeted intravenous antibiotics have been shown to be effective in improving outcomes for patients, with a 4% increase in odds of mortality for every hour's delay in administration of intravenous antibiotics.[5–7]

The need for rapid treatment has led to the development of clinical criteria and 'screening tools' have been proposed to identify patients with sepsis. These include Sequential (Sepsis related) Organ Failure assessment, Systemic Inflammatory Response Syndrome (SIRS) criteria[8] and in England the National Early Warning Score (NEWS).[9] NEWS2 is recommended by NICE and the Royal College of Physicians as the most effective screening tool for sepsis in the UK.[10,11] Available tools are based on current observations which clinicians are able to take and quickly calculate a score but there is a paucity of evidence as to which tool to use and their effect on patient outcomes. Many of these have been embedded into electronic health systems which generate electronic alerts.

Potential pathways for the effectiveness of alerts when clinical deterioration is due to sepsis are likely to include an increase in the proportion of patients receiving intravenous antibiotics in one hour,[12] and other 'sepsis six' measures.[13] Improved communication and changes in dialogue between healthcare teams has been suggested as an important pathway for improvements in clinical outcomes.[14] In addition, the introduction of sepsis alerts is often accompanied by treatment plans as well as education and training activities. Little is known about the contribution of these and other potential mediators on the effectiveness of alerts.

Systematic reviews examining the effect of digital sepsis alerts have found low diagnostic accuracy and modest improvement in sepsis related outcomes.[15-16] Most existing evidence comes from small, ICU based studies in hospitals in the United States (US). There has been no large-scale study investigating the effects of digital alerts on patient outcomes, particularly in the UK healthcare system.

Using routine clinical datasets, the mechanisms and mediators of effectiveness and consequences of digital alerting in outcomes for patients with sepsis will be assessed. A framework comprised of a series of methods guided by clinical effectiveness research principles will be used to achieve this.

This project specifically focuses on digital alerts used to identify clinical deterioration due to sepsis or serious infectious disease. We will describe these as 'digital alerts' whether they are specific to sepsis or more general EWS.

Previous qualitative research with healthcare professionals has highlighted problems in identification and management of sepsis including limits in professionals' capacity to identify sepsis, difficulties in handover of patients and errors in communication.[17-21] These studies highlight both the requirement for healthcare professionals to feel confident in their assessment of patients and for clinical and organisations structures to work efficiently to provide optimal patient care. Previous qualitative research with patients has reported on patients' decisions to seek help with symptoms, experiences of hospitalisation and how patients have managed life after surviving sepsis.[22-24] Additional studies with caregivers have described the burden on those caring for sepsis survivors and their role in advocating for their loved ones.[24,25] Another study has looked at the words patients and call handlers use to describe symptoms of sepsis when patients seek help.[26] These topics can help to inform how patients and clinicians could use and potentially benefit from the use of digital alerts in hospitals.

The quantitative study will treat the introduction of alerts as a natural experiment and use appropriate methods to analyse routinely collected data to make causal inference.
The qualitative study will include three methods of data collection; observation of healthcare professionals working in hospitals, one-on-one interviews with healthcare professionals and focus groups with patients/carers.
Healthcare professionals will include doctors, nurses and other professionals who use, or help implement, sepsis alerts in NHS hospital trusts. Patients/carers will include patients recruited from NHS trusts and community settings, who have previously had sepsis or are carers or family members of patients who have had sepsis.
Interviews and focus groups will include topics which may be upsetting for some patients/carers or healthcare professionals. All participants will be made aware of sources of support available to them through the NHS.
The quantitative findings of WS2 and the qualitative findings of WS3 will be combined using Directed Acyclic Graphs (DAGS) and a converging approach.[27-28]

6. AIMS and OBJECTIVES

Aim / Research Questions / Objectives

Aim (WS1) - Map the digital alerts currently in use in multiple UK hospitals to identify patients at risk of having sepsis.

Objectives

1.1. Determine the details of algorithms in use at each of the Trusts involved and any local adaptations

1.2. Describe the introduction of alerts in each Trust

1.3. Collate relevant care pathways and treatment plans

1.4. Agree a final data-dictionary

1.5. Build and curate comparable data sets across Trusts.

Aim (WS2) - Evaluate the impact of digital alerts on outcomes for patients at risk of sepsis (WS2).

Objectives

2.1. Describe the total sample of patients in each Trust and across the study who are affected by the alert and baseline outcome data

2.2. Describe the frequency of the alert across different Trusts, departments within Trusts and specific patient groups

2.3. Describe any seasonal and temporal variations in alerts

2.4. Quantify the impact of a digital alert on key patient outcomes and process measures.

2.5. Examine potential unintended consequences associated with the introduction of digital alerts.

Aim (WS3) - Explore the views and experiences of healthcare professionals and patients/carers on the use of digital sepsis alert systems in hospitals.

Objectives

3.1. To understand how healthcare professionals use sepsis alerts and how alerts influence their decision making.

3.2. To observe healthcare professionals use of sepsis alerts during routine hospital shifts.

3.3. To identify barriers and facilitators to the implementation and use of digital sepsis alerts in NHS hospital settings.

3.4. To explore patients' and carers' views of sepsis alert systems and management of sepsis in hospitals.

Aim (WS4) - Make recommendations on the effectiveness of different digital alerts and the most effective method of implementation using a systems modelling approach to assess causality of effects, including a mediation analysis (WS4)

Objectives

4.1. Identify the most effective digital alert for improving outcomes for patients with sepsis

4.2. Update our current understanding of QI implementation methodologies, with digital alerts as a specific example.

4.3. Identify more challenging aspects of the implementation of digital alerts in order to improve sustainability of digital interventions, if appropriate

4.4. Using mediation analysis, establish causal pathways between digital alert interventions and impact, incorporating qualitative and quantitative findings from WS1-3

7. STUDY DESIGN

Each workstream has a different methodological approach, suitable for the aims and objectives for each works stream.

7.1 WorkStream 1 – Map the digital alerts currently in use in multiple UK hospitals to identify patients at risk of having sepsis.

Methodology

In order to determine the details of algorithms in use at each of the Trusts and any local adaptations, their introduction and relevant care pathways and treatment plans we will carry out qualitative document analysis, a systematic procedure for reviewing documents. It is an efficient cost-effective method of data collection and will allow us to quickly collate information on digital alert introduction and implementation in Trusts. Document analysis is recorded without a researcher's intervention and can be used to track change and development of policies over time. We will discuss with the co-investigator from each NHS site the algorithm in use and the introduction. In order to contextualise the details of the digital alerts in use in the six Trusts included in the study we will carry out a Freedom of Information (FoI) request targeting NHS hospitals in England and Wales.

Sampling Strategy

The six NHS trusts included in the detailed discussions and document collection and the six NHS Trusts included in the project outline – these were included as a result of our networks and being digitally mature.

Methods of Data Collection

Discussions with co-investigators and collation of written material. FoI request will be sent to all NHS Trusts in England and Wales.
Notes will be made during discussions and summaries of discussions and notes from documents will be shared with the co-investigators to confirm summaries are accurate.
Results of FoI requests will be collated in an excel spreadsheet. A second researcher will confirm data extraction from FoI responses. Data will be summarised.

Methods of Data Analysis

Descriptive summaries of FoI.

Study Sequence and Duration

Initial discussions and document requests will take place in the first six months of the project. In the second six months the FoI request will be made and summarised.

7.2 WorkStream 2 – Evaluate the impact of digital alerts on outcomes for patients at risk of sepsis.

Methodology

This is an epidemiological study, analysing routinely collected data. We will treat the introduction of the alert in individual Trusts as a natural experiment and use approaches appropriate to the analysis of natural experiments.
The study will collect data on patient outcomes prior to the introduction of the alert for a maximum of five years and up to three years post the duration of the alert. We may have to use shorter time periods for certain Trusts.

Sampling Strategy

We have identified five digitally mature NHS Trusts in England, each operating a digital sepsis alerts. In addition, we are working with a Trust in Wales which is still paper based.

Methods of Data Collection

A detailed data specification and data dictionary will be compiled, with associated SNOMED codes for each observation. All data items are routinely collected and recorded in patient electronic records. All data will be de-identified. We will use the NIHR-HIC data infrastructure to enable data transfer. Please see Section for more details.

Outcomes

The primary outcome will be **all-cause in-hospital mortality within 30 days**.
Secondary outcomes (including process measures):

- Transfer to ICU
- Length of stay
- Readmission within 30 days
- Administration of IV antibiotics
- Venous blood tests including lactate and white blood cell count
- Blood cultures ordered

The primary reason for the introduction of EWS systems, including digital alerts, is to prevent avoidable clinical deterioration. Mortality is a key measure of clinical deterioration and the majority of EWS have been validated by assessing their ability to predict mortality. Mortality is recorded in hospital patient records and reported as part of the Secondary Users Service (SUS). It is therefore a reliable and commonly used measure of clinical deterioration. Transfer to ICU is often used as an additional measure of clinical deterioration and is available in EHRs.

Length of stay and readmission within 30 days are important indicators of patient experience and are key targets for hospitals. The aim of early recognition of sepsis is to enable prompt and appropriate treatment. We will therefore assess whether the introduction of digital alerts has impacted on appropriate treatment.

Assessment of unintended consequences

Based on discussion in the Sepsis Big Room clinical teams are concerned about potential increases in unnecessary treatment as an unintended consequence of digital alerting. We will consider four potential measures of unintended consequences:

- Increase in *Clostridium difficile* Infections (CDI): Beta-lactam use is associated with an increased risk of acquisition of CDI, with the elderly being a group particularly at risk. We will monitor *C*DI rates within each Trust over time and investigate any changes in CDI rates following introduction of digital sepsis alerts.
- Increase in short term admissions: We will examine changes in short term admissions (<24 and <48 hours) in patients diagnosed with a bacterial infectious disease.
- Increases in administration of IV antibiotics which are deemed unnecessary. We will assess through monitoring changes in numbers of patients who are administered IV antibiotics and are discharged without a Suspicion of Sepsis or other infection code.
- Increases in the use of carbapenems and/or antibiotics from the AWaRe list[29] - these indicators are part of the sepsis CQUIN, so will be reported by each Trust

Methods of Data Analysis

Descriptive analysis

We will summarise the number of inpatient alerts and alerts in A&Es for patients aged 18 and over in each Trust, standardised by inpatient admissions and A&E attendances respectively. As alerts can fire multiple times for one patient encounter with a hospital, we will include the first alert for each patient encounter. Simple descriptive statistics will allow us to describe variations in the numbers of alerts by Trust and, where Trusts are made up of multiple sites, by site. We will describe variation in standardised alert rates with and without taking into account patient characteristics, which will include patient age, sex and pre-existing comorbidities where this information is available. Standard statistical approaches including Chi-squared tests to determine if there are differences in the characteristics of patients across Trusts and sites. Regression models will examine seasonal variations in alert frequency and whether there are trends in standardised rates over time. We will summarise patient outcomes for each Trust based on all patients who alert and patients who received a code included in the Suspicion of Sepsis list. Where Trusts utilise the same alerting approach we will compare rates of alerts, patient characteristics and patient outcomes by alert type.

Primary analysis

For the primary analysis we will identify patient hospital encounters where the alert was active and visible to clinicians and use EHRs to identify a cohort of patients who have the same clinical characteristics as the alerting patients, based on routinely recorded vital signs or alerting software. These will act as a control group. Statistical analysis plans will be dependent on the implementation approach in individual Trusts. In line with the approaches recommended in the MRC guidance, methods to be included are those where the factors which determine the exposure can be measured: matching; regression adjustment; and propensity score approaches. We will also utilise methods which are best suited for adjusting for pre-implementation trends including interrupted time series. All analyses will be adjusted for clustering of patients within wards or Trust sites.

Secondary analysis

We will use a controlled multilevel interrupted time series regression to examine trends in mortality for patients with codes defined as ‘suspicion of sepsis’ and a more robust definition of sepsis. utilise this method to examine unintended consequences identified above.

Sensitivity analysis

We will consider mortality following an A&E attendance for stroke and/or trauma as an unrelated outcome in a sensitivity analysis. Although these patients may trigger an alert, we would not expect their treatment to be different after the introduction of the alert as they are likely to be identified rapidly on arrival. This will enable an assessment of the specificity of effect. This will be included in primary and secondary analysis. These conditions will be included as controls in controlled interrupted time series.

Study Sequence and Duration
Data extraction will commence in March 2022 and be completed by May 2022. Analysis will be completed by December 2022.

7.3 WorkStream 3 – To explore the views and experiences of healthcare professionals and patients/carers on the use of digital sepsis alert systems in hospitals.

Methodology
This study takes a critical realist approach using interviews, observations, and focus groups to understand the use and implementation of sepsis alerting systems in NHS hospital trusts. This will enable us to answer the aim and objectives of the research by asking stakeholders their views and experiences of sepsis alerts and observing use of alerts during routine clinical practice. Speaking to healthcare professionals, patients and carers will allow us to consider how sepsis alerts impact clinical decision making, patient experience and the actors involved.[30] Unstructured observations will allow us to identify any influences on clinician decision making and sepsis alert use which healthcare professionals and patients may not be fully aware of and have shown to be useful in sepsis research previously.[31]

Sampling Strategy
We will conduct interviews with a range of healthcare professionals recruited from NHS trusts. We will use a combination of purposive and convenience sampling. We will use our existing networks within each Trust and ask appropriate contacts to identify eligible healthcare professionals who can be invited to the study. For potential participants who express interest we will ask their job role, years of experience, expertise in sepsis/infection (if any) and experience of using (digital) alerts for sepsis (if any). If we get several expressions of interest for interviews, we will use this information to select participants to give a maximum variation sample in terms of job role, experience and expertise related to sepsis/digital alerts. A maximum variation sample will help us to identify a range of stakeholder who should provide insights into a variety of facilitators and barriers to healthcare professionals using digital alerts for sepsis.
Unstructured observations of clinical practice will be undertaken in the emergency departments, and other wards if applicable, of NHS trusts. We will seek to observe clinical practice on different days of the week and times of day to identify whether sepsis alerts are used differently by healthcare professionals in different roles.
We will conduct focus groups with patients and carers/family members recruited from NHS trusts and through community channels. We will select patients and carers to give variation in age and sex and to capture breadth of experience with sepsis where possible. We will prioritise including patients over carers but will include carers specifically where patients are not able to give an account of their experience of sepsis/hospital care. Again, a maximum variation sample, where possible, will help us identify patients with a range of experiences which should provide diversity in views on digital alerts for sepsis and sepsis management in hospitals.

Methods of Data Collection
Interviews and focus groups will be carried out in person, where possible, or remotely using telephone or video-conferencing software (Microsoft Teams).
Where interviews and focus groups are carried out in person, interviews with healthcare professionals will be carried out at their place of work. Focus groups with patients and carers will be carried out on NHS Trust hospital premises, where facilities are available, or on University of Oxford or the Institute of Cancer Research premises.

Interviews and focus groups will follow a semi-structured design to ensure that key questions are asked to all participants but to allow flexibility for follow up questions. Participants will be encouraged to talk about any topics which are of importance to them in relation to the research aims. Questions will ask healthcare professionals about their experiences of managing patients with sepsis and their experiences of using (digital) alerts and other screening tools for sepsis. Patients and carers will be asked about their previous experience of management of sepsis in hospital settings and their views on the use of digital alerts for sepsis. Interview and focus group questions will be piloted prior to recruitment to ensure questions are understandable and that the interview/focus group duration does not exceed the proposed maximum time.
Interviews are expected to last between 45 and 60 minutes but may be longer where a participant wishes to provide more information and is happy to continue. Focus groups are expected to last between 1-2 hours and, if lasting longer than an hour, will include a short break. Focus groups will include small groups (around 6 participants) to enable everyone to have sufficient time to share their views and discuss the topic. Interviews and focus groups will be audio-recorded using a stand-alone audio-recorder (i.e. not using a recording function in any video-conferencing software). Audio-recordings will be transferred onto the University IT network immediately after the interview/focus group, labelled with an anonymous identifier and stored in a folder with access restricted to the research team only. The audio-recordings will be transcribed verbatim or detailed notes will be made based on the recordings.

Methods of Data Analysis

Data from interviews, focus groups and field notes from observations will be analysed inductively using thematic analysis.[32-33] Each dataset will initially be analysed separately although interviews and observations may be combined later. Thematic analysis allows the research team to take a pragmatic approach to data collection, remaining grounded in the data but ensuring that the analysis answers the research objectives. Similarities and differences between transcripts will be assessed using a constant comparison approach.[34] Codes will be compared with one another to create categories, grouping similar codes together. All categories will be clearly defined to ensure that only related data are coded to that category. Thematic frameworks will be developed to represent each dataset as required.

Study Sequence and Duration

Healthcare professionals will take part in one interview and/or be observed at work on up to 10 occasions over a maximum period of 6 months.
Patients/cares will take part in one focus group and will not be followed up.

7.4 WorkStream 4 – Make recommendations on the effectiveness of different digital alerts and the most effective method of implementation using a systems modelling approach to assess causality of effects, including a mediation analysis

Methodology

In order to identify the most effective digital alert for improving outcomes we will integrate findings from previous workstreams. WS4 will draw strongly on principles of systems modelling and the emerging field of causal inference epidemiology. Combining the results of the document analysis in WS1, the quantitative findings of WS2 and the qualitative findings of WS3 using a converging approach[27] the next step will be to assign causation. Directed Acyclic Graphs (DAGs)[28] are helpful in diagnosing sources of bias and helping investigators select a set of covariates that allow the estimation of causal effects from observed data. A workshop will be convened for this purpose. Using the results from WS1-3 and the conceptual framework (see Figure 1) a DAG will be produced to establish the causal pathways of the mechanism of action of the digital alerts.

Sampling Strategy

Not applicable for this part of the study.

Methods of Data Collection

This WorkStream will be based on the data collection from WS1-3

Methods of Data Analysis

We will use combined the results of WS1-3 using a converging approach and focussed workshops with Co-Investigators.

Study Sequence and Duration

WorkStream 4 will begin in January 2023 and be complete by July 2023.

8. PARTICIPANT IDENTIFICATION

WS2 – Participants, Inclusion and Exclusion Criteria

Study Participants

Patients aged over 18 attending the Emergency Departments and admitted as inpatients who are included in the scope of the alert in each trust.
From the hospital population we will identify patients aged between 18 and 110 who attend the Trust and lie within the scope of the alert. The scope of the alert will vary between Trusts, for example at ICHNT patients who are attend maternity wards and outpatient clinics are not currently included in the alert scope.

Inclusion Criteria

Patients who, on discharge or death, have an ICD-10 code included in the list of codes identified as Suspicion of Sepsis used in the Sepsis Insight Dashboard [www.sos-insights.co.uk];
Patients who 'alerted' - this is a binary indicator within electronic health records, this will depend on system the Trust uses to identify patients at risk of sepsis and/or deterioration related to sepsis.
In order to carry out sensitivity analysis we will extract clinical information for patients with an ICD-10 code related to a condition as identified as being appropriate to the local health economy.

Exclusion Criteria

There are no pre-registration evaluations, no specific inclusion and exclusion criteria are there is no withdrawal from the study.

WS3 – Participants, Inclusion and Exclusion Criteria

Study Participants

Participants will include hospital healthcare professionals and patients/carers in the UK.
The sample size will depend on saturation[33-34], i.e. no new themes are identified in data from later interviews/focus groups, however it is estimated that around 25 healthcare professionals and 20 patients/carers will participate.
Analysis of data from the interviews and the focus groups will occur concurrently to data collection, where possible, to inform future sampling and data collection.

Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Any gender aged 18 years or above (no upper age limit).
- Fluent in English (or able to participate in an interview with other measures in place, e.g. interpreter).
- For clinicians: Currently working as a healthcare professional (e.g. doctor, nurse) in an NHS hospital trust.
- For patients/carers: Member of the public who has previously been diagnosed with sepsis and treated in hospital or carer/relative of someone who has previously had sepsis.

Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Healthcare professional has less than 3 months experience working in relevant role. This is estimated to be a reasonable amount of time for them to have good experience of identifying patients with sepsis and/or using sepsis alert systems.

9. STUDY ACTIVITIES

WorkStream 2

Data extraction □ Quality check □ Data cleaning □ Data analysis □
Presentation of results to co-investigators □ Write up of results and discussion

WorkStream 3

Recruitment

The study is multicentre, involving recruitment of participants from several NHS hospital trusts and from community settings.
We will use our existing networks within Trusts, to identify suitable contacts and ask them to identify eligible healthcare professionals. We will ask contacts to invite any individuals to the study by email and will ask them to send emails out to relevant group email lists within the trust, where applicable, to advertise the study.
We will ask contacts in NHS trusts to advertise the study to eligible patients. This will involve staff sharing study adverts with eligible patients either in person or by email. This will include advertising the study to any existing patient groups linked to trusts (e.g., an 'ICU survivors' group present in one Trust). Those inviting patients will be part of the existing care team who already have access to patient details. Patient details will not be shared outside of the existing care team prior to patients contacting the research team. We will also advertise the study in hospital waiting areas and wards where relevant. We will also seek to recruit patients and carers through community channels. This will include advertising the study through relevant organisations, (e.g., UK Sepsis Trust), on social media websites (e.g., Twitter, Facebook) and though research participation websites (e.g., www.bepartofresearch.nihr.ac.uk).
Potential participants will be asked to contact the research team if they are interested in joining the study.

Informed Consent

Written versions of the Participant Information Leaflet (PIL) and (Informed Consent Form) ICF will be provided to participants in advance of an interview or focus group. Potential participants will be allowed as much time as they wish to consider the information, and the opportunity to question the Investigator or other independent parties to decide whether they will participate in the study. At the start of the interview, the researcher will ask if the participant has any questions or would like to clarify any aspect of the PIL or consent. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.
Informed consent will be taken at the start of interviews, either verbally if an interview is carried out remotely or taken as written consent for interviews carried out in person. Informed consent for focus groups will be taken either in person at the start of focus groups or prior to virtual focus groups, where each participant will be telephoned and asked to give verbal consent. A written record of any verbal consent will be made by the interviewer. The researcher will sign and date written consent forms and the written records of verbal consent and will email a copy to the participant. All records of consent will be retained electronically on the University of Oxford computer network.
The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Principal Investigator.

Screening and Eligibility Assessment

A member of the research team will assess potential participants eligibility to take part in the research when they receive expressions of interest in response to emails and study adverts and when potential participants are identified by NHS trusts. Each participant must satisfy all the approved relevant inclusion and exclusion criteria of the protocol.

Subsequent Visits

Participants will take part in one interview or focus group. Health care professionals taking part in an interview may also be observed at work but they, as an individual, will not be followed up.

Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time without giving a reason. Any data collected from that participant up to point of withdrawal will still be included in analysis. Participants who withdraw will not be replaced once recruitment has ended.
The Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (arising during the interview)
- Withdrawal of Consent

The reason for withdrawal by researcher (and by participant, if this information is volunteered) will be recorded in a study file.

Definition of End of Study

The end of study is 31st March 2023 at which point all study data will have been collected.

10. ANALYSIS

WS2 – Description of Analytical Methods

Detailed statistical plans are included in Appendix 1.

WS3 - Description of Analytical Methods

Data from interviews, focus groups and field notes from observations will be analysed inductively using thematic analysis.[32-33] Thematic analysis allows the research team to take a pragmatic approach to data collection, remaining grounded in the data but ensuring that the analysis answers the research objectives. NVivo 12 software will be used to assist with the organisation and coding of data. We will support the rigour and trustworthiness of the analysis by triangulating healthcare professional and patient data to get a fuller understanding of how sepsis is managed in hospitals. We will assess the transferability of findings by comparing findings across the several Trusts taking part in the research and will describe the context of each Trust in detail to help establish what is common and different in findings between contexts.
Confirmability will be established by making clear records of processes involved in data analysis and ensuring that findings can be tracked back to the original source(s).
To inform analysis we will collect data on healthcare professionals' sex, job role, years of experience in current role, and clinical expertise. We will collect data on patients' and carers' sex, age, nationality and ethnicity.

11. DATA MANAGEMENT

WS2 – Access to Data

Data will be stored in the Trusted Research Environment provided by Imperial College Healthcare Trust. All data transferred to the Research Informatics Team at ICNHT will be de-identified. Outside of this team only Dr Kate Honeyford will have access to the data.

WS3 - Access to Data

The Investigators listed on the title page will have direct access to the data. Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

WS3 - Data Recording and Record Keeping

Each interview and focus group will be audio recorded with the participant's permission. Recordings will allow verbatim transcription in Microsoft Word. Audio recordings will be labelled with anonymous identifiers (IDs) and will be stored in a restricted-access folder on the University of Oxford computer network. Audio recordings will be deleted at the end of the study. Transcription will be completed by an independent transcriptionist/transcription company who holds a contract with the University of Oxford. Transcripts will be labelled with anonymous IDs and any identifiable data (e.g., identifying the participant(s) or their place of work) will be removed from the transcripts.

Participant characteristics will be entered on a separate Microsoft Excel spreadsheet with unique participant IDs only. Observation field notes will be stored as Word documents with unique site IDs and no mention of individual hospital staff so that Trusts cannot be identified. Participant characteristics, field notes and anonymised transcripts will be stored as Excel or Word documents a study folder with access restricted to the study team.

Transcripts will be uploaded to NVivo 12 software to aid analysis.

Names and contact details of participants will be kept in a password-protected document until the end of the study and then deleted. Electronic copies of ICFs, which contain participants' names, will be stored in password-protected files in a restricted-access study folder on the University of Oxford network and the Institute of Cancer Research network. Transcripts, field notes and ICFs will be stored securely for 10 years following the end of the study at the University of Oxford and the Institute of Cancer Research.

12. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, relevant regulations and standard operating procedures.

13. ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki

The Lead Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

Approvals

For WorkStream 2, the Sponsor will be the Institute of Cancer Research. The Health Regulator Authority (HRA) has confirmed that the study does not need formal review by a research ethics committee, as the study will only retrospectively use routine collected clinical data in anonymous

and aggregated form. The study has received HRA approval, which is now being amended due to a change in sponsor form Imperial College to the Institute of Cancer Research.
For WorkStream 3, the Sponsor will be the University Oxford. Following Sponsor approval the protocol, informed consent forms, participant information sheets, invitation letters/emails and any advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), and host institution(s) for written approval.
The Investigators will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Other Ethical Considerations

There are no additional, specific ethical considerations.

Reporting

Lead Investigators will report regularly to the Con-Investiagtors and the Steering Committee. We shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required), host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

Participant Confidentiality

WS2 - This project utilises an established data de-identification and data sharing protocol developed by the NIHR Health Informatics Collaborative. A data specification and dictionary will be specified, defining the secure data transport mechanisms, patient cohort, data model, each data point to be collected (including standardisation and normalisation) and the steps to be taken at each site to ensure that appropriate de-identification is applied. This is signed off locally to enable legal transfer of the data (usually by the Caldicott guardian). The HIC provides support in this process via the informatics technical network of staff and a framework for data de-identification.
ICHNT have established secure infrastructure to enable data transfers (n3 256AES encryption) and secure data storage and analysis in the ICHNT NHS research data warehouse. The warehouse is fully secured and part of the ICHNT Data Security Protection Toolkit return, therefore can hold either de-identified or identifiable patient data
De-identified data will meet the expectations of the UK Information Commissioner's Office.
In the case of clinical data, this will mean that: 1. any identifiers directly related to an individual (names, NHS numbers, hospital numbers, phone numbers, personal email addresses) will not be transferred between Trusts or shared with researchers. 2. Any spatial identifiers directly related to an individual (addresses and full postcodes) will not be transferred between Trusts of shared with researchers. 3. any elements of dates (except year) directly related to an individual (date of birth, date of admission, date of treatment, date of discharge, date of death) and all ages over 89 (and all elements of dates indicative of such ages) will not be transferred between Trusts or shared with researchers.
The originating centre will maintain a detailed record of the data transferred, including the mappings from original identifiers (in particular, the NHS number) to the de-identified version of the data. This means that the data transferred is de-identified, and that access to these mappings, as well as the overall information content of the data transferred, must be carefully controlled if the data is to be 'rendered anonymous' for the purposes of the General Data Protection Regulations (GDPR).
Where geographical information is required, one of two approaches may be adopted: a) the provision of a partial postcode, for example the first two outbound digits, common to approximately 200,000 households, or b) the provision of derived information required for the specific purpose, for example the English Index of Multiple Deprivation (IMD) 2015 Where temporal information is required, then a) only the year part of each date may be supplied, or b)

every date should be shifted by a randomly-chosen period of time, with the same period applied to each date pertaining to a particular individual, and that period being stored as part of the mapping from the direct identifiers for that individual to the data transferred.

Data will be stored in the Imperial College Healthcare NHS Trust (ICHNT) Clinical Analysis, Research and Evaluation (iCARE) platform. iCARE enables routinely captured clinical information to be appropriately utilised in research, evaluation and analysis within a highly secure Trusted Research Environment (TRE). The environment is approved by the ICHNT Caldecott Guardian, ICHNT Information and Communications Technology (ICT) team and ICHNT Data Protection offices for hosting and managing ICHNT patient level data for use in direct care and research. The environment is also approved by the Sector Caldicott Guardian and Information governance group to process data for the Whole Systems Integrated Care system for the purposes of COVID-19. The secure processing environment and the secure research environment are maintained on ICHNT infrastructure and cloud based platform hosted as a data processor by UKCloud. All infrastructure form part of the Trusts Data Security and Protection Toolkit, as prescribed by NHS Digital, and overseen by the Information Governance team of ICHT. The chief custodian is the Head of ICT at ICHNT. All ICHNT staff undertake annual data protection, information security and governance training, this includes all any researchers or analysts accessing the data. ICHNT have completed data protection privacy assessments on all processing in iCARE, and these are reviewed periodically. ICHNT information systems and external suppliers are subject to regular audits and independent reviews.

WS3 - The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents (except the ICFs and the document with participant names and contact details which will be password-protected and deleted at the end of the study) and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

Expenses and Benefits

Participation will be on a voluntary basis. If participants incur costs travelling to take part in focus groups, reasonable travel expenses will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

14. FINANCE AND INSURANCE

Funding

This study is funded by the NIHR HSDR Programme (project reference NIHR129082). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Insurance

WS1, 2 & 4 – The Institure of Cancer Research maintains Public Liability and Professional Liability insurance which will operate in this respect.
WS3 The University of Oxford maintains Public Liability and Professional Liability insurance which will operate in this respect.

Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR HS&DR. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.
We will seek to report results of the study both in peer-reviewed academic publications and articles written for a lay audience, e.g. writing articles for The Conversation (www.theconversation.com). We will seek input from patient and public representatives about potential additional dissemination activities.

16. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

17. ARCHIVING

All de-identified research data and (records of) consent forms will be stored for 10 years after the end of the study. Responsible members of the University of Oxford or the Institute of Cancer Research where appropriate may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

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19. APPENDIX

Comparison of different alerting algorithms across five NHS hospital Trusts: Descriptive analysis of patient characteristics and frequency of process and clinical outcomes

A mainly descriptive project, with some modelling and statistical analysis, comparing groups of patients.
Main cohort: patients (18+) who alerted and patients who were discharged with a SoS code (ICD-10).
Time period: introduction of EHRs to March 2021.
General data description: patient information, admission & discharge information, antibiotic prescribing, microbiology tests ordered and results, ICU admission, alert details (including location of alert)
Introduction

1. Background/rationale

National guidelines for screening for sepsis have been implemented in NHS Trusts. As hospitals in England introduce electronic health records, different screening algorithms have been adopted (summarised in Table 1).

Table 1 Alert algorithms in different Trusts included in the study.

		NEWS	Red Flag	SJSA	Combination*
Trust		UCLH	CW & RB	ICHT	OUHT
Question re infection as part of EHR alert		Yes	Yes	No	Yes
Lungs	Respiratory rate	Yes	Yes	Yes	Yes
	O_2	Yes	Yes	No	Yes
CV	Heart Rate	Yes – low & high	Yes – high only	Yes – high only	Yes – low & high
	Blood Pressure	Yes – low & high (SBP)	Yes – low only (SBP)	Yes – low only (SBP)	Yes – low & high (SBP)
Temperature		Yes – low & high	Amber alert – low	Yes – low & high	Yes
Level of consciousness		Yes (VPU)	Yes (VPU)	No	Yes (VPU)
Fluid balance		No	Yes	No	No
Lactate		No	Yes	No	Yes
Bilirubin		No	No	Yes	No
Creatinine		No	No	Yes	Yes
White blood cell count		No	No	Yes	Yes
AKI		No	No	No	Yes

*OUHT use red flag sepsis and NEWS2

In this study we will compare the characteristics of patients who alert, the frequency of alerts across time (staff shifts, weeks and months) and patient outcomes. In addition, we will describe the completion of process measures associated with treatment of patients with sepsis. Process measures we have included are: blood cultures, lactate measure and IV-antibiotics. It is important to note that not all patients who alert will actually have clinically defined sepsis. Therefore, not all process measures will have been completed, particularly IV antibiotics. We will capture this variation in cohort and process measures across NHS Trusts.

In order to determine if differences between Trusts are algorithm dependent or intake/case mix dependent we will compare patient characteristics in those who 1) alert and 2) in those who had a discharge summary diagnosis of 'at risk of developing sepsis'. We will define those at risk of infection as those discharged with an ICD-10 code from the Suspicion of Sepsis list compiled by Inada-Kim et al.[1]

1.1 Objectives (these are the objectives in the NIHR Application)

a) Describe the total sample of patients who are affected by the alert and baseline outcome data
b) Describe the frequency of the alert across different Trusts, departments within Trusts and specific patient groups
c) Describe any seasonal and temporal variations in alerts across different Trusts.
d) Describe the impact of the Covid-19 pandemic on alerting in terms of total sample, frequency, patient demographics and seasonal/temporal variations.

2. Methods

2.1 Study design & Setting

This is a cross sectional study across five NHS Trusts in England. The period of study is 1st February 2019 to 31st January 2021, divided into two years starting 01/02/19 and 01/02/20 to consider the impact of Covid-19. The time period was selected based on the latest introduction of electronic health records across the five NHS Trusts and to separately consider patients with Covid-19 affecting the pattern of sepsis alerts.

2.2 Participants

All adult (18+) inpatients admitted between 01/02/19 and 31/01/21 are initially eligible for inclusion in the study. We will liaise with data managers at each NHS Trust and identify all patients who triggered a sepsis alert in each Trust. The sample of patients included in the study are adult inpatients who triggered a sepsis alert at any point in their inpatient stay or time in A&E in the 24 months of the study.
The NHS Trusts included in the study are of differing sizes and may differ in case mix. In order to compare hospitals we will use patients with a serios infection, and therefore at risk of sepsis to adjust outcomes for patients with an alert. In order to identify patients with a serious infection will use the ICD-10 codes suggested by Inada-Kim et al and classed as 'Suspicion-of-Sepsis' (SoS). Patients are identified if a patient has an SoS ICD-10 code at discharge or at death.

2.3 Variables

The main aim of this study is to describe and quantify differences in patients who alert in different NHS Trusts. The 'key exposure' is the algorithm used to define the sepsis alert in the five NHS Trusts. Variables of interest are identified in Table 2.

Table 2 Empty table to illustrate proposed data collection for Study 1. Superscript numbers refer to specific questions shown at the end of the document.

NHS Trust	**A**		**B**		**C**		**D**		**E**	
Sepsis alert algorithm	**Red Flag**	**SoS**	**NEWS2**	**SoS**	**Red Flag**	**SoS**	**Oxford's alert**	**SoS**	**SJSA**	**SoS**
Frequency										
Total Number of alerts in 12 months										
Seasonal variation in alerts										
Shift (time) of alert[1]										
Patient characteristics[2]										
%Male										
Age – median and IQR										
Ethnicity										
Comorbidities[3]/Conditions on discharge >Diabetes > Immuno-compromised										
Deprivation										
Location of alerts[4]										
%ED										
%other key wards										
Process measures[5]										
Received IV antibiotics										
Received IV antibiotics within 3 hrs of alert		NA		NA		NA		NA		NA
Blood test ordered										

Blood test ordered within 3 hrs of alert.		NA		NA		NA		NA		NA
Lactate measurement										
Lactate measurement within 3 hrs of alert		NA		NA		NA		NA		NA
Outcomes										
Length of stay for those who alert in the ED										
Admission to ICU after alert										
Mortality – 7 days										
Mortality – 30 days										
Impact on coding/formal diagnosis										
Proportion with a sepsis code at discharge/death										
Proportion with a SoS code at discharge/death		NA		NA		NA		NA		NA
Alert specific response		NA		NA		NA		NA		NA

2.4 Data sources/ measurement

All data are extracted from electronic health records and are part of routinely collected data stored within patient records. As part of the NIHR-Health Informatics Collaborative data managers at each trust shared data through a secure data-sharing platform All data was quality checked and processed by the data warehouse team at ICHT.

2.5 Bias

In order to compare the impact of different algorithms on the characteristics and patterns of alerting, the case-mix being admitted to the hospital is the key source of bias. All hospitals are in a similar region of England, but the intake of the five hospitals is different in terms of ethnicity, age and deprivation. In order to determine if the algorithm is the key factor determining differences in the profiles of the patients who alert we compared the profile with patients discharged with an ICD-10 SoS code.

2.6 Study size

Five NHS Trusts are included in this study. The number of patients included in the study is determined by the number of patients who alerted. The power to detect differences will be determined post-hoc.

2.7 Quantitative variables -

Ethnicity – ethnicity coding is based on recorded ethnicity using NHS ethnicity codes. Due to small numbers some groups will be combined into standard combinations for statistical comparisons.
Age – We will categorise age into 10-year age groups. For statistical comparisons we will combine smaller groups.
Ward of alert – The primary factor for analysis is whether alerts fired in the ED or inpatient wards. This is consistently documented across the NHS Trusts. For some Trusts we were able to determine whether alerts fired in acute wards,
IV antibiotics – Within EHRs medications are categorised as antibiotics and route of administration.
Blood tests – EHRs contain orders for microbiology tests, including the date and time.
Lactate - EHRs include lactate results. Lactate is a point of care test in all Trusts included in the study.
Length of stay - Length of stay, measured in hours, was determined from the date and time of admission and discharge recorded in the patient record. For this descriptive study we will quantify length of stay for patients who are discharged alive.
Mortality – mortality was based on discharge destination recorded in the EHR. For the purposes of this study only in-hospital mortality was available for all NHS trusts.

2.8 Missing data

Patient admissions will not be excluded if patient data is missing, an additional category of missing will be included for age, gender, ethnicity and deprivation. As part of quality checks, we will confirm whether there are any patterns in missing data, for example periods of time where no lactate were reported. Our experience of EHRs indicate that there can be periods of missing data relating to EHR downtime.

3. Statistical methods

(a) Describe all statistical methods, including those used to control for confounding

3.1 Differences in alerting over time and between patient subgroups.

We will describe the number of first alerts in each Trust in total and over different time periods.
In order to compare between Trusts we will consider the number of available overnight beds as an indication of hospital size.[2]
In addition, we will compare the alerts in the ED compared to the number of consultants in the ED.
We will use a Poisson model to determine if there are significant differences in alerts during different 'shifts' days of the week and seasons. The SoS admissions in the same period will be the offset in the Poisson model.
Differences in alert frequency in patient sub-groups will be assessed within and between NHS Trusts. We will use all patients discharged with an SoS diagnosis to adjust between hospitals as a case-mix adjustment.
We will describe differences in percentages of all patients and sub-groups of patients alerting between Trusts and assess the significances in differences using chi-squared tests. As there are many patient sub-groups and therefore multiple significance tests, we will use a p-value of 0.01 to assess significance.

3.2 Association between alerting and process measures

Process measures for inclusion are IV antibiotics, blood samples taken for microbiology and lactate measurement. We will describe process measure completion in alerting patients across Trusts, and subgroups of patients including alert location, age-groups and other sub-groups. We will consider completion of individual process measures and completion of all three within three-hours.
We will model process measure completion using a logistic regression adjusted for confounding factors, primarily patient characteristics which have been identified by clinicians as clinically associated with non-completion of process measures.
We will determine the association between the alert and completion of individual process measures, completion of the three measures, and whether the associations are different for different patient sub-groups.
We will model each Trust separately and also model all patients in a multi-level model with clustering at Trust level. We will determine the sensitivity of results to the modelling approach.

Association between alerting and patient outcomes

We will assess the association between alerting and patient outcomes using a competing risks survival analysis with discharge and death as competing risks. This will allow us to fully adjust for patient factors and consider both patients who survive to discharge and those who do not. We will include process measure completion as time varying covariates.
In addition, we will separately model ICU admission after alerting using both a survival analysis and logistic model.

Association between alerting and coding

We will describe the coding of alerting patients between Trusts. The Trust which does not have a sepsis specific alert will be excluded. We determine if the differences are significant using chi-squared test.
We will use descriptive approaches to compare sepsis coding between Trusts in patients with a SoS code. We will also consider whether the patterns are the same across the main patient subgroups. Statistical significance will be assessed using chi-squared tests.

(*b*) Methods used to examine subgroups and interactions

Within each model we will separately consider subgroups when we perform our analysis. We will consider a priori interactions.

(*c*) Missing data

Missing data will be included as a category on its own for factors such as ethnicity and deprivation. We will inspect data to identify periods of missing data which may be a result of EHR downtime, if necessary we will consider imputation.
We will ensure from clinicians that all process outcomes are likely to be recorded in the EHR and policy for carrying out the processes are the same across all Trusts.

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Quantifying the impact of a digital sepsis alert on key patient outcomes and process measures.

We will use interrupted time series with a control to determine the impact of the introduction of alerts on patient outcomes and process measures
Main cohort: patients (18+) with an SoS ICD-10 code (intervention group) at discharge OR a falls ICD-10 code (control group).
Time period: April 2010 to March 2021
General data description: patient information, admission & discharge information, A&E information and ICU admission if possible

1.Introduction

1.1 Background/rationale

To improve care for patients with sepsis, comply with national financial incentive programmes, and make best use of the introduction of electronic health records hospitals in England have introduced digital sepsis alerts. A variety of algorithms have been used, with different workflows and with different implementation strategies.
A variety of studies have demonstrated that digital sepsis alerts, and more general deteriorating early warning scores such as NEWS2, have high predictive power for mortality.[1] A small number of studies have shown that introducing digital alerts to identify patients at risk of deterioration have had an impact on patient outcomes.[2-3]
Although randomised control trials are considered the gold standard for evidence, digital alerts have generally been introduced across hospitals without randomisation or phased across the hospital. In ICHT sepsis alerts were introduced in a phased approach and we used a propensity score based causal inference method (inverse probability of treatment weighting), common in the analysis of natural experiments, to emulate as much as possible a RCT using real world healthcare data. In ICHT the introduction of digital sepsis alerts was associated with a 23% lower risk of death within 30 days.[4]

In this study we aim to analyse the impact of the introduction digital alerts across five NHS Trusts. With the exception of ICHT the introduction of alerts was part of the introduction of electronic health records (EHR). This presents challenges, for example:

- Data availability prior to the introduction of EHRs is limited to data routinely collected for administrative purposes. This includes admission, discharge and formal diagnosis information, but excludes detailed microbiology information and detailed patient treatment information such as the administration of antibiotics.
- The impact of the alerts on patient outcomes will be confounded by the introduction of EHRs, a major change in the hospital system.

Although we would expect digital sepsis alerts to have the main impact on patients with sepsis, and this is the stated aim of many commercial sepsis alerts, administrative data may not be sufficient to identify patients with sepsis, particularly as national guidance on sepsis coding changed in 2014, effectively increasing the number of patients with an official diagnosis of sepsis.[5] In addition, efficient clinical response to digital sepsis alerts may result in a decrease in disease progression to sepsis. We have therefore decided to focus on outcomes of patients with an ICD-10 Suspicion of Sepsis code.[6]
We will use interrupted time series with a control to determine the impact of the introduction of alerts on patient outcomes and process measures. Interrupted time series is an important methodology which allows

before and after comparisons whilst taking trends prior to the intervention into account and is considered a robust methodology for analysing natural experiments. However, confounding due to other 'interventions' occurring at the same time as the intervention of interest can confound interpretation. A control is an appropriate method to take this type of confounding into account.[7]
For the control we have selected patients with an ICD-10 code included in the category gastrointestinal bleeding. This is a suitable control as we would not expect these patients to trigger a sepsis alert and outcomes should not be impacted by patients being identified as having sepsis. The ICD-10 codes included in this indicator are shown in Table 1.

Objective - Quantify the impact of a digital alert on the key patient outcomes and process outcomes

Primary outcome: in-hospital mortality within 30 days
Secondary outcome: length of stay
ICU admission

2.Methods
2.1Study design
Setting - Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
This is a time series analysis across five NHS Trusts in England and one NHS Trust in Wales. The period of study is 1st April 2010 to 31st March 2021.
2.2 Participants - the eligibility criteria, and the sources and methods of selection of participants
All adult (18+) inpatients admitted as emergency patients between 01/04/10 and 31/03/2 are initially eligible for inclusion in the study.
Intervention group: patients with a discharge diagnosis including one of the SoS sepsis codes at any place in the diagnosis.
Control group: patients with a discharge diagnosis which is use by the NHS to identify patients with a 'Fall' code.
2.3 Variables - Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Primary outcome: in-hospital mortality within 30 days of admission
Secondary:

- In-hospital mortality within 7 days of admission
- Length of stay
- ICU admission

Intervention: Introduction of digital alerts or changes in screening programmes
Potential confounders:

- Age
- Sex
- Comorbidities which increase the risk of poor patient outcomes
- Ethnicity
- Season

Sub-group analysis
Age-groups
Patients who are immune-compromised
2.4 Data sources/ measurement - For each variable of interest, give sources of data and details of methods of assessment (measurement).
Data are routinely collected data to comply with NHS requirements for Secondary Users Service. Data is quality checked by individual Trust before it is submitted to the NHS, and is compiled into Hospital Episode Statistics which have been widely used for research in the UK.
As part of the NIHR-Health Informatics Collaborative data managers at each trust shared data through a secure data platform. All data was quality checked and processed by the data warehouse team at ICHT.

Bias – Describe any efforts to address potential sources of bias
We are using a control intervention group to address the main source of bias – that is that for four of the six Trusts alerts were introduced at the same time as digital alerts.
Study size
Six NHS Trusts were recruited to take part in the study. The number of patients included in the study is determined by the number of patients who were discharged with an SoS ICD-10 code. The power to detect differences will be determined post-hoc.
Quantitative variables - Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Ethnicity – ethnicity coding is based on recorded ethnicity using NHS ethnicity codes. Due to small groups of some ethnic groups we will combine into standard combinations for statistical comparisons. Full details of ethnic groups are included in the supplementary materials.
Age – We broke age into 10-year age groups. For statistical comparisons we combined smaller groups. Full details are included in the supplementary materials.
Length of stay - length of stay, measured in hours, was determined from the date and time of admission and discharge recorded in the patient record. For this descriptive study we will quantify length of stay for patients who are discharged alive.
Mortality – mortality was based on discharge destination recorded. For the purposes of this study only in-hospital mortality was available for all NHS trusts.
Missing data
Patient admissions will not be excluded if patient data is missing, an additional category of missing will be included for age, gender, ethnicity and deprivation. As part of quality checks we will confirm whether there are any patterns in missing data.
Statistical methods
***(a)* Describe all statistical methods, including those used to control for confounding**
Descriptive analysis
We will describe trends in patient mix over time using graphical methods, we will use time series to determine if there were changes in patient mix, including sub-groups of patients, patients with SoS and falls patients.
We will use break point approaches to identify potential key points in time where changes occurred. This will aid in interpretation of results.
Comparative analysis
We will use interrupted time series with a control, adjusted for patient case mix and season. Each Trust will be modelled separately as the introduction of sepsis alerts and electronic health records is different for each Trust. Comparisons will be made between the change in slope and step change in counts.
(*b*) Describe any methods which will be used to examine subgroups and interactions
Within each model we will separately consider subgroups when we perform our analysis. We will consider a priori interactions.
(*c*) Explain how missing data will addressed
Missing data will be included as a category on its own for factors such as ethnicity and deprivation. We will inspect data to identify periods of missing data, and consider imputation.

ICD-10 Code	ICD-10 Description
I850	Oesophageal varices with bleeding
K226	Gastro-oesophageal laceration - haemorrhage syndrome K228 Other specified diseases of oesophagus
K250	Gastric ulcer, acute with haemorrhage
K252	Gastric ulcer, acute with both haemorrhage and perforation
K254	Gastric ulcer, chronic or unspecified with haemorrhage K256 Chronic or unspecified Gastric ulcer with both haemorrage and perforation
K260	K260 Duodenal ulcer, acute with haemorrhage
K262	K262 Duodenal ulcer, acute with both haemorrhage and perforation

K264	K264 Duodenal ulcer, chronic or unspecified with haemorrhage K266 Chronic or unspecified Duodenal ulcer with both haemorrage and perforation
K270	K270 Peptic ulcer, acute with haemorrhage
K272	Peptic ulcer, acute with both haemorrhage and perforation
K274	Peptic ulcer, chronic or unspecified with haemorrhage
K276	Chronic or unspecified peptic ulcer with both haemorrhage and perforation
K280	Gastrojejunal ulcer, acute with haemorrhage
K282	Gastrojejunal ulcer, acute with both haemorrhage and perforation
K284	Gastrojejunal ulcer, chronic or unspecified with haemorrhage
K286	Chronic or unspecified Gastrojejunal ulcer with both haemorrhage and perforation
K290	Acute haemorrhagic gastritis
K920	Haematemesis
K921	Melaena
K922	Gastrointestinal haemorrhage, unspecified

Table 1: ICD-10 codes for gastrointestinal bleeding [8]

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