THE IMPACT OF ELECTRONIC HEALTH RECORDS ON HEALTHCARE QUALITY

by

SUZY GALLIER

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Supervisors

Professor Elizabeth Sapey

Professor Krish Nirantharakumar

Institute of Inflammation and Ageing

College of Medical and Dental Sciences

University of Birmingham

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ABSTRACT

Background

The NHS is investing significantly in digital transformation, particularly in electronic health records (EHRs), which have rapidly advanced over the past decade. While EHRs are crucial for modernisation, achieving full digital maturity requires substantial investment in teams and approaches to ensure safe and effective use. EHRs have the potential to revolutionise healthcare, yet evidence demonstrating their effectiveness is limited, necessitating rigorous research. Health data can transform healthcare through disease understanding, clinical decision support, service redesign modelling, and policy development, requiring diverse data types. Varying digital maturity across UK health organisations necessitates support for innovation and AI implementation to prevent exacerbating health inequalities.

Methods

The overall methods were the use of real-world health data from the PIONEER Hub for Acute Care to undertake retrospective cohort studies to examine the impact of EHRs on differing aspects of healthcare quality. Synthetically generated EHR and pollution data were generated to enable the implementation and testing of federated analytics.

Results

The retrospective cohort studies presented demonstrate several key findings regarding the impact of EHRs on healthcare. EHRs significantly enhance

healthcare quality by streamlining processes, improving accuracy, and supporting evidence-based decision-making. Utilisation of EHR data improves patient outcomes by reducing unnecessary treatments and procedures. The implementation of systems like Computerised Physician Order Entry (CPOE) leads to sustained efficiency improvements in laboratory and clinical processes. Real-World Data (RWD) effectively supports healthcare pathways and policy decisions, though rigorous modelling and testing are necessary to ensure cost-effectiveness. Advancements in data techniques, especially federated analytics, offer innovative solutions to navigating the complexities of health data. These findings underscore the transformative potential of EHRs in healthcare. However, organisations need to ensure consideration is given to the limitations of RWD in respect of quality and cover. Furthermore, with the pace of innovation, especially around AI ensuring that people and organisations with less access to digital tools are not disadvantaged is crucial. Technology should be an enabler to reduce health inequalities, not a reason the divide increases.

Conclusion

In conclusion, EHR data has demonstrated significant potential to enhance healthcare quality. Implementing an EHR can be disruptive to a health care system, but the evidence suggests that staff and patients will benefit in the long-term. The impact has been observed in improved prescribing, efficient pathways and greater accuracy.

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THESIS FORMAT

This thesis is formatted in accordance with the University of Birmingham alternative format thesis guidelines; Regulation 7.4.1 (g)

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Manuscripts that have been published (Chapters 2, 3, 5 & 6) or that are under submission (Chapters 4,7, & 8) have been inserted directly into the thesis. These are stand-alone manuscripts, so there will be duplication across chapters. Chapters 1 and 9 set the context for this thesis and provided further in-depth contextual information surrounding the publications. A copy of each publication has been included in the Appendices, these are not included in the pagination sequence. A page has been inserted before each manuscript, as per the guidance to provide details about the publication such as title and author contributions.

As per the alternate thesis guidelines, the pages of publications will not be included in the pagination sequence of the submitted thesis.

Main Thesis

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LIST OF ABBREVIATIONS

A&E/ ED	Accident and Emergency or Emergency Department
AAT	Age-adjusted threshold (D-dimer)
ABPI	Association of the British Pharmaceutical Industry
AF	Atrial Fibrillation
AHS	Automated Health Scoring
AI	Artificial Intelligence
AIaMD	Artificial Intelligence as a Medical Device
AMU	Acute Medical Unit
ANOVA	Analysis of variance
APACHE	Acute Physiology and Chronic Health Evaluation
API	Application Programme Interface
ART	Article
AUROC	Area under the receiver operating characteristic curve
Bd	Twice daily
BMI	Body mass index
BORD	Birmingham Out of Hours GP Research Data base
CAG	Confidentiality Advisory Group
CDM	Common Data Model
CDS	Clinical decision support
CDSS	Clinical decision support system
CEDA	Centre for Environmental Data Analysis
CI	Chief Investigator
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disorder
CPOE	Computerised Provide Order Entry systems
CQUIN	Commissioning for Quality and Innovation
CT-GAN	Conditional Transformation Generative Adversarial Network
CTPA	Computed tomography pulmonary angiography
CVW	COVID Virtual Ward
DB	Database
DDU	D-dimer units
DHSC	Department of Health and Social Care
DRF	Data Request Form
DTB	Data Trust Board
DTC	Data Trust Committee
DVT	Deep vein thrombosis
ED	Emergency Department (see also A&E)
EHS	Electronic Health Systems
EHR	Electronic Health Records
EMA	European Medicines Agency
EMR	Electronic Medical Record
EPR	Electronic Prescribing Record
EPS	Electronic Prescribing System
FDA	US Food and Drug Administration
FHIR	Fast Healthcare Interoperability Resources
GDPR	General Data Protection Regulation
GLMs	General Linear Models
GP	General Practitioner
HAT	Hospital Acquired Thrombosis
HDRH	Health Data Research Hub
HDR-UK	Health Data Research UK
HDU	High Dependency Unit
HES	Hospital Episode Statistics
HL7	Health Level Seven
HSD	Honesty significance difference

HTA	Health Technology Assessment
ICU	Intensive Care Unit
IMD	Index of Multiple Deprivation
IQR	Interquartile range
ISO	International Organization for Standardization
ITS	Interrupted time series
ITU	Intensive Care Unit
LMWH	low molecular weight heparin
LSOA	Lower layer Super Output Area
LTAT	Laboratory turnaround time
ML	Machine Learning
MHRA	Medicines and Healthcare products Regulatory Agency
MPI	Master Patient Index
NDOO	National Data Opt-Out
NEWS2	National Early Warning Score 2
NHS	National Health Service
NHSE	National Health Service England
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIV	Non-invasive ventilation
NLP	National Language Processing
NPV	Negative predictive value
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
OMOP	Observational Medical Outcomes Partnership
PAS	Patient Administration System
PE	Pulmonary embolism
PICs	Birmingham Systems Prescribing Information and Communications System
PM2.5	Particular Matter 2.5 particle count
PM10	Particular matter 10 particle count
PPI/E	Patient and Public Involvement and Engagement
PPV	Positive predictive value
QA	Quality Assurance
QC	Quality Control
QEH	Queen Elizabeth Hospital
QEHB	Queen Elizabeth Hospital Birmingham
R2R	Reason to Reside
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
RIS	Radiology Information System
RWD	Real World Data
RWE	Real World Evidence
SAIL	Secure Anonymised Information Linkage Databank
SAMBA	Society Acute Medicine Benchmarking audit
SaMD	Software as a Medical Device
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SDCS	Strategic Data Collection Service
SDE	Secure Data Environment
SDV	Synthetic Data Vault
SEWS	Standardised early warning score system
SLA	Service Level Agreement
SNCT	Safer Nursing Care Tool
SNOMED	Systematized Nomenclature of Medicine
SNOMED-CT	Systematized Nomenclature of Medicine Clinical Terms
SSq	Sum of Squared Deviations
ST	Standard Threshold (D-dimer)
Tds	Three times a day
TNR	True negative rate

TPR	True positive rate
TREs	Trusted Research Environments
UHB	University Hospitals Birmingham NHS Foundation Trust
UK	United Kingdom
USS	Ultrasound scans
VTE	Venous Thromboembolism
VQ	Ventilation-perfusion scan
WGLL	What Good Looks Like
WHO	World Health Organisation
WM	West Midlands
WMAS	West Midlands Ambulance Service

List of achievements throughout PhD studies

Grants awarded as Co-Applicant

- HDR-UK Health Data Hub in acute care. Deputy Director/Technical Director. (2019 – 2022). £1.2M
- UKRI PIONEER Platform extension funding. (2020 – 2021) £615,000 – Infrastructure expansion: real-time information and support services including multiple AI projects on multi-modal data.
- EPSRC: DECOVID. Technical and Data workstream lead (2020 -2021) £1.5M -
- UK-RI Risk prediction models in COVID-19 Co-A (2020 – 2020) £150,000 - To develop and externally validate novel prognostic models for adverse outcomes (death and intensive therapy unit (ITU) admission) in UK secondary care and externally validate the existing 4C score.
- MRC: ADMISSION – Co-morbidity clusters in acutely admitted patients. Co-A (2021 – 2024). £3.4M - ADMISSION is an interdisciplinary UK Research Collaborative that will transform our understanding of the burden, causes, treatment and prevention of multiple long-term conditions in hospitalised patients.
- NIHR AI Multi-multi-morbidity (OPTIMAL – predicting outcomes in secondary care) (2021 – 2023) £3.3M - OPTIMising therapies, discovering therapeutic targets and AI assisted clinical management for patients Living with complex multimorbidity (OPTIMAL study)
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- HDR-UK PIONEER expansion funds (2021 – 2022) £300,000 – funding to expand the acute care database service offerings.
- MRC Health Data award (2021 – 2022) £600,000 funding to provide advanced infrastructure to further advance data science and common data models for AI and advanced statistical modelling.
- UKRI DARE Sprint. Building a federated TRE system. Co-A. (2022-2022) £349,999 - DARE: Creating the blueprint for a federated network of next generation, cross-council Trusted Research Environments.
- Patient Safety Research Collaboration. Digital decision support tools in acute care. £1.6M 2023 – 2028 - The PSRC will bring together NHS trusts, universities, and private business to evaluate how digital tools can support clinical decision making and reduce risks of harm for expectant mums and anyone in need of emergency treatment.

Poster Award

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Publications related to this thesis

1. **Gallier S**, Price G, Pandya H, McCarmack G, James C, Ruane B, Forty L, Crosby BL, Atkin C, Evans R, Dunn KW, Marston E, Crawford C, Levermore M, Modhwadia S, Attwood J, Perks S, Doal R, Gkoutos G, Dormer R, Rosser A, Fanning H, Sapey E. Infrastructure and operating processes of PIONEER, the HDR-UK Data Hub in Acute Care and the workings of the Data Trust Committee: a protocol paper. BMJ Health Care Inform. 2021 Apr;28(1):e100294. doi: 10.1136/bmjhci-2020-100294. PMID: 33849921; PMCID: PMC8051388.
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3. Sapey E, **Gallier S**, Mainey C, Nightingale P, McNulty D, Crothers H, Evison F, Reeves K, Pagano D, Denniston AK, Nirantharakumar K, Diggle P, Ball S; All clinicians and students at University Hospitals Birmingham NHS Foundation Trust. Ethnicity and risk of death in patients hospitalised for COVID-19 infection in the UK: an observational cohort study in an urban catchment area. BMJ Open Respir Res. 2020 Sep;7(1):e000644. doi: 10.1136/bmjresp-2020-000644. PMID: 32873607; PMCID: PMC7467523.
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Manuscripts under review from the thesis

1. **S. Gallier**, X. Zou, F. Evison, J. Hodson, J. Atia, C Webster, M. Garrick, J. Coleman, T. Pankhurst, S. Ball, K. Nirantharakumar, E. Sapey. The Impact of Electronic Order Communications on Laboratory Turnaround Times in Acute Hospital Care. medRxiv 2024.01.06.24300924; doi: https://doi.org/10.1101/2024.01.06.24300924
2. S. Gallier, F. Evison, J. Hodson, R. Khosla, T. Ranasinghe, L. Rickard, C. Atkin, V. Reddy-Kolanu, K. Nirantharakumar, W. Lester, B. Holloway, E. Sapey. The safety and efficacy of using age-adjusted D-dimers in hospitalised patients in a diverse urban centre: a real-world data study. medRxiv 2024.06.02.24308329; doi: https://doi.org/10.1101/2024.06.02.24308329
3. **S. Gallier**, A. Topham, J. Hodson, D. McNulty, T. Giles, S. Cox, J. Chaganty, L. Cooper, S. Perks, P. Quinlan, E. Sapey. Testing federated analytics across secure data environments using differing statistical approaches on cross-disciplinary data. medRxiv 2024.01.06.23300659; doi: https://doi.org/10.1101/2024.01.06.23300659

Chapter 1: Introduction

1.1 Background

The unprecedented transition from paper medical reports to Electronic Health Records (EHR) is transforming healthcare and has the potential to revolutionise future medicine.[1] The rationale for implementing EHR systems in healthcare systems is improved quality, efficiency and safety, though the evidence to support this is limited. The data generated and stored within EHR has emerged as a critical asset for research into healthcare practices, offering healthcare workers, service providers, researchers and policymakers significant opportunities to derive insights.

1.2 Transition to Digital Healthcare – the evolution of the medical record

The establishment of medical records can be traced back over 4000 years. In ancient times, medical observations were documented on papyrus and stone, serving as the earliest instances of noting relating to health.[2] By the 5th century BC, figures like Hippocrates were making notes that resembled modern medical records.[3] These records were rudimentary, focusing primarily on case histories and treatments.[4] During medieval times, doctors continued this practice, often documenting case studies and treatment outcomes.[5]

Figure 1.1: Example of an electronic health record data entry screen

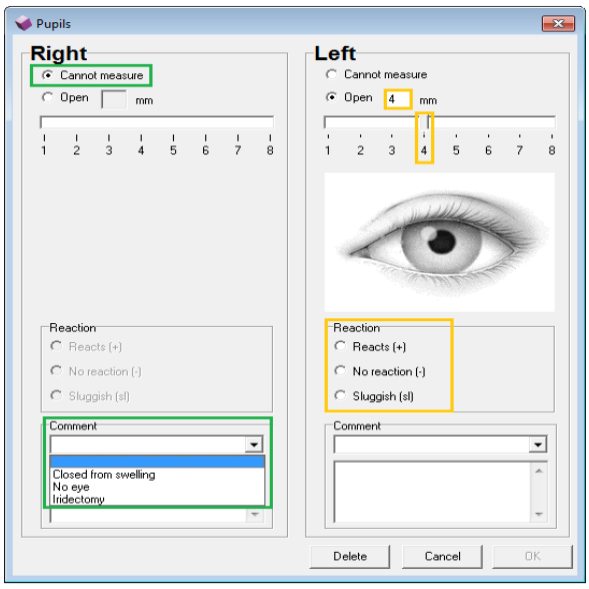
The formal advent of medical records began in the 19th century within major European teaching hospitals.[2]

This period marked a shift towards more systematic real-time record keeping from retrospective note-taking.[6] In this period, the records became more detailed, with healthcare workers capturing detailed patient histories, treatments, and outcomes for improving patient care and clinical research.[7] The format and content of medical records became more standardised, allowing for easier sharing and comparison of medical information across practitioners and institutions.[2, 8] However, the effectiveness of these records was constrained as the handwriting was often illegible.[3, 9]

The 20th century signalled a significant transformation in how medical records were maintained. The introduction of standardised formats meant records were more organised and accessible. Detailed clinical data about each patient was recorded, including personal information, medical history, treatment plans, and outcomes (**Figure 1.1**). This period saw the initial stages of digitisation of medical records, aimed at improving accessibility and accuracy. However, reports indicated that the initial predicted potential were not being realised.[10]

The advent of digital technology has revolutionised medical records. **Figure 1.2** illustrates how the EHR assists with data entry. Clinicians can select from

Figure 1.2: Example of an electronic health record data entry screen for dilation of pupils



dropdown boxes and sliders to accurately represent their assessment, in the example to capture the dilation of a patient's pupils. Another advantage of these systems is the facilitation of data sharing between healthcare providers, leading to improved coordination and quality of care. Despite these reported benefits, the transition presented challenges, including concerns over privacy, security, and the need for standardisation.[10]

1.3 Understanding Electronic Health Records

An EHR is a digital system used to manage and store clinical and administrative data collected during the delivery of healthcare[11, 12]. This record contains health information of patients over time with a healthcare provider, and even today, it is often still a hybrid collection of structured digital data and scanned paper records.[13, 14] Within most healthcare systems there is no single, unified EHR for each patient, and instead patients will have numerous electronic health and paper records with each provider they have been treated by, such as their General Practitioner (GP), mental health providers, community care settings and hospitals (acute and specialist).

EHRs provide a broad longitudinal view of a patient's care. They contain various data, including diagnoses, demographics, medical history, medication, allergies, laboratory test results, radiology images, vital signs, and personal statistics such as age and weight.[15] The prime function of an EHR is to improve the communication and management of a patient's health data.[16] The secondary use

of these data for research and improving health services is increasing; the challenges and opportunities associated with this are explored below. The implementation and use of EHRs raise important considerations around data security, privacy, interoperability, and the standardisation of health information technology.

In the academic context, EHRs are often discussed regarding their implications for healthcare delivery, data management, patient outcomes, and policy implications. Moreover, their role in supporting evidence-based practice, enhancing patient engagement, and facilitating healthcare research through data analytics is a significant area of ongoing study and debate.

1.4 The Promise of Electronic Health Records – Projected savings and financial benefits

The anticipated financial benefits of EHRs are a pivotal consideration in the broader discussion around healthcare digitisation. Advocates of EHRs have long argued that they hold the potential to yield considerable cost savings.[17] These cost savings are hypothesised to arise from enhanced efficiencies in healthcare delivery, such as improved accuracy for financial reimbursement, reduced paperwork, and the elimination of duplicate tests.[18]

The literature assessing the economic impact of EHR implementation provides a complex and sometimes ambiguous picture. While some studies have identified a positive correlation between EHR adoption and operational cost savings, these

findings are not universally corroborated.[19] A systematic review of 27 studies assessing the economic impact of clinical decision support (CDS) interventions based on EHRs published in 2020 suggested that although some studies lacked cost-outcome metrics, the findings are highly promising[20] with 22 of the studies demonstrated a reduction in healthcare expenditure following EHR implementation. It is believed that the variability in financial returns is influenced by multiple factors, including the scale of EHR implementation, the adaptability of the healthcare workforce, the initial costs of EHR systems, and the ongoing maintenance expenses.

Assessing the financial benefits of EHRs systems is complex due to the need to consider the long-term horizon over which savings might materialise. While the initial outlay for EHR systems can be substantial, often costing hundreds of millions of pounds, the expectation is that efficiencies gained through their use will offset these costs over time. For example, a recent deal reported by Digital Health News involved Epic, a leading Electronic Prescribing Record (EPR) solution provider, and Manchester University National Health Service (NHS) Foundation Trust. The contract, signed in December 2019, was valued at £181 million.[21] These investments are expected to yield indirect savings from improved patient health outcomes, leading to reduced hospital readmission rates and lower long-term healthcare expenditures.[22]

The overarching aim for implementing an EHR is patient safety, however with the significant investment required organisations are looking to achieve financial efficiencies. The growing body of evidence suggests that realising financial benefits is not just contingent on the technology. Healthcare organisations need to focus on factors such as change management and user training to maximise the potential benefits of their EHR. One crucial aspect is to ensure that EHRs are integrated into existing clinical workflows.

While the literature presents a nuanced view of the financial benefits associated with EHRs, it underscores the potential for cost savings as an incentive for their continued adoption and integration within healthcare systems. Further empirical research is essential to explore the direct and indirect financial implications of EHRs and to inform policy and investment decisions in this critical aspect of healthcare infrastructure.[23]

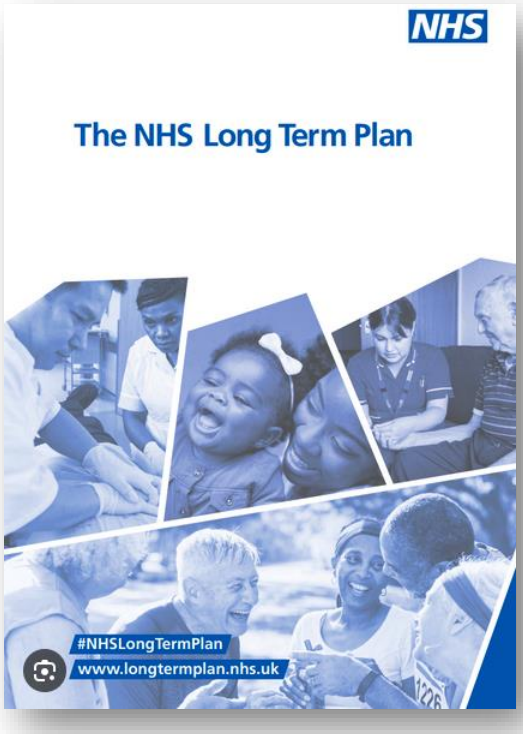
1.5 The NHS Digital Horizon – Long-term plan for Digital Transformation

The National Health Service (NHS) in the United Kingdom (UK) has embarked on an ambitious trajectory toward digital transformation. The NHS Long Term plan outlines a comprehensive strategy for integrating digital technology across the healthcare system[24] (**Figure 1.3**). The NHS has written this plan to ensure it has a service fit for the future. The scope of the plan reflects concerns around funding, staffing, increasing inequalities. Furthermore, there is acknowledgement of the pressures on the service from a growing and ageing population. For the purpose of

this thesis, the focus will only be on Chapter 5 of the NHS Long Term Plan entitled "Digitally-enabled care will go mainstream across the NHS".

Chapter Five of the plan lays out the wide-ranging ten-year funded programme to update technology and digital solutions. The chapter identifies key milestones and defines the costed building blocks to achieve this. The core high level themes of Chapter Five range from empowering people, supporting healthcare professionals and clinical care, improving population health, clinical efficiency and safety.

Figure 1.3: Image of The NHS Long Term Plan report



The plan offers practical priorities that will drive digital solutions to streamline operational efficiency, enhance patient outcomes, and empower healthcare professionals through advanced tools and resources.

Central to the NHS vision is the digitisation of patient interactions with the health service, facilitating more personalised and accessible care. The Long-Term Plan commits to the widespread adoption of EHRs, ensuring that healthcare professionals can access and update patient records across different services seamlessly. This digital integration aims to foster a more collaborative

approach to patient care, breaking down traditional silos between primary, secondary, and tertiary services.

Moreover, a key priority is to leverage data analytics and artificial intelligence (AI) to predict patient admissions and personalise health care interventions, improving resource allocation and preventative care strategies. AI and decision support is promoted as a practical solution to assist clinicians to apply best practice. It is hoped that these tools will eliminate unwarranted variation across all pathways. The horizon also extends the use of these tools to patient self-management, with the introduction of mobile health applications and online platforms that allow patients to take a more active role in managing their health conditions.

The digital agenda also encompasses the advancement of telemedicine, which promises to increase the accessibility of care, particularly for patients in remote or underserved regions. Through video consultations and remote monitoring systems, patients can receive timely medical advice and interventions, reducing the need for in-person visits and alleviating the pressure on healthcare facilities.

However, the Long-Term Plan also acknowledges the challenges that accompany such a widespread digital transformation. These include safeguarding patient data privacy, overcoming the digital divide to ensure equitable access to technology, and addressing the workforce's training needs to adapt to new digital systems and tools. The plan acknowledges the fact that the NHS is made up of hundreds of separate organisations suggesting data interoperability as an opportunity to free

up time and resources. Furthermore, there is increased support through data interoperability for patients with long-term conditions with connected home technologies and access to health records.

In summary, the NHS's Long-Term Plan represents a strategic pivot towards a digitally-enabled healthcare system, with the dual aims of improving healthcare delivery efficiency and enhancing patient care quality. A particular aspect of relevance to this thesis is the focus on improving population health through the use of de-personalised health record data. The plan sets out a commitment to the development of Application Programme Interfaces (APIs) (explained in **Section 1.12** below) to expedite innovation through integration with other digital products. Furthermore, there is a section on 'Improving clinical efficient and safety', that states pathology networks will mean quicker turnaround times for test, as explored in **Chapter 4**. The successful implementation of the Long term plan will require a concerted effort across the entire healthcare ecosystem, underpinned by robust policy frameworks, continuous stakeholder engagement, and an resolute commitment to innovation.

1.6 Evidence on Electronic Health Records – Assessing the impact on Healthcare Outcomes

Implementing EHRs is hypothesised to substantially enhance outcomes by streamlining care coordination, improving the accessibility and quality of patient data, and facilitating the implementation of evidence-based practices. The underlying premise is that EHRs can reduce medical errors and foster a more

efficient and effective healthcare system. Despite these recognised benefits it is suggested that the full potential of EHRs is yet to be realised.[25]

The empirical evidence regarding the impact of EHRs on health outcomes is a subject of ongoing debate within the academic and medical communities.[26-28] Several studies have suggested that EHRs are associated with improved outcomes in various healthcare domains, such as chronic disease management, preventive care, and medication safety.[29, 30] These studies often highlight the potential of EHRs to provide clinicians with comprehensive patient information, enabling better-informed clinical decisions and more coordinated care.[31]

Conversely, a considerable volume of research presents a more critical view of the effectiveness of EHRs.[32-34] Some studies have revealed minimal or no significant improvements in health outcomes and suggest that implementing EHRs may introduce new complexities into clinical practice[35, 36]. Such complexities can stem from issues like workflow disruption, data overload, and user interface design problems, which can impede the potential benefits of EHRs.[37] A systematic review examining how EHR interoperability affects patient safety assessed 12 studies and reported that whilst EHR positively impacted on medication safety and reduced safety events, the benefits on quality and safety of care remained unclear.[38]

The variation in the reported effects of EHRs on health outcomes can be attributed to the diversity of EHR systems, differences in the extent and manner of their implementation, the varied clinical settings in which they are deployed, and

methodological differences across studies.[39] For instance, the degree to which EHRs are integrated into clinical workflows and the level of clinician engagement with these systems can significantly influence their impact on patient care.

Furthermore, EHRs have features designed to reduce medical errors, such as decision support algorithms and electronic medication prescribing. However, the effectiveness of these tools rely heavily on their appropriate integration into the healthcare delivery process. Issues like alert fatigue, where the high volume of automated warnings leads to desensitisation among clinicians, can offset the potential error-reducing benefits of EHRs.[40-43] **Section 1.9** provides more detailed evidence around alert fatigue.

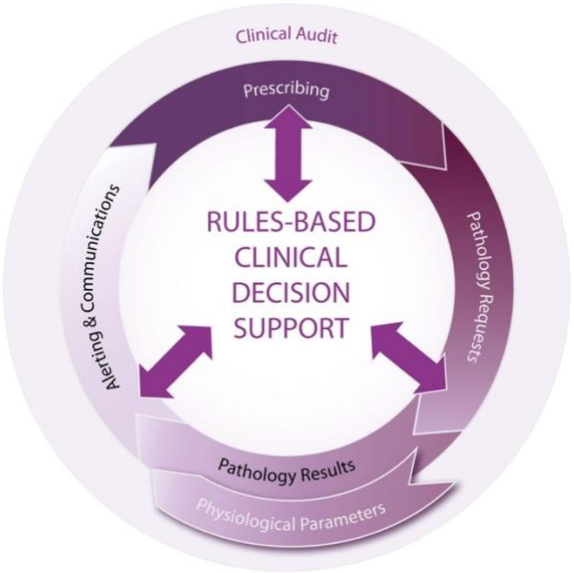
The belief in EHRs as a catalyst for improved health outcomes remains widely held and intensely contested. The body of literature reflects this dichotomy, underscoring the need for continued research. This research should focus on identifying the circumstances under which EHRs most effectively contribute to positive health outcomes, as well as how their design and implementation can be optimised to reach their full potential in enhancing patient care.

1.7 Guideline Compliance – Integrating Monitoring tools into Electronic Health Records

The integration of clinical decision support systems (CDSSs) into EHRs represents a significant advancement in healthcare, offering the potential to enhance clinical safety by enhancing medical decisions with targeted clinical information[44]. There

are numerous reported benefits to the adoption of CDSSs, such as improving efficiency, reduction of medication errors, reducing laboratory ordered tests and misdiagnosis.[45] By automating aspects of the decision-making process, they aim to reduce human error and optimise the use of medical resources. University Hospitals Birmingham NHS Foundation Trust (UHB) developed an EHR called the Birmingham Systems Prescribing Information and communications system (PICS) in 1999. PICS has been continuously developed with input from senior clinicians to include numerous rules-based clinical decision support tools. **Figure 1.4** provides a graphical illustration of how these tools interact providing alerts and communications in relation to prescribing linked to pathology results and physiological parameters.

Figure 1.4. Image from Birmingham Systems Prescribing Information and communication system illustrating features of rules-based clinical decision making



However, this integration comes with challenges. Ensuring clinical safety is paramount, as introducing software systems into healthcare environments must be rigorously evaluated to understand if medical device regulations are required[46]. Additionally, the design and implementation of these tools must be critically assessed to prevent the introduction of bias or health disparities, ensuring equitable care across diverse patient populations.

Navigating the regulatory landscape is equally important, as compliance with medical device regulations ensures patient safety and efficacy of medical interventions. As healthcare technology rapidly advances, these regulations must adapt accordingly to maintain stringent safety standards. **Section 1.8** provides an explanation on Medical Device categories and classification.

The literature on the effectiveness of these tools within EHRs is mixed, indicating that while some studies report improvements in outcomes and adherence to guidelines, others suggest limited impact. Furthermore, there are studies that detail several disadvantages to CDSSs such as the cost to implement and support, alongside a threat to clinical autonomy, alert fatigue and an increase in referrals.[44, 45] The variability in outcomes highlights the need for further research to understand the conditions that influence the effectiveness of integrated monitoring tools.

While the potential benefits of integrating monitoring tools into EHRs are clear, realising these benefits requires careful consideration of the associated risks, regulatory requirements, and ethical implications. The complexity of these issues and the mixed evidence of their impact on healthcare outcomes underscore the need for ongoing evaluation and refinement of these technological integrations.

1.8 Medical Devices – overview of categories and classification

The formal definition of a medical device by the World Health Organisation (WHO) is “any instrument, apparatus, implement, machine, appliance, implant, reagent

for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used alone, or in combination, for human beings, for one or more specific medical purpose(s)....and does not achieve its primary intended action by pharmacological, immunological, or metabolic means, but which may be assisted in its intended function by such means".[47] **Figure 1.5** provides examples of different medical devices.

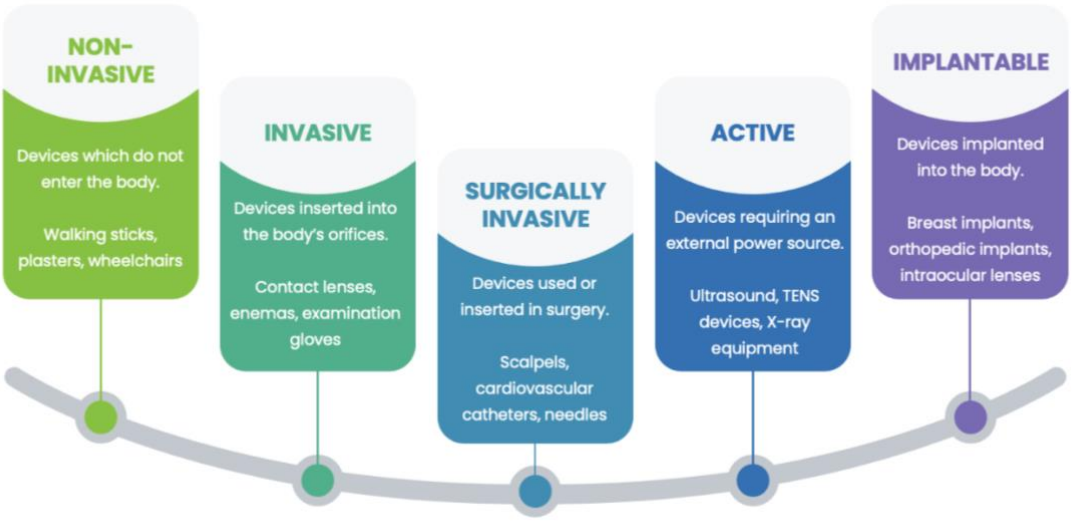
Figure 1.5: Examples of medical devices

Legend. *Examples of medical devices, all images are licenced via Adobe Stock.* ***A****: Medical equipment background, close-up ultrasound machine © okrasiuk/Adobe Stock.* ***B****: Image of syringe with needle and plastic tubes for central venous catheter insertion © pirke/Adobe Stock.* ***C****: Smart watch technology © woravut/Adobe Stock.* ***D****: Wheelchair © adimas/Adobe Stock.*

All medical devices marketed in the UK have both a Medicines and Healthcare products Regulatory Agency (MHRA) category and a classification. The category of a medical device is determined by their use, defined in **Figure 1.6**. Once categorised as a medical device a product is then classified based on risk. Risk factors take into consideration the intended purpose, duration and whether it is

invasive and active. A breakdown of the classifications and risk categories are provided in **Figure 1.7**.

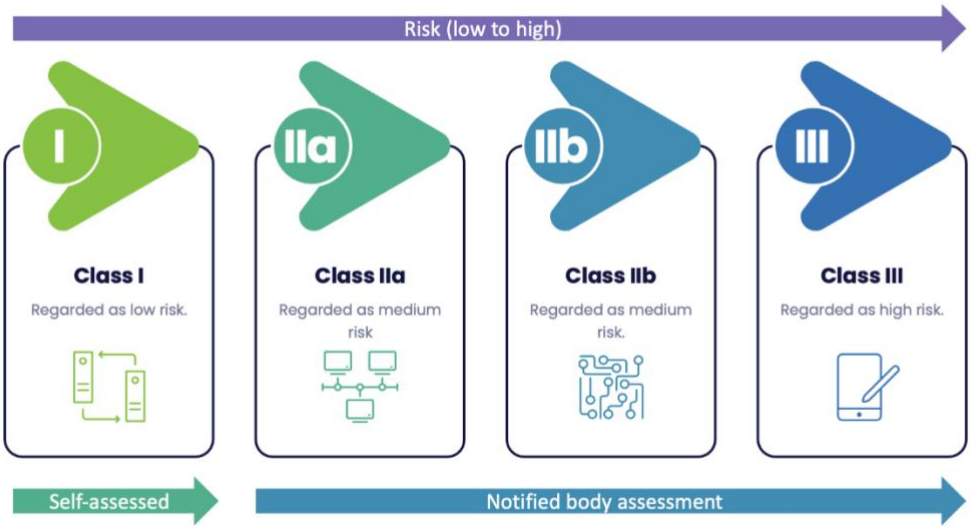
Figure 1.6: MHRA medical device categories



Legend. *Medical devices in the UK have a category assigned by the MHRA. The figure above has been produced using the MHRA category of medical devices*[48].

MHRA= Medicines and Healthcare products Regulatory Agency

Figure 1.7: MHRA medical device classification guide



Legend. *Medical devices in the UK have a classification assigned by the MHRA. The figure above has been produced using the MHRA category of medical devices*[48].

MHRA= Medicines and Healthcare products Regulatory Agency.

Medical devices in the UK are regulated by the Medical Devices Regulations 2002.[49] This act protects consumers by ensuring all medical devices conform with an assessment before allowing to be sold in the UK. Globally it is recognised that the current definitions and classifications of medical devices are complex and difficult to navigate.[50] Confusion is further compounded as discrepancies arise between differing global jurisdictions such as with the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). However, for the purpose of this thesis, the focus will be on the laws affecting UK medical devices.

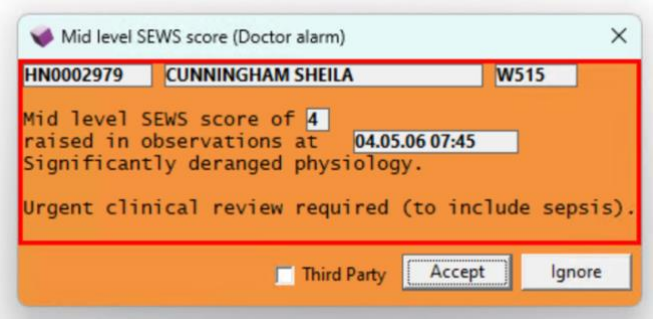
A policy paper from the MHRA updated in January 2021 suggested there are approximately 600,000 medical devices available on the UK market.[48] The key aspects relevant to the thesis is the Use of Software as a Medical Device (SaMD), specifically CDSS and AI as a Medical Device (AIaMD). Digital health tools may now be classified as a medical device, and this sector has seen significant innovations in recent years.[51] Examples of digital health medical device tools are wearable devices, remote monitoring systems, telemedicine devices, AI/Machine Learning (ML)-based algorithms.[52] MHRA have established a Software Group who are responsible for assuring the safety of SaMD, ensuring patients have access to technologies that meets clinical needs. Furthermore, the Software Group will ensure there is appropriate evidence to satisfy regulatory approval including addressing the issues of transparency around AI model (explainability and interpretability).[53] SaMD that is intended to provide information to make decisions with diagnosis or therapeutic purposes is classified by the MHRA as a Class IIa

device. If the monitoring includes vital physiological parameters, where variation in these could result in immediate danger to a patient then it will be classified as Class IIb. If any decisions could cause death or an irreversible deterioration of health, then it will be in Class III.

1.9 Combatting Alert Fatigue – Balancing Notifications and Clinical Relevance

The phenomenon of alert fatigue in healthcare settings has emerged as a significant by-product of the increasing reliance on EHRs and automated alert systems.[54-56] Alert fatigue is characterised by a desensitisation to safety alerts and can lead to healthcare professionals overlooking critical warnings. Alerts can be classified into active and passive groups with three levels of severity (minor, major and severe). **Figure 1.8** provides an example of a Mid-level Standardised early warning score system (SEWS) score alert for a dummy patient in a training EHR system. This alert appears as a pop-up window in the EHR that the clinician needs to either “accept” or “ignore”. As a multitude of alerts vie for attention, the likelihood of critical warnings being disregarded or missed entirely escalates, potentially compromising patient safety.[57] A review in 2016 indicated that between 22% and 96% of clinical alerts are ignored.[58]

Figure 1.8: Example of a dummy patient EHR alert from the PICS training system



Legend. *EHR alert from Training Prescribing Information & Communication Systems (PICS) EHR. All information is based on dummy patient data for training purposes. Alert warns of a mid-level SEWS score.*

SEWS=Standardised Early Warning Score.

The mechanism underlying alert fatigue is multifaceted, with cognitive overload playing a pivotal role.[59] Clinicians are required to process substantial amounts of information. The additional cognitive burden of frequent alerts can impair their ability to distinguish between alerts that warrant immediate action and those that are less critical. This overload is exacerbated by poorly designed alert systems that fail to prioritise and filter alerts according to clinical urgency. The consequence is a paradoxical situation wherein the tools designed to enhance patient safety inadvertently become a threat to it. Although the negative cognitive outcomes are reported in studies, its effect on burnout and other affective outcomes has been understudied.[60]

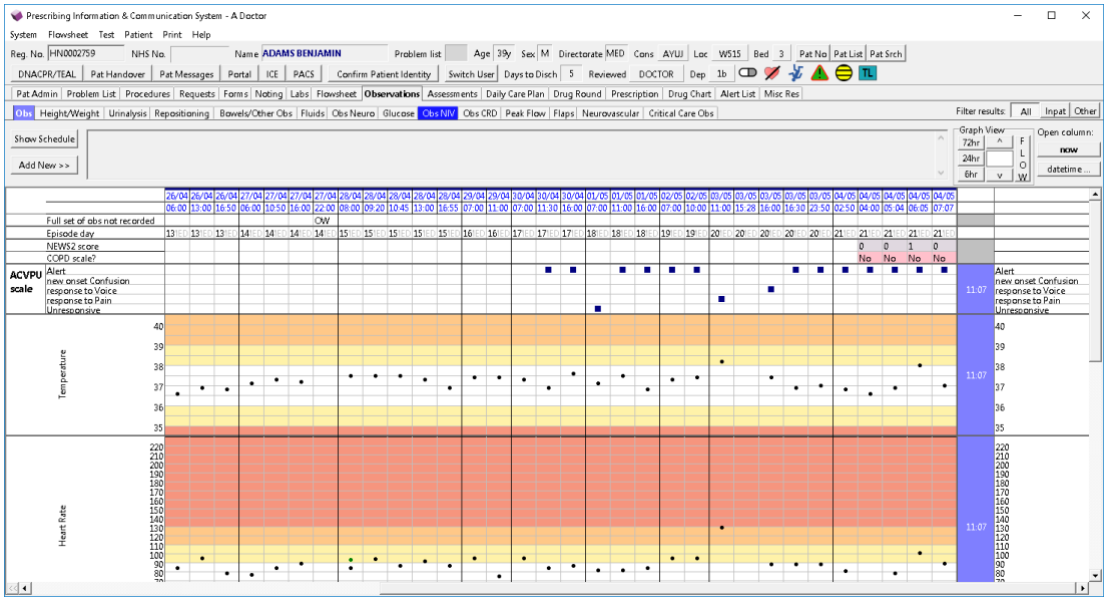
Research has shown that the consequences of alert fatigue can have serious consequences, such as medication errors and treatment delays.[61] Therefore, the main challenge is to improve alert systems to ensure they are sensitive and specific, reducing false positives while still flagging genuine risks. Addressing alert fatigue requires a comprehensive approach, including optimising alert thresholds,

and customising alert settings to match individual clinician and patient needs. Furthermore, it is important that proper training is provided for healthcare professionals to effectively use alert systems. These steps are necessary for the benefits of digital alert systems to be protected by the human limitations of attention and perception.

1.10 Automated Health Scoring – Enhancing triage and assessment with Electronic Health Records

Scores are used as a routine part of modern clinical practice to aid clinical decision making. These scoring systems have numerous functions, from diagnosis (Wells Criteria), assessment of illness severity (National Early Warning Score 2 (NEWS2)), to risk of developing a disease (Cardiovascular Disease risk score).[62] These scores range from simple summation through to complex models requiring multiple factors, such as the Acute Physiology and Chronic Health Evaluation (APACHE) score that had 34 variables to be considered in the original version.[63] **Figure 1.9** demonstrates how the EHR displays the observation parameters, such as temperature, heart rate, which are used to automatically calculate a NEWS2 score. The system uses colour-coding to identify elevated scores (red) that enables clinicians to visually note any physiological changes. The system automatically sends alerts for raised NEWS scores to ensure prompt action is taken.

Figure 1.9: Example of an EHR observation screen with automated NEWS2 score from the PICS training system



Legend. *EHR observation screen from Training PICS EHR showing parameters for NEWS2 and score. All information is based on dummy patient data for training purposes.*

EHR=Electronic Health Record; NEWS2=National Early Warning Score; PICS=Prescribing Information & Communication Systems.

Automated Health Scoring (AHS) integrated within EHRs offers a forward-looking approach to refining medical triage and patient assessment. This innovative intersection between technology and healthcare leverages the rich data landscape of EHRs with an aim to enhance decision-making processes, improve patient outcomes, and increase operational efficiency. AHS employs computation and algorithms, which in more recent times includes machine learning to parse through EHR data.

Automating clinical scores is not always possible as the data required to calculate the score are not available or retrievable. In a study published in 2017 which identified 534 unique variables nearly half (265/534, 49.6%) were not retrievable.[63]

There are further challenges associated with the implementation of AHS such as ensuring data privacy, mitigating algorithmic bias, and establishing comprehensive data governance frameworks. These issues necessitate a collaborative effort among healthcare practitioners, data scientists, and policy makers to foster an ethical, transparent, and equitable use of AHS technologies.

The application of AHS in clinical settings demonstrates its potential to transform traditional triage methods by identifying high-risk patients early and accurately. This capability ensures that critical resources are allocated efficiently, optimising healthcare delivery. In patient assessment, AHS tools contribute to a more personalised healthcare approach by forecasting patient outcomes, guiding therapeutic choices, and tracking disease progression over time.

AHS integrated with EHRs represents a promising avenue for enhancing healthcare triage and patient assessment. Its success hinges on addressing the technical, ethical, and governance challenges that accompany its implementation.

1.11 Revolutionising Health Data Research – from Silos to Hubs to National Secure Data Environments

The strategic shift in the NHS digital landscape, as outlined above, marks a significant advancement in harnessing, accessing and analysing real-world health data, revolutionising the approach to healthcare research. The transformation of the health data research landscape has seen a move from siloed databases towards the creation of integrated health data research hubs.

Despite the progress being made, many healthcare systems today continue to struggle with information silos in direct patient care. These silos manifest as fragmented medical records scattered across different healthcare providers and institutions, impeding the seamless flow of patient information. This fragmentation not only hinders the efficiency of direct care by obscuring a comprehensive view of patient health histories but also poses significant risks to patient safety. Critical information such as allergies, current medications, and past medical interventions may not be readily available across all points of care, increasing the likelihood of medical errors. Moreover, these silos have a direct impact on the ability to collate longitudinal data for research purposes. The challenge of aggregating fragmented data into a coherent, longitudinal patient record complicates efforts to conduct wide-ranging health data analysis.

The advent of health data research hubs in 2019 represents a paradigm shift in this landscape.[64] These hubs serve as centralised repositories that aggregate and standardise health data from various sources, including EHRs and patient registries. By breaking down the silos that previously compartmentalised health data, these hubs facilitate a more holistic longitudinal view of patient health. One exemplary model of this innovative approach is the PIONEER Health Data Research Hub for Acute Care Data, which exemplifies how real-world health data can be leveraged to drive research, improve patient outcomes, and inform clinical practice in acute care settings.[65]

There are two main options for sharing data for research. Until recently, the standard approach involved releasing data to the requestor's systems with appropriate safeguards, such as data minimisation and audits, to ensure security and ethical use. This method allowed researchers to handle data within their own systems, provided they adhered to strict protocols to protect the data.

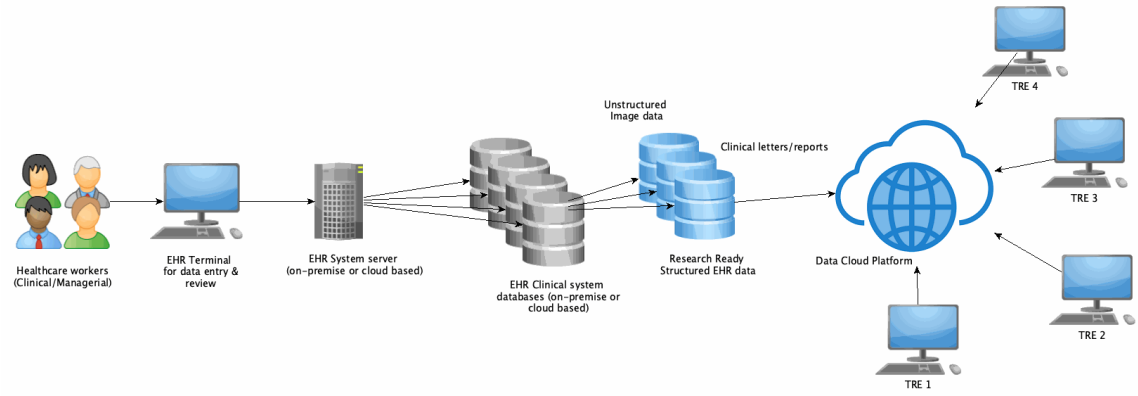
However, with the advent of new technology solutions, many organisations, including the Office for National Statistics (ONS), the Secure Anonymised Information Linkage (SAIL) Databank, and PIONEER, are now opting to provide data access within Trusted Research Environments (TREs). The use of TREs shifts the model from data release to data access. As these environments are designed to support the “Five-Safes” framework security and privacy are enhanced. The framework encompasses Safe people; Safe projects; Safe settings; Safe outputs; Safe data.[66]

A significant advantage of TREs is the increased control they offer over data security. The data remains within a secure platform, and only validated researchers can access it along with the necessary tools for analysis. This method was a key recommendation from Ben Goldacre's "Better, Broader, Safer: Using Health Data for Research and Analysis" report in April 2022. The report suggested that TREs should be "...the norm for all analysis of NHS patient records data by academics, NHS analysts, and innovators, wherever there is any privacy risk to patients, unless those patients have consented to their data flowing elsewhere." [67]

Figure 1.10 provides a graphical illustration of how data are entered and utilised as part of routine clinical care in an EHR system through to loading into a TRE for research to be undertaken. In a typical TRE setup, health data entered by clinical and administrative staff into EHRs is stored on secure servers. Approved technical experts extract the necessary data for research, ensuring it is valid and de-identified, applying the National Data Opt-out (NDOO) to protect individual identities (**Section 1.13** provides information on the application of NDOO). This de-identified data is then moved into a TRE, where only validated researchers can access it.

Furthermore, TREs allow researchers access to more granular data than that supported with data release models as control is maintained to prevent any data being egressed. The challenge that is facing those managing TREs arise at the point where researchers are ready to egress their models and results. These models are becoming increasingly complex and there is no guidance or tools to assist with their egress from TREs. Currently, technical experts must manually review the code, outputs and figures which can be time-consuming depending on the volume and complexity of outputs produced.

Figure 1.10: High-level flow of clinical data from an EHR to a TRE for researcher access



Legend. *Data are entered and reviewed at EHR terminals (mobile and computers) and stored in multiples database accessed via a server (physical or cloud-based). Data is extracted, transformed and loaded into research ready databases. Each research request is serviced via loading data (anonymised) into a secure data cloud platform and from there into a controlled access trusted research environment.*

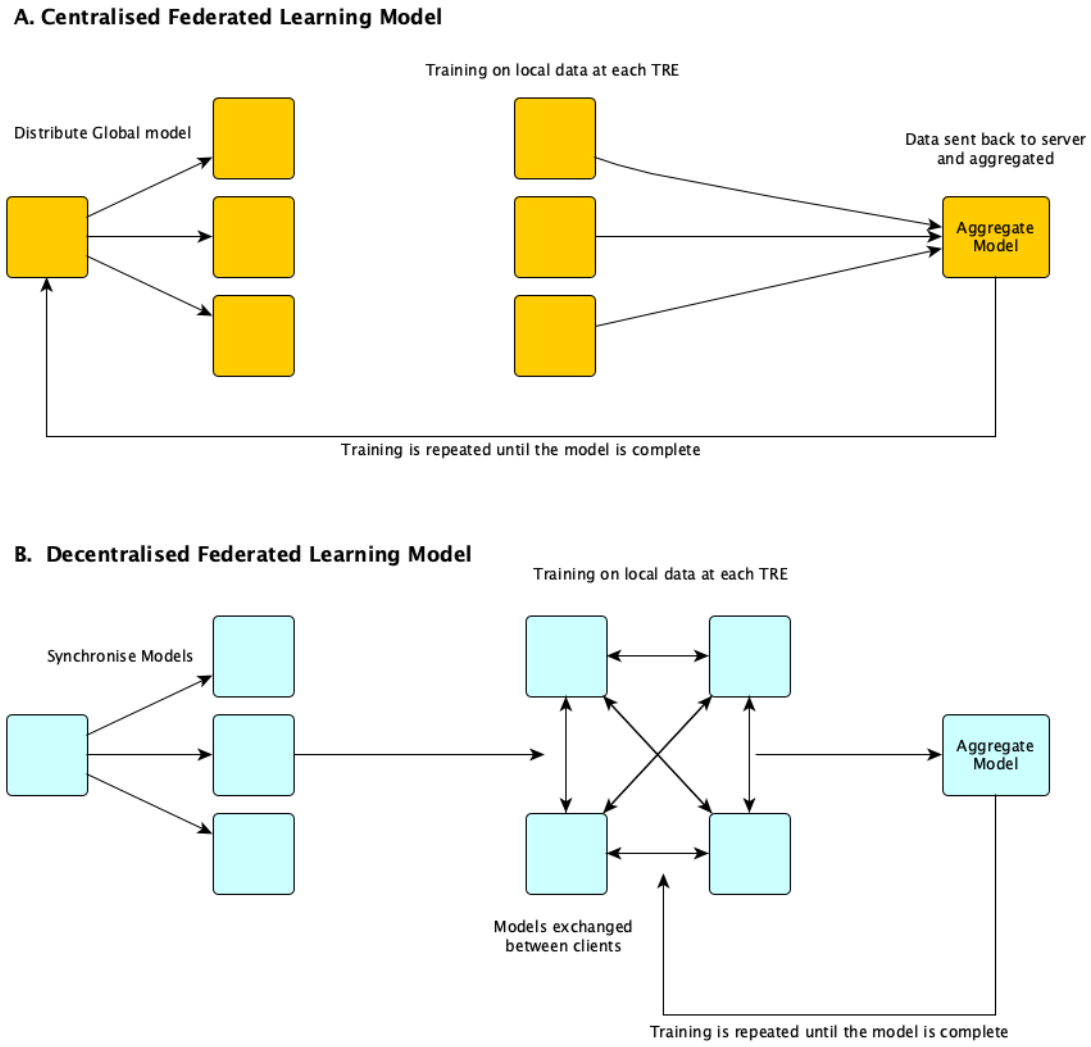
EHR=Electronic Health System; TRE =Trusted Research Environment.

Federated learning is a concept proposed by Google in 2016 as a new model of ML.[68] As datasets become larger and models more complex there is an increasing need to optimise the parameters over multiple machines. However, it has been the expanding network of data across multiple regions that has driven the requirement for federated learning within the digital health arena. The ability to conduct federated learning will enable large-scale studies across these environments (hubs, SDEs).

Federated learning has a series of clients (TRE, server, mobile device) that holds a dataset. The objective of federated learning is to build and run ML models over distributed data. Data privacy is upheld as only the model and results are returned to the researcher. Centralised machine learning distributes the global across the clients where it is trained locally and only the parameters are returned. The global model is updated via a process over iteration by collecting the model parameters

from the clients without sharing any raw data [69] (**Figure 1.11** Centralised Federated Learning Setup). Decentralised Federated Learning models eliminate the requirement to transfer all the data to one global server. Each client exchanges updates with other clients in the network to share model updates and aggregate them collectively (**Figure 1.11** Decentralised Federated Learning Setup). Each option has strengths and weakness, centralised models offer efficiency and control but have a single point of failure. Decentralised models remove the central server, and therefore the single point of failure but introduces issues around efficiency and aggregation.

Figure 1.11: Diagram to illustrate the centralised and decentralised federated learning model cycles



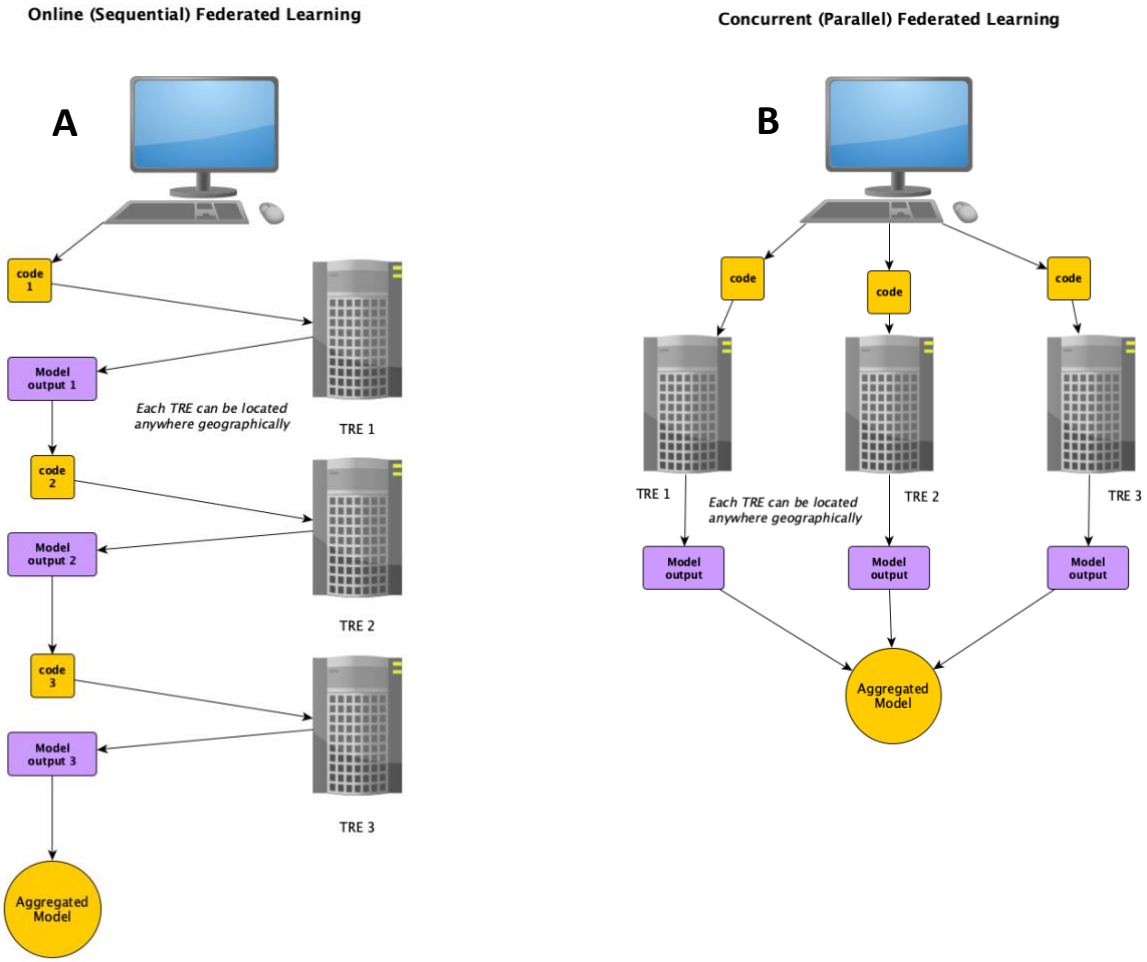
Legend. Figure A *illustrates the Centralised Federated Learning model where a global model is distributed across multiple clients and trained locally. The outputs of each model are aggregated and returned to the initial server. The iterated and revised model is then redistributed to the clients and trained again until the model is complete.* ***Figure B*** *illustrates the Decentralised Federated Learning Model where there is an initial synchronised across all the clients. The training then exchanges models between all the clients before being aggregated. Iterative cycles take place in the clients without the need of a central server.*

TRE=Trusted Research Environment.

Furthermore, there are two types of learning methods available to researchers, namely Online learning (also known as sequential learning) or Concurrent Learning (also known as parallel learning). Data arrives in a sequential manner for online learning with the model being updated incrementally (**Figure 1.12 A**). This type of

model is suitable for real-time applications as it can adapt rapidly to changes in data patterns as it is continuously updating. In concurrent learning multiple models are trained simultaneously and the results combined to produce a final model (**Figure 1.12 B**). Concurrent learning highly scalable and suitable for analysing large volumes of data, as the workload can be distributed across clients. However, this method adds complexity to the system with managing the parallel tasks.

Figure 1.12: Differences between online and concurrent federated learning



Legend. *In Figure A the model is trained sequentially based on the predictions from the previous client (TRE) until final model is produced. In Figure B the model is trained on each client independently before being aggregated.*

TRE= Trusted Research Environment.

Following the success of the health data hubs, initiatives like NHS England's Secure Data Environments (SDEs) demonstrate the continued commitment to managing and utilising health data securely, as set out in Data saves lives: reshaping health and social care with data Policy Paper.[70] The funding for these environments, announced in March 2022, aims to ensure that data is not only accessible but also protected, balancing the imperative for privacy with the need for comprehensive data analysis.[71] The implementation of the SDEs underscores the importance of ethical considerations and data security in expanding access to health data for research purposes.

These developments signal a shift towards more collaborative, efficient, and secure frameworks for health data research. By fostering an ecosystem where data can be shared and analysed within secure parameters, health data research hubs and secure data environments are instrumental in unlocking the potential of real-world health data. This evolution paves the way for advancements in medical research, enabling the development of evidence-based healthcare interventions and policies that are responsive to the nuanced needs of the population.

1.12 Complexities in Real-World Health Data – Overcoming Research Barriers

The increasing number of EHRs has contributed to larger amounts of potential data available for research. Advances in digital health have given rise to new types of biomedical data, such as genetic and imaging data.[72] Such data are referred to as real-world data (RWD), as it relates to patient health status and/or the routine

delivery of health care collected from a variety of sources, as shown in **Figure 1.13.**[73] When this data are analysed the information produced is referred to as real-world evidence (RWE). The FDA defines RWE as "…clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD".[74]

Figure 1.13: Examples of different sources of real-world health data

Legend. *Examples of different sources of real-world health data. The examples provided are not comprehensive but provide indication of the key sources.*

EHR= Electronic Health Record.

In December 2021, the MHRA published guidance on the use of real-world data in clinical studies to support regulatory decisions.[75] The guide was developed as RWD has traditionally been used less frequently for demonstrating safety and efficacy of an intervention. Previously use had focussed on monitoring the performance and impact of medicines post regulatory approval. A report from a joint meeting between the Academy of Medical Sciences and the Association of the British Pharmaceutical Industry (ABPI) held on September 2015 suggested that

evidence from RWD has the potential to impact all stages of a product's lifecycle. The report indicated that RWE could even replace evidence collected from the 'gold standard' of experimental design: the Randomised Clinical Trial (RCT).[76]

RWD studies are more straightforward and cost-effective to establish compared to the complexity and higher expenses associated with RCTs in the UK. These benefits allow for more efficient allocation of resources, thereby enhancing the evaluation of new medications and accelerating patient access to these treatments. There is now global recognition of the role that RWE can play in decision-making in the context of regulatory and health technology appraisals (HTA).[77, 78]

A key strength of RWD is that the evidence from analyses are more representative of the treatment, especially if the data are from a diverse population.[79] Furthermore, the findings are more generalisable than those from an RCT. An important consideration for the use of RWD that the MHRA guidance highlights is the quality of the source data. Data provenance is a key feature to help assess if the quality and reliability is sufficient to support the analyses. Other aspects to be understood are the validity, reliability, variability and accuracy. These features will help to manage any limitations and to manage discrepancies whilst avoiding any potential bias. A key assumption is that any bias or known issues can be identified and mitigated. However, it should be recognised that this work required significant domain level expertise, both clinical and statistical.

1.12.1 Data quality and standardisation

EHRs may not reliably capture all the elements necessary for analysis. This could result in missing values, a problem exacerbated by differences in data collection practices across institutions. This situation necessitates a discussion on the responsibility of data checks. Should they be study-specific and undertaken by the researcher and/or the data controller(s)?

The wide variation in data types, granularity, and quality due to differences in data capture across disparate sources and clinical areas poses a significant challenge to achieving standardisation. Furthermore, data might be recorded in an unstructured format in a clinical note. Natural language processing (NLP) is evolving as a method to address the issue; however, it is an advanced skill, and whilst the use is growing it is still an emerging field of research.

Systematized Nomenclature of Medicine Clinical Terms (SNOMED CT) is a structured clinical vocabulary used in EHRs used to exchange of clinical information. One solution to standardisation for research is the use of a common data model (CDM). A CDM facilitates the transformation of data in multiple databases to a common format.[80] Several studies have evaluated CDMs to determine which is best suited for use with large EHR databases. The criteria reviewed included coverage, flexibility, ease of querying, integrity and linkage and results showed the Observational Medical Outcomes Partnership (OMOP) CDM met most of these desired features.[80, 81]

1.12.2 Integration and interoperability

Another significant challenge with RWD is the ability to integrate or connect data from multiple sources. As discussed in **Section 1.11**, there are increasing efforts to link data at a population level. Data linkage is the "…bringing together of two or more sources of information which relate to the same individual, event, institution or place."[82] Successful linkage can be resource intensive as data controllers will need to ensure they have addressed any legal, ethical and regulatory challenges. However, linkage is critical to ensuring a better understanding of broader health populations. To link data from multiple sources a unique and common identifier is required such as NHS number. NHS number is frequently used by data processors with access to identifiable data as a master patient index (MPI) to create longitudinal data records. However, using this approach might not always be possible due to ethical issues or risk of re-identification.

One practical issue to consider is weak linkage due to data quality or missing data. These issues could lead to errors in linkage and misleading conclusions, which could increase health inequalities. This emphasises the importance of standardisation as, for example, NHS numbers are recorded in differing formats across EHRs. One matching technique employed to assist complex linkage is probabilistic matching, also known as 'fuzzy matching'. Matching is achieved by algorithms that score and weight inconsistencies in the variables to determine if they belong to the same individual.

Interoperability is recognised as a key factor to improving direct care and research as it can provide a comprehensive view of patient records. It is defined as the ability of two or more systems to exchange information and to use the information that was exchanged.[83] An issue faced with achieving data interoperability is that legacy data systems were not typically designed to share information. A solution proposed to address this issue are integration layers that act as a translation layer to aid with data processing. APIs allow IT software and systems to request and receive information in real time. The format of the messages sent depends on the specific use case. Pathology messages use the Health Level Seven (HL7) format which is an international standard to exchange medical information between EHRs[84]. Fast Healthcare Interoperability Resources (FHIR) is the latest standard developed as part of the HL7 family.[85] FHIR is best described as a set of building blocks for APIs to support structured messaging between systems. EPIC and Cerner's Millennium EHR platform integrate FHIR APIs to enable interoperability and data exchange between healthcare providers.

Overcoming these barriers to the effective use of real-world health data for research necessitates a multifaceted approach. Strategies include the development of standardised data collection and reporting protocols to reduce heterogeneity, applying advanced statistical methods to address missing data, adopting interoperability standards to facilitate data integration, and establishing ethical and legal guidelines to enable secure data access.[86] These efforts are

crucial for harnessing the full potential of real-world health data in advancing healthcare research and improving patient outcomes.

1.13 Navigating Regulation and Ethics – Addressing AI, Bias and Governance in Healthcare

The secondary use, or re-use, of health data is the processing health data for purposes other than the initial reason of the direct delivery of care.[87] Examples of these uses include public health, analyses, research and other business applications. Accessing and re-using existing healthcare data offers the opportunity to reduce the time and cost for researchers.[88] However, this widespread use of data raises important ethical and legal issues due to the sensitive nature of the information being utilised.

The ethical considerations and governance structures surrounding the secondary use of healthcare data are critical elements that require distinct attention.[89] Ethics in the context of secondary use of data involve complex issues with the need to ensure that the privacy and autonomy of individuals are respected.[90] The first option for researchers to consider is anonymous data, as it aligns with the principle of data minimisation and mitigates data privacy risks. Anonymous data, which is not classified as personal data, falls outside the scope of data protection laws (**Figure 1.14 A)**. According to Article 5(1)(c) of the General Data Protection Regulation (GDPR), personal data should be "...adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed (data minimisation).”[91]. Therefore, the use of anonymous data should be prioritised.

However, this type of data may not always fulfil the research purpose, particularly in studies requiring longitudinal data to link and track patient outcomes over time. In such cases, the lack of identifiers in anonymous data prevents the necessary data linkage and tracking.

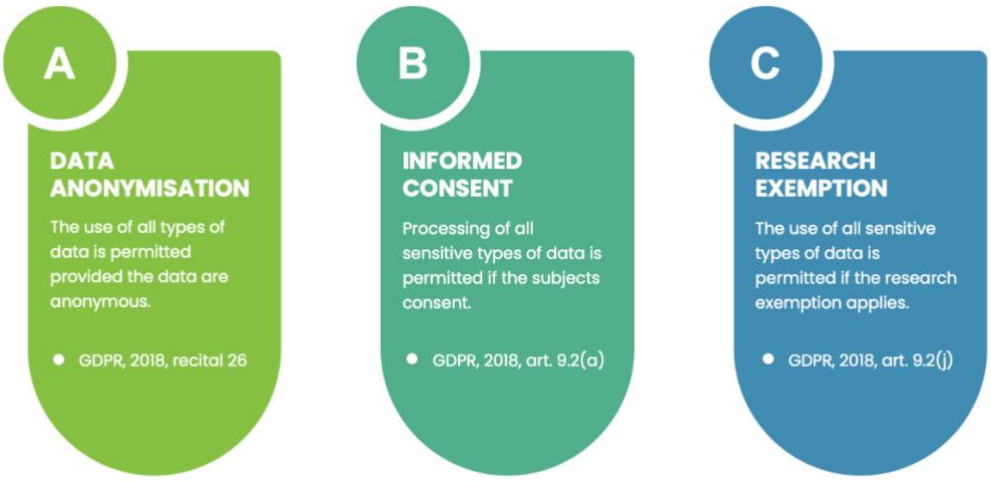
If the research requires the use of sensitive health data, then consideration should be given to whether subjects (patients) will provide consent after being informed about the aims of a specific study (**Figure 1.14 B**). The legal framework for undertaking research with informed consent research is through the GDPR, 2018, article 9.2 (a). Where it is not possible to obtain consent from all subjects the legal basis for processing relies on public interest and is justified by the societal benefit of the research (**Figure 1.14 C**). Section 251 Confidentiality Advisory Group (CAG) approval provides the necessary legal and ethical framework within the UK to support the processing activities permitted under Article 9.2(j) of the GDPR.

Ethical approvals can be obtained either on a project-by-project basis or for a research database. An example of the latter is the PIONEER Hub, which has secured research database ethics and Section 251 approvals. Researchers submitting applications must undergo review by the data controller(s) and a public panel to ensure that the study aligns with the ethical scope of the database and is considered to bring patient benefits. Once approved, the study falls under the research database ethics, facilitating more rapid access to health data. However,

a potential disadvantage is that if a study falls outside the ethical scope of the research database, it would not be approved.

In summary, while both types of ethics share common goals of protecting participants and ensuring ethical conduct, research database ethics focus on broad, long-term considerations for data use and governance, whereas individual research project ethics concentrate on the specific, immediate ethical aspects of a single study.

Figure 1.14: Ethical requirements for the secondary use of data required to undertake research



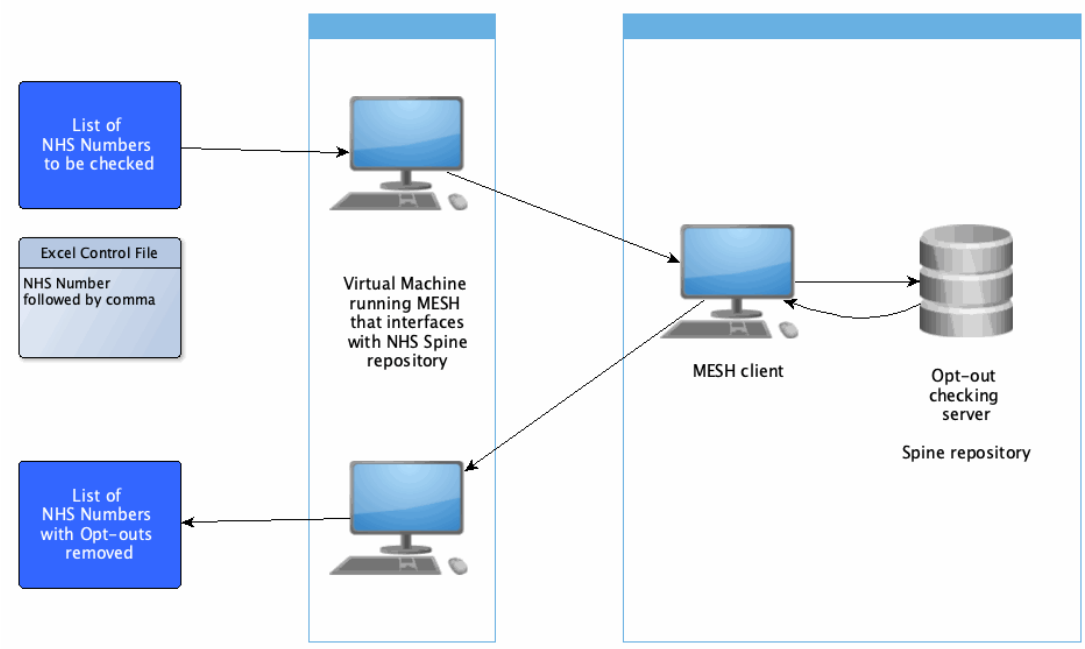
Legend. *The three categories apply globally to the secondary use of data for research. The legal basis and acts quoted for each category only apply to the European Union/UK.*

ART=article, GDPR=General Data Protection Regulation.

The National Data Opt-out (NDOO) allows patients in England to opt out of having their confidential patient information used for research and planning purposes, balancing the need for health data in improving services with respecting individual

privacy. This policy must be upheld by all health and adult social care organisations in England. The NDOO aligns with the common law duty of confidentiality (CLDC) for sharing a patient's data. The opt-out does not apply to studies where an individual has consented to their data being shared. The other exemption is "...the disclosure of confidential patient information required for the monitoring and control of communicable disease and other risks to public health."[91] NHS Digital provide a service called Message Exchange for Social and Health (MESH) that check NHS numbers against the national data opt-out repository on the Spine. The process of using the MESH service is shown provided in **Figure 1.15**.

Figure 1.15: Process of applying national data opt-out using the NHS England MESH Service



Legend. *The process commences with a Health and Care Organisation sending a list of NHS numbers in an Excel control file to the Opt-out MESH spine repository. Data are encrypted in transit through use of MESH.*

NHS= National Health Service; MESH= Message Exchange for Social Care and Health.

Governance, on the other hand, relates to the policies and oversight mechanisms that regulate the secondary use of data.[92] This includes the development of clear procedures for data access, de-identification protocols to protect patient information, and the establishment of data stewardship roles. Effective governance ensures that data is used responsibly, ethically, and with accountability, mitigating risks associated with data misuse and maintaining public trust in healthcare institutions.

When considering the specific issues related to the use of AI in healthcare, additional layers of complexity arise. AI systems, particularly those employing machine learning, can process and analyse healthcare data on a scale and with a sophistication beyond traditional methods. However, these systems can inadvertently perpetuate and amplify biases present in the data, leading to unequal treatment and outcomes among different patient groups. Thus, the ethical use of AI in healthcare requires rigorous validation and testing to identify and address biases, ensuring that AI tools perform equitably across diverse populations.[93]

As the use of AI in healthcare grows, so does the demand for larger datasets, resulting in an increased demand for data from EHRs. Furthermore, the governance of AI in healthcare demands oversight not only of data use but also of the algorithms themselves. This includes evaluating the methodology of AI systems, the interpretability of their outputs, and their integration into clinical workflows. Given the rapid pace of innovation in AI, governance frameworks must

be both robust and agile, capable of evolving in response to the continuous advancements in AI technologies.

In the coming years, AI is expected to transform the field of medicine significantly. Since the initial ground-breaking achievements of AI algorithms capable of diagnosing diseases from medical images with expert-level accuracy, the domain of medical AI has evolved markedly. Presently, the integration of AI systems into regular clinical practice offers a crucial, albeit largely unrealised, prospect.[94] The healthcare AI community is currently confronting a range of intricate ethical, technical, regulatory and human-centric hurdles to ensure these technologies' safe and effective implementation. This transition period is pivotal as it shapes the trajectory for leveraging AI to enhance healthcare delivery and patient outcomes.

The regulatory environment encompassing AI in healthcare is fraught with considerable challenges, primarily due to the rapid evolution of technology and the complexities associated with embedding AI solutions within the existing medical infrastructures.[95] Regulatory bodies are faced with the significant task of fostering innovation whilst concurrently safeguarding patient safety and ensuring the confidentiality of patient data. The dynamic nature of certain AI algorithms, characterised by their capacity for continuous learning and adaptation, poses a significant challenge to conventional regulatory standards, which are predominantly designed for devices with static functionalities.

In essence, while the secondary use of healthcare data holds immense potential for advancing medical knowledge and improving public health outcomes, it necessitates careful ethical and governance consideration. The implementation of AI systems amplifies these needs, introducing unique challenges that require specialised attention to ensure that its deployment in healthcare settings is appropriately regulated, standardised and integrated with EHR systems.[96]

1.14 Rationale for the thesis

This thesis explores the significant potential of health data to enhance healthcare through research, service evaluations, and quality improvement programs. The effective use of health data for research requires not only appropriate governance and ethical considerations but also public trust in data usage. To facilitate this, a co-created protocol, detailed in **Chapter 2**, was developed to ensure transparency and trustworthiness.

Given the increasing interest in EHRs as tools to improve care quality and safety, alongside a lack of clear evidence supporting EHRs in providing such improvements, this thesis explores the following key areas:

1. Assessing whether EHRs can be used to evaluate the safety and effectiveness of guideline implementation and improve guideline adoption, with a specific focus on Venous Thromboembolism (VTE) and D-dimer testing.

2. Investigating if EHRs can test the effectiveness of new care pathways proposed by policymakers, with a focus on the "Reason to Reside" (R2R) criteria and the COVID-19 Virtual Ward.
3. Examining whether EHRs can enhance efficiencies in healthcare systems, particularly within the context of ward order communications for blood tests.

Additionally, considering the transition from a data egress to a data access model, **Chapter 8** examines whether federated analytics can facilitate accurate analysis of data across multiple healthcare settings.

1.15 Hypothesis

Data from EHR and systems can be accessed for research and innovation with public oversight and appropriate governance and approvals. These data can be used by an organisation to improve care efficiencies and guideline compliance and better understand the effectiveness of centrally driven care policies. Furthermore, such insights can be gained from a federated analytical approach to data access, supporting greater data security.

1.16 Aims

The aims of this thesis are as follows:

- To set up a framework in consultation with patients and public for the PIONEER Health Data Research Hub.

- To understand if systematic prescribing interventions via an EHR would be effective in achieving full VTE guideline compliance.
- To assess the impact on Computerised Provide Order Entry systems (CPOE) on the turnaround times for processing blood results over a two year period.
- To retrospectively assess the impact of a potential COVID-19 Virtual Ward and to evaluate outcomes of patients discharged within 24 hours of admission without the support of a virtual ward.
- To examine the ability to federate analytics using traditional statistics and machine learning by comparison to a gold standard of pooled data.

Chapter 2: Infrastructure and operating processes of PIONEER, the HDR-UK Data hub in Acute Care and the workings of the Data Trust Committee: A Protocol Paper

This chapter has been published in BMJ Health & Care Informatics entitled "*Infrastructure and operating processes of PIONEER, the HDR-UK Data Hub in Acute Care and the workings of the Data Trust Committee: a protocol paper*" [(65)] (see **Appendices for Chapter 2**, **Supplementary File 2.1**).

S. Gallier[1], G. Price[2], H. Pandya[3], G. Mccarmack[4], C. James[5], B. Ruane[6], L Forty[7] B Crosby[8], C Atkin[9], R.Evans[10], K Dunn[11], E Marston[12], C Crawford[13], M. Levermore[14], S. Modhwadia[15], J. Attwood[16], S Perks[17], R. Doal[18], G Gkoutos[19], R. Dormer[20], A. Rosser[21] H Fanning[22], E Sapey[23]

1. Technical Director, PIONEER HDR-UK Data Hub in Acute Care, Institute of Inflammation and Ageing, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
2. Data Trust Committee public member. Patient Involvement and Engagement Lead, PIONEER [redacted]
3. Data Trust Committee public member. Patient Involvement and Engagement Lead, PIONEER [redacted]
4. Data Trust Committee public member. Patient Involvement and Engagement Lead, PIONEER, [redacted]
5. Data Trust Committee public member. Patient Involvement and Engagement Lead, PIONEER [redacted]
6. Data Trust Committee public member. Patient Involvement and Engagement Lead, PIONEER, [redacted]
7. PIONEER Hub in Acute Care, Institute of Inflammation and Ageing, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK [redacted]
8. PIONEER Hub in Acute Care, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, Birmingham, B15 2GW, UK. Email: [redacted]
9. PIONEER Hub in Acute Care, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, Birmingham, B15 2GW, UK. Email: [redacted]. ORCiD ID = 0000-0003-0596-8515
10. PIONEER HDR-UK Data Hub in Acute Care, Institute of Inflammation and Ageing, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
11. HDR-UK Midlands Physical Site, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. Email: [redacted]

12. Research Support Services, University of Birmingham, Edgbaston, Birmingham, B15 2TT. [redacted]
13. Research and Development, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. Email: [redacted]
14. a. Chief Executive Officer, Medical Devices Technology International Limited (MDTi) , The KaCe Building, Victoria Passage, Wolverhampton, West Midlands, WV1 4LG, United Kingdom.

    b. Visiting Professor in Health, Education and Life Sciences, Birmingham City University, Birmingham, West Midlands, UK. [redacted]
15. PIONEER HDR-UK Data Hub in Acute Care, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
16. Informatics, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
17. Informatics, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
18. Informatics, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
19. Turing Fellow, Alan Turing Institute, HDR-UK Associated Researcher, Institute of Cancer and Genomic Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
20. Insignia Medical Systems Limited, Paterson House, Hatch Warren Lane, Basingstoke, Hampshire RG22 4RA, UK [redacted]
21. Research Lead, West Midlands Ambulance Service Foundation Trust, Millennium Point, Waterfront Business Park, Waterfront Way, Brierley Hill, West Midlands, DY5 1LX. [redacted]
22. Research and Development, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. Email: [redacted]
23. A. Director of PIONEER, HDR-UK Health Data Research Hub in Acute Care, Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, B15, 2GW

    B. Department of Acute Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2GW. ORCiD ID: 0000-0003-3454-5482, Email [redacted]

    C. Managing Director of NIHR CRF, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2GW

Authors' contributions

SG contributed to the protocol design and wrote the first full version of the manuscript. SG, GP, HP, GM, CJ, BR, LF, BC, CA, KD, EM, CC, ML, SM, SP, JA, RD, AR, HF, GG, ES designed the protocol. LF and ES contributed to writing the first version of the manuscript through review. All authors approved the final version.

2.1 Introduction

The National Health Service (NHS) is the publicly-funded health provider for the United Kingdom (UK). Specific NHS organisations hold identifiable patients' medical information,[97-99] increasingly within electronic health records (EHRs). EHRs facilitate health data sharing for personal medical care (the primary purpose of the health data) and also for health service planning, research and innovation, collectively termed 'secondary uses'.[90]

Health Data Research UK (HDR-UK), the national institute for health data science, was formed to unite the UK's health data to enable discoveries that improve people's lives. HDR-UK coordinated the designation of seven Health Data Hubs in alignment with the UK's Industrial Strategy to improve the quality, discoverability and accessibility of health data, with robust governance measures.

PIONEER is a Health Data Research Hub which focuses on acute care. It was developed to curate routinely-collected health data from unplanned healthcare contacts across community, ambulance and hospital providers and then facilitate the transparent and ethical use of de-identified data for research and innovation purposes. PIONEER has a principle aim of improving patient care and well-being.

‘Acute care’ is any unplanned health episode. Each year the NHS provides approximately 110 million urgent same-day patient contacts[100] with the numbers rising year on year. There are also known health inequalities associated with acute care, as people from lower socioeconomic groups are more likely to present to Emergency departments.[101, 102] Acute care also provides a unique and useful microcosm of wider health service challenges: one in five patients with cancer are diagnosed as an emergency, with significant implications for long-term outcomes; [103-105] 6.5% of acute presentations relate to adverse drug reactions or side effects from prescribed medications;[106] and chronic disease accounts for two-thirds of emergency medical admissions.[107]

Despite the scale and cost of acute care, this specialty has not benefited from significant innovation. [108] There is a critical need for new patient pathways, diagnostic processes, therapeutics, and devices in acute care, based on real-world evidence. Licensed access to acute care health data could offer unique insights and potential solutions to some of the challenges this health sector faces.

Previous research suggests there is public support for data sharing,[109] but with key concerns.[98, 110-112] The PIONEER hub conducted a series of public and patient events and developed a framework for health data secondary use, in collaboration with patients and public stakeholders[113]. The agreed framework included health data use with the potential for benefits back to patients and citizens, and a commitment to transparency: data sharing overseen by the NHS and

patient/public involvement in data access decisions. Other studies have described greater confidence in data sharing when the NHS is involved,[114-116] that public involvement is important[117] and that the principles of data minimisation should be applied.[114] The PIONEER Hub protocol was developed to ensure this framework was embedded within all operating processes.

2.2 Methods and PIONEER operating processes

2.2.1 The principle of public good

PIONEER is a partnership between patient and public members, the NHS, universities, data scientists and selected industry partners. For the full protocol, please see the online supplement.

The aim of PIONEER is to link routinely collected health data from acute care providers and use this in an anonymised form to innovate health care provision.

PIONEER supports the following objectives:

1. To develop a research database and analytics platform of linked, routinely-collected health data from different healthcare providers, to improve acute health care and reduce the long-term consequences for patients admitted to hospital.
2. To work with patients, the public and other stakeholders to ensure that data access through PIONEER is in the public interest.

3. To make datasets discoverable and appropriately accessible to research organisations, NHS bodies and commercial organisations, where access is likely to lead to patient benefit.
4. To provide an environment of cross-sector collaboration with strong relationships between patients, the NHS, industry and academic partners to support research, development and innovation within a robust governance system.

The potential uses of the PIONEER dataset include but are not limited to improvements to service delivery; reducing diagnostic delay; reducing chronic disease burden; and development of new treatments and technologies such as point of care testing, self-management software and live data streaming to provide interventions closer to home and avoid unwanted or unnecessary hospital admissions.

2.2.2 Proximity to the NHS

University Hospitals Birmingham NHS Foundation Trust (UHB) is the Data Controller for PIONEER. UHB is one of the largest NHS Trusts in England, with 2750 beds, more than 22,000 staff, an in-house built and clinically lead EHR (Prescribing Information and Communication System) and secondary care record (Your Care Connected).

2.2.3 Patient inclusion criteria

Any patient with an acute health issue who has sought medical advice/care from a PIONEER data partner. Any and all acute episodes can be included with no restriction on disease, condition or age. Patient data within PIONEER is collected as part of routine care. Longitudinal data will be eligible if it relates to, leads to or stems from an acute

care contact. Patients will not need to specifically consent to their health data being used within PIONEER, but patients will not be included if they have chosen to opt out of the use or disclosure of their data for research and planning via the NHS National Data Opt-Out[118] or if they have opted out of PIONEER specifically (see ethical considerations).

2.2.4 Included data

PIONEER includes data about patient demographics (age, gender, ethnicity), past and current medical diagnoses, medications, allergies and healthcare contacts. There is serial data on vital signs, investigations including laboratory, pathology, physiology and imaging, all acute medical prescriptions and administrations and health process data (clinical review specialty, ward type). This is supplemented with health data prior to and after the acute care contact, linked across healthcare providers, to enable assessment of preceding health and subsequent outcome. The PIONEER dataset adds to publicly available datasets, as highlighted in the examples provided in **Table 2.1**.

Table 2.1: A summary of related data sources

Name	Country	Subject areas	Update period	Description
HES	UK	All healthcare	Daily (A&E is quarterly)	High-level, does not include physiological measurements outside of classifications in main diagnoses
MIMIC	USA	Intensive care	Static	Deidentified data covering period '01–'12, in high detail
WHO Global Health Observatory	Global	All healthcare	Variable	High-level count data, on a global scale, does not go to the level of individual patients
Global Health Data Exchange	Global	All healthcare		Catalogue of existing datasets, generating novel data is outside of its scope
NIHR Health Informatics Collaborative	UK	Thematic		Open only to member of the HIC for collaboration, does not provide a TRE
PIONEER	UK	Acute care including preceding and subsequent health contacts	On demand	Datasets tailored to specific use cases, updated on demand and available via a secure TRE. Individual patient level data that includes medications, physiological measurements, images over 20 years. Individually linked data from primary care, ambulance and secondary care.

Legend. This should not be considered fully comprehensive, but highlights the differences between currently available datasets and PIONEER. HES=Hospital Episode Statistics [119]. MIMIC Critical Care Dataset [120], Global Health Observatory [121],Global Health Data Exchange [122],

NIHR HIC=National Institute for Health Research Health Informatics Collaborative [123]; TRE=trusted research environment.

2.2.5 Research Database design and security

Data will be stored on a secure, UHB-controlled Microsoft Azure cloud platform in accordance with the 14 UK Cyber Cloud Principles[124] which include data protection in transit; asset protection and resilience; separation between users; a robust governance framework; operational security; secure user management; identity and authentication; and audit. The cloud provision will follow the International Organization for Standardization (ISO) 27001 standards, an international specification for information security management.[125] This ISO outlines a broad range of quality control processes, many of which apply to data collection, processing and management with a strong emphasis on information

security. An example of how this will be met for PIONEER is that data transferred between organisations will be mathematically checked to ensure it has not been tampered with.

The database platform will comply with the Department of Health Information Governance policies and standards for secure processing of patient healthcare data, as set out in the Information Governance Toolkit of the Health and Social Care Information Centre.[126] The database platform will undergo cyber-security checks by an independent and external company. The platform's design enables the rapid build of bespoke trusted research environments (TREs) which provide approved and licensed researchers with access to specific curated, deidentified datasets and a suite of analytical tools (description available from corresponding author). The use of a TRE circumvents data travel from the data controller to the data user. PIONEER is committed to promoting the protection of privacy and data security in line with the Organisation for Economic Co-operation and Development (OECD) Recommendation of the Council on Health Data Governance.[127]

2.2.6 Data processing

Data is extracted, transformed and securely transmitted to PIONEER/UHB's managed cloud environment. The data held internally within the PIONEER Research Database is pseudonymised (with personal identifiers replaced with other values (pseudonyms), from which the identities of individuals cannot be intrinsically inferred). Pseudonymisation does not change the status of the data as personal data. Only anonymised data is released to our approved partners (where

identifiable data features are removed). The PIONEER Research Database does not contain direct and recognisable identifiers such as name, full address, images of a face or NHS number.

Risk will be managed proportionately when providing access to data that might, alone or through combination, lead to a risk of identification of an individual. A specific example is a postcode. PIONEER holds postcode data to support studies into equity and social deprivation. To reduce risk, a postcode will not be provided directly to researchers. Instead, PIONEER will provide a less specific geographical unit such as the Lower layer Super Output Area (LSOA),[128] or the associated data of interest such as the Index of Multiple Deprivation score.[129]

Diagnoses including rare diseases are included within PIONEER. A rare diagnosis may enable identification if combined with enough additional indirect identifiers. Access decisions will be evaluated on a case-by-case basis and appropriate restrictions will be placed on accompanying data that might significantly increase the risk of identification. Of note, PIONEER processes were developed after discussion with patients with rare conditions, and they explicitly supported the inclusion of rare diseases in PIONEER (even very rare diseases which risk identification due to rarity) to improve acute care services for these conditions.

2.2.7 Data quality

Each healthcare provider who uses electronic systems will conduct quality checks on their data to ensure that it is suitable to provide clinical care (the primary

purpose of data collection). Data quality assurance (QA) checks will also take place within PIONEER and to ensure the quality of data contained within datasets and PIONEER works towards meeting particular standards, including to the metadata catalogue (ISO 11179),[130] data quality (ISO 8000)[131] and quality assurance (ISO 25012).[132]

Metadata catalogue (ISO 11179)

A metadata catalogue is used to help the potential user of a database to understand what it contains. The referenced standard addresses the semantics of data, how data is represented and the registration of the data descriptions. ISO 11179 specifically specifies the kind and quality of metadata necessary to describe data as well as the management and administration of that metadata in a metadata registry. The purpose of this standard is to promote the standard description of data and a common understanding of data across and between organisations. PIONEER works to meet this standard through organising data using data element concepts, data elements, conceptual domains and value domains. The 11 179 standard also provides a way to depict relationships among concepts. We use this feature to represent relationships among data. PIONEER links to the HDR-UK Innovation Gateway, which allows researchers to explore datasets, tools, papers and related resources used in health research across the UK through a metadata catalogue, which includes many of the features described above (see https://www.healthdatagateway.org).

Data quality (ISO 8000)

Data quality is a broad term that encompasses a range of evaluation and data management techniques. Generally, to be of high-quality data must be considered to be accurate, complete, fit for the required purpose (meeting the needs of the end user) and assessable via a good quality management framework such as those described in ISO 8000. An example of how this will be met for PIONEER is that each table will be inspected to identify fields that are intended to link with other data, and these links will be tested.

Quality assurance (ISO 25012)

'Quality assurance' is the overarching term for a range of steps that are designed to ensure that a process meets a quality goal; this is distinct from 'quality control' that relates to testing the outputs of a QA process. The data quality management framework defines the activities to be undertaken to ensure that data is collected accurately and completely, meeting predefined quality targets and governance constraints. PIONEER data officers will be trained in current information governance good practice and work to a predefined standard operating procedure to meet this standard.

PIONEER improves data quality through checks applied during the processing stage, examples are to identify common data errors such as values that exceed the prescribed limit of characters, to ensure the values are in line and format with those in the NHS Data Dictionary and to ensure all mandatory data fields are

complete, including completeness and count checks on the number of NULL values.

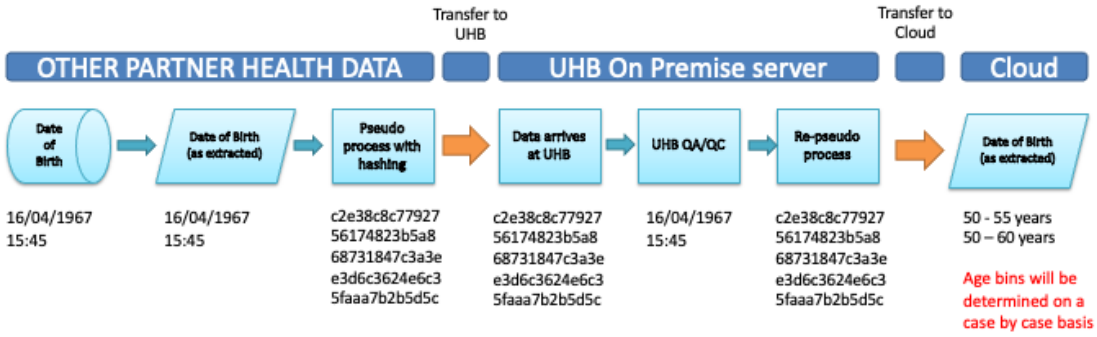
If any issues are identified, there is an iterative support loop in place to assist with feeding back and working through if it is a system or user error. The data is then re-extracted and the process of checking resumes until it is ready to stage.

Data deidentification

Pseudonymisation is needed for linkage purposes. As PIONEER processes healthcare data, industry standard best practices have been adopted, which ensures compliance with the Information Commissioner's Office and UK GDPR. These techniques are field level encryption (where the value is replaced with an encrypted version with a key) and hashing. See **Figure 2.1** for a diagram of this process. Hashing is a technique that uses standard functions based on mathematical algorithms to create new values. The selected value is represented by a 32-character hexadecimal string (combined letters and numbers), to enhance this security a random 'salt' is added. The data are then transferred to the PIONEER database via secure file transfer. Once received by PIONEER the data are reidentified to enable linkage (where applicable) and for QA and quality control checks, before being re-pseudonymised and moved to a secure safe-haven on Microsoft Azure for final processing. Prior to staging for research purposes, data is anonymised and K-anonymity modelling[133] is performed, to objectively assess the

potential for reidentification. The acceptable value will be assessed case by case with data controller and public oversight and agreement.

Figure 2.1: The process of pseudonymising health data in PIONEER



Legend. *The process of pseudonymising health data in PIONEER. This describes the process to move data using a salt code. Data partners contain identifiable health data, as shown by the date and time of birth. This is extracted from the record in an identifiable form, and then made pseudonymised using a salt code. The date and time of birth cannot be calculated from this hash. The data is then transferred by secure and encrypted pathways to University Hospitals Birmingham NHS Foundation Trust (UHB). At UHB, a proportion of records will have the data made reidentifiable, for QA/QC purposes, but it then remains in the hashed format. If that data is requested, the hash will be transformed into an age in years or into appropriate age bins, as determined on a case-by-case basis, and as approved by the Data Trust Committee (DTC).*

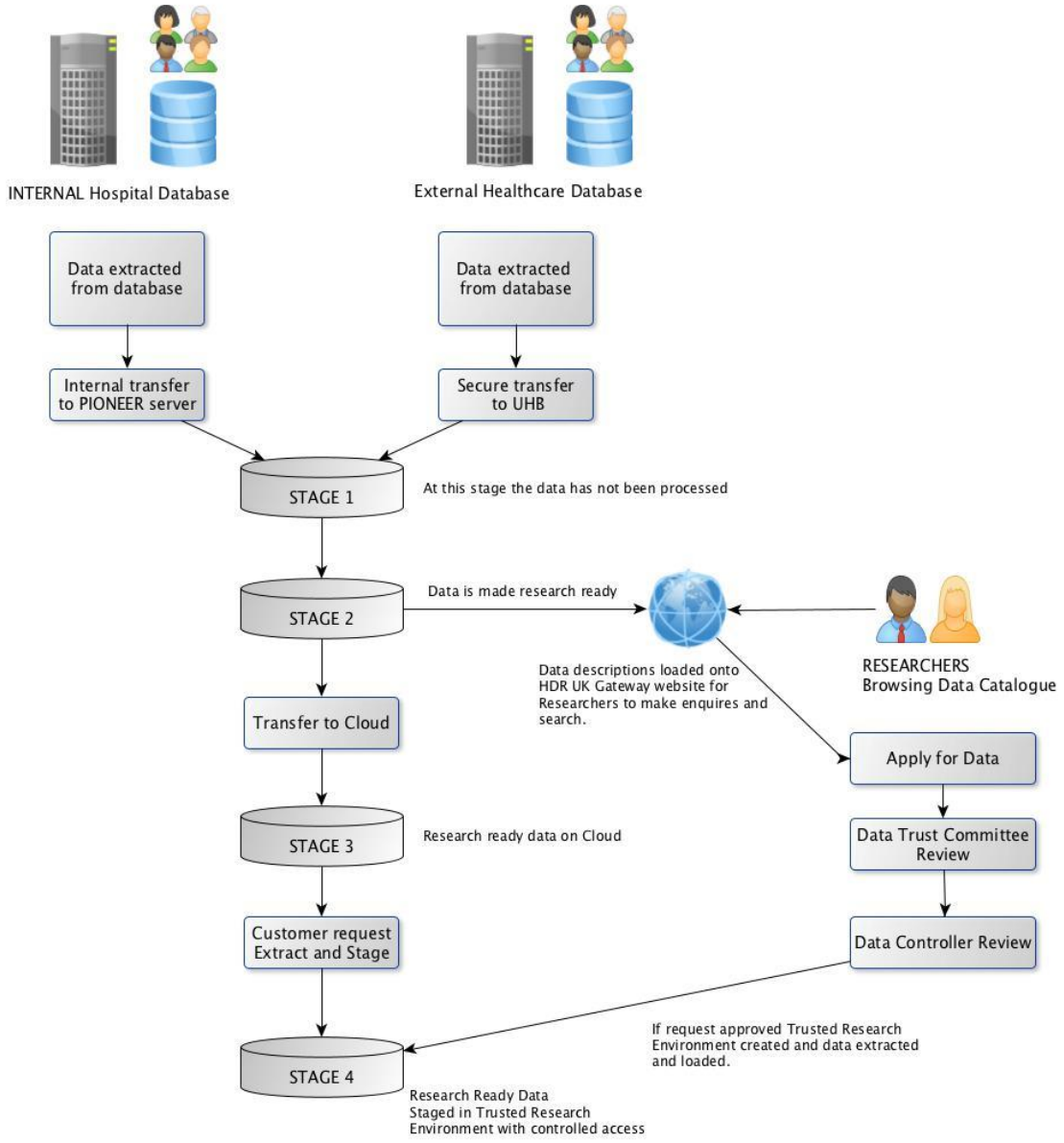
DTC=Data Trust Committee; QA/QC=Quality Assurance/Quality Control; UHB=University Hospitals Birmingham NHS Foundation Trust.

Figure 2.2 is a description of the data preparation process. Data made accessible via PIONEER will be necessary and proportionate to the purposes required, ensuring data minimisation. Data minimisation is assessed on a case-by-case basis. Data fields shared are only those deemed relevant to the specific research question and limited to what is necessary for the purposes for which they are processed as part of that research question. PIONEER can offer clinical expert consultancy to support this process. Approaches taken include to coarsening some potentially identifiable data (such as age into age groups) or to move a date

to the start of a week and adjust all date and time-stamped data accordingly. A risk-based approach to deidentification was adopted to assess the required level of protection, while ensuring the utility and scalability levels required were considered. The data controller maintains the overarching decision to approve the technique selected.

Deidentification of image files involves multiple steps for the three areas requiring attention—image filename; image metadata and identifiers burned onto the image. The image filename is checked to ensure it does not contain any patient identifiers, which are linkable outside the curating organisation, for example, the patient's NHS number would be replaced with a new unique key value associated with the patient's clinical data. The image metadata is examined, depending on the type of image (tags for the DICOM standard or EXIF fields for JPG images) to ensure they retain essential clinical information, such as modality, but do not contain any patient identifiers. Where found, identifiers are either removed or replaced with a new unique key value associated with the patient's clinical data. Lastly, the image is checked to ensure that it does not contain any burned-in patient identifiers. This is done using a combination of manual visual scanning and an evolving AI algorithm, which is being trained to take over this task. Burned-in patient identifiable data is manually removed by obfuscation, while ensuring that any burned-in clinical data is retained.

Figure 2.2: The data staging and access process



Legend. *The data staging and access process. Data can enter PIONEER from internal (UHB) and external data providers. At stage 1, data has been cleansed, normalised and sent to UHB in a pseudonymised form. At stage 2, the pseudonymised data is checked, cleansed and undergoes QA/QC by the PIONEER team. From this data, a metadata catalogue is formed, providing high-level data descriptions, which describe the kind of data PIONEER holds. The metadata catalogue is available for researchers to browse. At stage 3, the pseudonymised data is moved to the secure cloud, only accessible by PIONEER team members for further QA/QC processes. If a data request is received, it is reviewed by the Data Trust Committee (DTC) and PIONEER team. The PIONEER team perform a due diligence check and assess the request in terms of risk (see table 1). If the DTC do not support data access, no data access occurs. If the DTC support data access, a data licensing agreement is formed and the exact cut of data required is anonymised, extracted and staged in a bespoke trusted research environment (TRE). At stage 4, this staged and anonymised data can then be accessed by the researchers using specific log on processes and only approved data can leave the TRE (which would be aggregate data and not individual data lines).*

DTC=Data Trust Committee; QA/QC=Quality Assurance/Quality Control; TRE=Trusted Research Environment; UHB=University Hospitals Birmingham NHS Foundation Trust.

2.2.8 Data access

All requests for licensed data access will be reviewed against the principles of the Five Safes'[134] by the Data Trust Committee, the PIONEER management team and the PIONEER data controller. The 'Five Safes' framework is increasingly adopted by health data providers and includes an assessment of the safety of the project, safety of the researchers requesting access to the data, safety of the data (the risk of disclosure or reidentification) and safety of the data setting. PIONEER has contractual safeguards, with data access licensed to expressly preclude any attempts at reidentification and limit the use of the data to the purposes described within the contract, within a specific time frame. The final 'Safe' refers to safe outputs, ensuring the statistical results of data analysis are non-disclosive. PIONEER reserves the right to refuse an application or limit the data fields available, based on concerns around possible identification.

2.2.9 Data request pathways

This process was developed in collaboration with patient and public contributors.

Data requests will be considered from organisations, companies, researchers, members of the public, or any agency or body, referred to as Data Requestors.

All requests for licensed access to data will be considered against core principles for data access:

1. Benefit to patients, to the NHS, or society.
2. No due diligence concerns

3. Data requests are ethical, appropriate and are not excessive in the data requested nor include data which has more than remote possibility of being reidentified by other data held by the requestor or in the public domain—that is, data requests which pass the risk evaluation.

Data requestors complete a Data Request Form (DRF). The DRF mandates specific training before health data access. This includes reading the Data Security and Protection Toolkit[135] and the National Data Guardian's Review of Data Security, Consent and Opt-Outs[97] as well as taking an e-learning course for data security training. PIONEER will undertake due diligence checking for all data requestors. Requests are then assigned a Data Request Risk Rating: green for low risk, amber for moderate and red for a failed risk assessment. The rating will be based on the data requested, potential for risk and potential for patient gain. See **Table 2.2** for an overview of this process.

The DRF, due diligence and risk register will be reviewed by the PIONEER senior team, data controller and Data Trust Committee. The specific cut of data required for the project is deidentified and moved to the PIONEER TRE. The data requestor receives specific permissions to access that data within the terms of the Data License Agreement.

Table 2.2: An overview of the Data Request Form and data access considerations

Heading	Requirements
The Data Request Form	
A summary of the data request	
The project: Technical summary	Project title, aims, scientific rationale and background in technical language

The project: Lay summary	Project title, aims, scientific rationale and background in lay language
Patient and public involvement	To describe the patient and public involvement and engagement (PPIE) work completed so far and to offer the opportunity for PIONEER supported PPIE.
Expected value of the project to the NHS and general public	To describe how the project is likely to lead to patient and public benefit
Data requirements and analysis plan	This includes an exact description of the data fields required, whether aggregate or individual data lines are needed, and the justification for this. PIONEER offers the ability to perform analysis on behalf of the researchers. If the researchers wish to perform their own analysis, a description of techniques and tooling required is requested.
Security	Data access is only permitted with a data licensing agreement, but if necessary, anonymised data can be sent to an external Trusted Research Environment (TRE). The security arrangements for this TRE will be listed and reviewed by the PIONEER team, including whether specific ISO standards are met.
Expertise	Listed to ensure the researchers have the relevant training and expertise to conduct the analysis.
Dissemination plan	PIONEER supports open access of data outputs to ensure insights benefit as many people as possible. The 'Five Safes' includes an assessment of whether data outputs could lead to patient re-identification, so the DRF includes a description of how this will be avoided.
Due Diligence	
An assessment of the data requestor which is completed for all data access requests	
Human rights violations and significant harm	All Data Requestors undergo a due diligence assessment to determine evidence of serious human rights violations, arms manufacturing or trade and tobacco industry involvement
Controversies and data breaches	All Data Requestors undergo a due diligence assessment to determine evidence of data breaches, falsified scientific reports or involvement in significant controversies including financial irregularities and health and safety fines
Risk Assessment	
A summary of the potential benefit versus risk of the project, the researcher, the data and the data environment	
Benefit	Designated as clear benefit to NHS patients or society, potential benefit, or no potential benefit
Data	Designated as data which is aggregated or highly unlikely to or may lead to patient identification or data which has a realistic potential patient identification.
Security	Designated as provides evidence of data security which meet all requirements, or meet most requirements with additional support or does not meet data security requirements
Potential reputational risk to PIONEER	Designated as low, moderate or high based on due diligence check
Previous dealings	To determine the outcome of previous data access activities
Overall assessment of risk	Low, moderate or high with a recommendation to support or not support data access.

The DRF, due diligence and risk register will be reviewed by the PIONEER Director, Data Controller and Data Trust Committee. If data access requests are supported, a license for data access will be agreed and signed, pending contractual negotiations. The specific cut of data required for the project is de-identified and moved to the PIONEER TRE. The Data Requestor receives specific permissions to access that data within the terms of the Data License Agreement.

2.2.10 The Data Trust Committee

The Data Trust Committee (DTC) is an advisory function for PIONEER and acts as the public conscience of PIONEER, advising on data release decisions. A decision to support licensed data access by the DTC will lead to data access as long as contractual safeguards are in place. A decision not to support licensed data access by the DTC will be binding for PIONEER and no data will be shared.

The DTC will be made up of individuals recruited by application. All members of the DTC must declare all relevant conflicts of interest. The DTC will be assisted, when needed, by experts in relevant healthcare specialities, data research, information governance and UK data law. These experts will have an advisory capacity only and will not be voting members of the DTC. All data requests will be regarded as confidential. The DTC will discuss each data request form, due diligence and risk assessment and form a consensus decision whether to support the data request. The DTC will seek to form a unanimous decision regarding data access through discussion and reflection. Where this is not possible, non-unanimous decisions to support data access will require 80% of the DTC to support data access. A quorum

of at least half of the DTC (rounded up) is required for the DTC to convene and the DTC will generate lay summaries of their activity for public review.

2.2.11 Building a framework for proportionate, retrospective data release reviews.

In time, it is envisaged that the DTC will form proportionate review criteria, categorising some reviews as low-risk based on self-developed and tested procedures which might allow retrospective reviews of some data requests. However, this will only occur when the DTC have been operating for sufficient time to form a view about what a low-risk application is, and after specific ethical approval.

2.2.12 Ethical Considerations and Opting out.

PIONEER operates within Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') to process confidential patient information without consent. The rationale for using health data without consent was that, to be effective, PIONEER will include data from millions of patients and be fully representative of the patient population as a whole. PIONEER will include data from people who have died following acute care contacts and data from people who may not have the capacity to consent, so that the acute health journeys of more vulnerable adults and children also have the potential to benefit from innovation.

As this is an important consideration, the use of data without explicit consent was specifically discussed with more than 300 members of the public prior to the

development of PIONEER,[113] to specifically test if the majority of the public would support data use in this way.

2.2.13 Transparency

PIONEER is committed to open and transparent communications which will support and acknowledge patient and public input and help maximise access for high-quality collaborative research, including an Open Science approach and open access publication. PIONEER will provide data in the public domain regarding its operation and purpose.

2.3 Conclusion

This protocol paper outlines the working operations of PIONEER, the Health Data Research Hub in acute care. The ethically approved protocol has been devised to ensure patient and public voices are central in data access decisions, and that PIONEER processes reflect the wishes and concerns of patient and public stakeholders. For more information about PIONEER projects and outputs, see www.PIONEERdatahub.co.uk).

Chapter 3: Electronic prescribing systems as tool to improve patient care: A learning health systems approach to increase guideline concordant prescribing for venous thromboembolism prevention

This chapter has been published in BMC Medical Informatics and Decision Making entitled "*Electronic prescribing systems as tools to improve patient care: a learning health systems approach to increase guideline concordant prescribing for venous thromboembolism prevention*" [136] (see **Appendices for Chapter 3**, **Supplementary File 3.1**).

S. Gallier[1], A. Topham[1], P. Nightingale[2], M. Garrick[3], I. Woolhouse[4], M. A. Berry[5], T. Pankhurst[6], E. Sapey, corresponding author[7] and S. Ball[8]

1. PIONEER Health Data Research Hub in Acute Care, Department of Health Informatics, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK
2. NIHR Clinical Research Facility, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK
3. Department of Health Informatics, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK
4. Respiratory Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK
5. Acute Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK
6. Digital Healthcare and Department of Renal Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK
7. PIONEER Health Data Research Hub in Acute Care, University of Birmingham, Edgbaston, Birmingham, B15 2TH UK
8. HDR-UK Midlands Site and Better Care Programme, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB UK

Authors' contributions

SG contributed to study design, undertook data curation, data analysis and wrote the first full version of the manuscript. SB, TP, MB, IW, ES designed the study, collated data, performed some analysis, contributed to the manuscript writing through review. AT curated data and performed some statistical analysis. PN

curated data and performed some statistical analysis and helped write the manuscript through review. MG supported data collection. All authors amended the manuscript and approved the final version. All authors read and approved the final manuscript.

3.1 Introduction

Hospital Acquired Thromboembolism is defined as a venous thromboembolic event (VTE) (a deep vein thrombosis and/or pulmonary embolus) which was not present on admission but diagnosed within hospital or within 90 days of hospital discharge.[137] Hospital acquired thrombosis accounts for a significant amount of potentially avoidable morbidity and mortality[138] with an incidence rate of 9.7 per 1000 hospital admissions, with 71% diagnosed post-discharge.[139]

The risk factors for VTE during admission are well known,[140] there is an effective prophylactic therapy[138] and there are well-validated guidelines to assist assessment of the risk of VTE and where prophylaxis therapy should be prescribed[141]. However, rates of concordance with guidelines vary across international providers, from 16 to 85%.[142, 143]

In England, a Commissioning for Quality and Innovation (CQUIN) framework set a threshold rate for acute hospital providers to undertake risk assessments for at least 90% of inpatients each month in 2010-2011,[144] which increased to 95% by 2013.[145] This reporting is nationally mandated with each acute care hospital providing the number of adults admitted each month who have had a VTE risk

assessment and the number of adults admitted in total, with specific groups of patients excluded from this analysis.[146] A recent National Health Service report suggests that the majority of acute hospitals in England are meeting the target of 95% of patients having a VTE risk assessment.[147] However, there is a difference in completing a risk assessment and acting upon it (either prescribing low molecular weight heparin (LMWH) when it is indicated or not when it is not). Currently, there are no figures to describe or targets to ensure full VTE guideline compliance (assessment and action on assessment).

Prescribing errors include inappropriate or erroneous inclusion or omission of drugs and an inappropriate assessment of the potential harm from giving or omitting a treatment.[148] Not acting on a VTE risk assessment is a prescribing error. The potential reasons for prescribing errors are complex but studies suggest that most mistakes were made because of slips in attention, or because prescribers did not apply relevant rules.[149] A number of reports have highlighted strategies to improve prescribing practices[150] including education, prescription aids (both paper and computerised),[151] mandated prescribing[152] and prescriber feedback and audit.[153] Given the relative short-term placements of junior medical staff within a specific hospital, targeting individual prescribing may be less effective for a single centre than implementing systems change to enhance safety.[154]

It is important to note that some guideline-discordant prescribing behaviour may be appropriate depending on the clinical circumstance. For example, prophylactic

low molecular weight heparin might not be appropriate in the last few days of life or those who are chronically bed ridden. Not all discordant prescribing should be viewed as an error.

Electronic prescribing systems (EPS) have been shown to improve inpatient medication management, especially by reducing medicine-reconciliation, dose, and avoidable delay-of-treatment errors.[154, 155] It is less clear whether EPS can reduce venous thromboembolic (VTE) prescribing errors associated with guideline non-compliance[156] and whether this is sustained or can be improved with further support in the prescribing process.

We hypothesised that systemic prescribing interventions would be more effective in improving full VTE guideline compliance, compared to face-to-face educational interventions, and that these improvements would be sustained.

Prescribing interventions were:

- Feedback of individual performance of doctors with identification and interviewing outliers (known as the Junior Doctor Clinical Dashboard)
- An EHR systems approach of adding mandatory VTE steps to the EHR during the admission processes.
- A systems approach change to the EHR VTE assessment form after clinician feedback to reduce options to "work around" mandated prescribing proposals.

3.2 Methods

3.2.1 Ethical approval

This research was conducted with Health Research Authority and Research Ethical Approvals (East Midlands – Derby Research ethics committee, reference 20/EM/0158).

3.2.2 Setting

The hospital trust included in this study (University Hospitals Birmingham NHS Foundation Trust UHB)) is one of the largest NHS Trusts in England. The analysis made use of an in-house built, clinically-led EHR. This is a rules-based prescription-support system that includes all clinical documentation for admission, physiological and laboratory measurements, provides real-time drug prescribing checks and recommendations by triangulating physiological and laboratory results, comorbidities and prescribing data, as well as supporting institutional and individual audit of prescribing practices.

UHB reported a VTE risk assessment completed in 98.5% of admitted patients for 2019-2020[147] and has met all national targets since 2010. However, hospital staff wanted to ensure that these risk assessments were being acted upon, with full guideline compliance (a risk assessment and appropriate prescription and administration of LMWH when indicated, or no prescription of LMWH when not indicated).

Prior to the implementation of the VTE prophylaxis interventions described in the current paper, all staff received a hospital induction to ensure familiarity with procedures and policies. This included a specific induction talk with a focus on VTE assessments and the importance of prescribing LMWH. Additionally, there were rolling lectures held by Consultant Haematologists to reinforce learning. Online videos were available on prescribing LMWH along with other key clinical focus areas.

3.2.3 Patients

All emergency and elective adult admissions to the NHS Foundation Trust from January 2011 to October 2020 were included. Post first intervention, all data collection and analyses were prospective.

3.3 Prescribing practices outcome

The primary outcome for this study was full VTE guideline concordance within 24 hours, defined as a risk assessment completed and the recommended treatment prescribed, expressed as a proportion for each week. Guideline non-compliance was defined as no VTE assessment performed, or where the VTE risk score suggested prophylaxis was needed and yet it was not prescribed or VTE prophylaxis was not indicated, yet it was prescribed.

3.4 Interventions

Interventions were developed in discussion with hospital management, pharmacists, hospital doctors of all grades and specialties and bio-informaticians.

Interventions were designed after discussion with clinical specialists in that field and were compliant with national guidelines for patient care.

3.4.1 Intervention 1 – Education by individual feedback: The Junior Doctor Clinical Dashboard

The Junior Doctor Clinical Dashboard was developed utilising z-scores. For VTE prophylaxis this was based on their correct assessment and prescription of VTE prophylaxis on the PICS against current guidelines.[141] Z-scores were calculated following standard z-score methodology and explained in full in the online supplement (see **Supplementary File 3.2**)

Each doctor was grouped according to their grade to ensure fair comparisons. Any doctor with a z-score less than -3 or greater than +3 was considered an outlier. The doctors were selected from the extreme of both lowest and highest, moving towards the threshold of 3 standard deviations and were required to attend a face-to-face interview with a senior clinician and a senior member of Hospital Management, where any learning points, positive and negative, were shared. A written summary of the session was provided to the doctor and their educational supervisor. Following these interviews performance was reviewed after one month for the low performing end. If there was no significant improvement, the doctor was recalled to further interview and the process repeated. The Junior Doctor Clinical Dashboard was implemented in January 2013.

3.4.2 Intervention 2 – Electronic Prescribing: A mandatory action for VTE assessment and prescribing

The PICS EHR was updated so that following completion of a VTE assessment module, an automatic prescription proposal was generated for either mechanical prophylaxis, pharmacological prophylaxis or both. The admitting doctor could authorise the VTE prophylaxis prescribing proposal or delete it but no further prescriptions could be added or modified to that patient record until a decision had been made on the VTE prophylaxis. Data on each step was captured in a structured form. This intervention was implemented in January 2014.

3.4.3 Intervention 3 – Amending the mandated proforma following clinician feedback

The previous version of the EHS allowed for the admitting clinician to choose 'no reduced mobility' early in the VTE prophylaxis proforma and thus quickly circumvent the automatic proposal for prescribing. After a risk review and feedback groups, it was apparent that in general, these decisions did not reflect actual VTE risk. A systems approach change to the VTE assessment form was made in consultation with prescribers, where the position of 'no reduced mobility' was moved from a check box at the top of the assessment to a much lower down part of the dropdown list of contra-indications, meaning the majority of the VTE assessment was completed prior to reaching this risk criteria. This change was made in October 2015.

3.4.4 Further changes to prescribing practices

During the period of this analysis the Trust changed the drug of Low Molecular Weight Heparin prescribed due to low stock levels from the drug company

nationally, from enoxaparin to tinzaparin. Once the stock levels were restored the Trust switched back to enoxaparin. Whilst this was not an intervention, it required the doctors to be trained on the new medication so the effect of these changes was measured as it occurred during this analysis.

For VTE, two-years of data were assessed prior to the implementation of the first intervention to gain baseline until October 2020 (a period of 9 years of prescribing practices)

3.5 Statistical Analysis

Weekly values were used to avoid any day-of-the-week effect. The proportions were plotted against the weeks in chronological order. A probit transformation was applied to the proportions prior to analysis to achieve best fit of the assumptions required to then use a segmented linear regression model to determine whether there were significant step changes and/or significant changes in gradient at the times corresponding to the three interventions. Proportions at the start and end of each segment were estimated from this model and equivalent rates of change calculated by treating the change in proportions within each segment as linear. All analyses were performed using IBM SPSS Statistics Version 22.0 (Armonk, NY: IBM Corp.)

3.6 Results

Data from 235,005 admissions were included in total, which represented all admitted adult patients during the study period. The number of patient admissions admitted in each timeframe, and the basic demographics of the patients are given in **Table 3.1**. There were no significant differences in patient characteristics during the study period.

Table 3.1: Demographics for patient admissions

	Pre- intervention: 2 year run in period for data collection (Jan 2011 – Nov 2012)	**After intervention 1: introduction of Junior Doctor Clinical Dashboard (Nov 2012 – Feb 2014)**	**After intervention 2: introduction of mandatory VTE assessment and prescribing (Feb 2014 – Nov 2015)**	**After intervention 3: change in order of 'no reduced mobility' (Nov 2015 – Nov 2020)**
n	31,071	26,260	39,931	13,7743
Female, n (%)	14,740 (47.4%)	12,675 (48.3%)	19,135 (47.9%)	67,340 (49.0%)
Age (years)*	74 (59-86)	73 (57-85)	72 (57-84)	68 (53-80)

Legend. *Values are counts (and percentages), except for age where they are medians and quartiles.*

VTE= venous thromboembolic event

The number of prescribers during the period was 5503. Although the prescribers changed during this time (reflecting doctor's rotations across regions during their postgraduate training) the seniority of doctor grades represented in the Trust did not alter over the study period, (assessed using Chi Squared, see **Table 3.2**).

Table 3.2: The distribution of prescriber seniority in the four main time intervals

Time interval	Consultant	Specialty grade	Core medical trainee	Foundation doctor	Staff Grade
Pre-intervention: 2 year run in period for data collection (Jan 2011 – Nov 2012)	19%	32%	17%	29%	4%
After intervention 1: introduction of Junior Doctor Clinical Dashboard (Nov 2012 – Feb 2014)	18%	33%	15%	27%	7%
After intervention 2: introduction of mandatory VTE assessment and prescribing (Feb 2014 – Nov 2015)	17%	34%	14%	27%	8%
After intervention 3: change in order of 'no reduced mobility' (Nov 2015 – Nov 2020)	16%	33%	11%	32%	8%

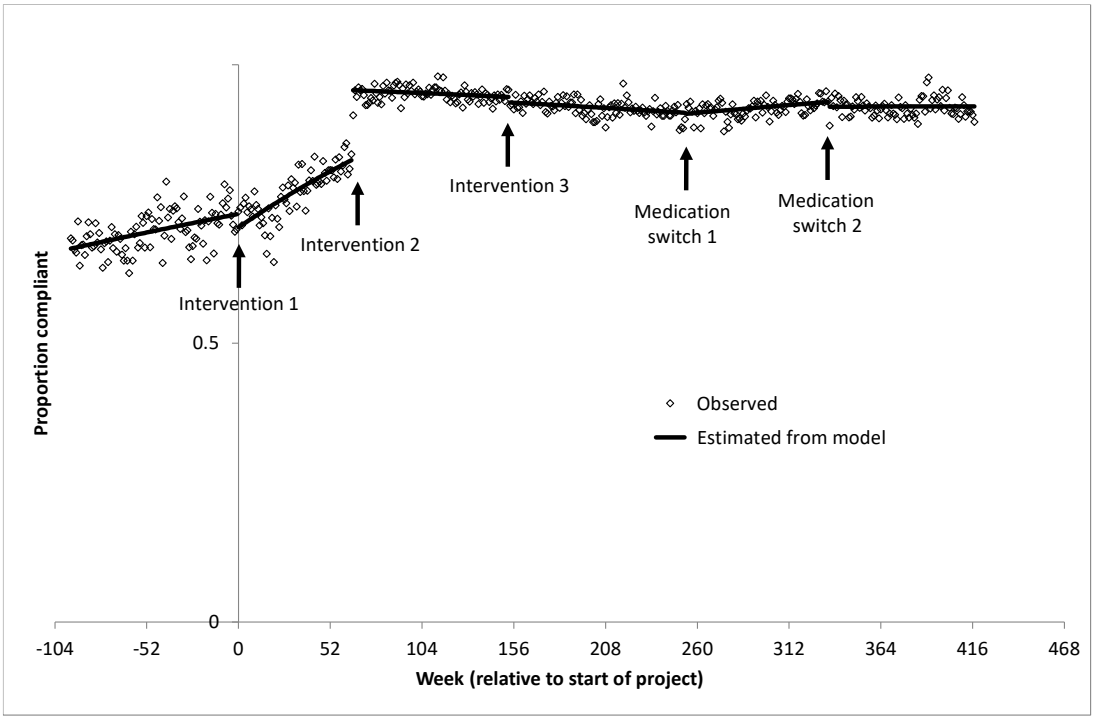
***Legend**. Distribution of user type in the four main time intervals (values are percentage frequencies). There were no differences in prescriber seniority over the study period.*

VTE= venous thromboembolic event

Full guideline VTE compliance (risk assessment and correct action) within 24 hours of recommendation was 70.2% (230 out of 327 in an average week) in the period prior to any intervention (Jan 2011 – Dec 2012). It increased significantly to 77.2% (312 out of 404) in the period after the initiation of the Junior Doctor Clinical Dashboard ($p<0.001$).

There was another significant increase in VTE compliance to 94.7% (425 out of 449) in the period following the change in the EPS with mandatory VTE assessment ($p<0.001$). There was a small but significant decrease to 92.2% (479 out of 520) following the amendment to relocate "no reduced mobility" from the initial VTE checklist to a subsequent drop-down box ($p<0.001$). Weekly compliance is shown in **Figure 3.1**.

Figure 3.1: The proportion of patients who were fully guideline compliant over time.



Legend: *Graph showing the proportion of patients who were fully VTE guideline compliant, meaning they had both a risk assessment and then were either appropriately prescribed VTE prophylaxis or not, depending on that risk assessment. The regression lines are fitted over the time periods before intervention 1 (education/doctor's dashboard), after intervention 2 (introduction of mandated VTE assessment action), after intervention 3 (change to PICS "no reduced mobility") and Medication switch 1 (from enoxaparin to tinzaparin and then return to enoxaparin (Medication switch 2) until study end.*

VTE= venous thromboembolic event

Table 3 summarised the VTE guideline compliance during six time periods. 1. Prior to any new intervention; 2. After the junior doctor dashboard interventions until the EHR mandate; 3. After the EHR mandate to the amendment of "no reduced mobility"; 4. After the amendment of the "no reduced mobility" option to the change from one LMWH to another brand; 5. To the use of this brand until a switch back to the original therapy; 6. From the reintroduction of the original therapy to study end.

Table 3.3: Observed full VTE guideline compliance over the study period

Time interval	Length of interval (weeks)	Total number of admissions	Total number with full VTE guideline compliance within 24 hours	Compliance (%)
Pre-intervention: Run in period for data collection (Jan 2011 – Nov 2012)	95	31,071	21,809	70.2
After intervention 1: introduction of Junior Doctor Clinical Dashboard (Nov 2012 – Feb 2014)	65	26,260	20,264	77.2
After intervention 2: introduction of mandatory VTE assessment and prescribing. (Feb 2014 – Nov 2015)	89	39,931	37,801	94.7
After intervention 3: change in order of 'no reduced mobility' (Nov 2015 – Oct 2017)	100	49,931	46,028	92.2
After medication change from enoxaparin to tinzaparin (Oct 2017 – Mar 2019)	81	45,092	41,583	92.2
After medication change back to enoxaparin to study end (Mar 2019 – Nov 2020)	83	42,234	38,955	92.2

Legend. Full VTE compliance is where a VTE risk assessment was completed and the correct action was taken. To be fully compliant, both VTE risk assessment and the correct action is needed. For example, non-compliance would be where a risk assessment was not completed, or a VTE assessment suggested LMWH was required and it was not prescribed or a VTE assessment suggested LMWH was not required (or contraindicated) and it was prescribed.

LMWH=Low molecular weight heparin, VTE= venous thromboembolic event

The estimates from the segmented linear regression model show that at time 0 (intervention 1: Junior doctor dashboard) compliance decreased from 73.2% to 70.7% but the rate of increase in compliance then changed from 3.4% per 52 weeks to 9.8% per 52 weeks. As a result, compliance increased to 82.9% by the time of the second intervention (the change in the EPS). After this intervention, there was a step increase to 95.4%. Subsequently, compliance remained relatively stable, although the third intervention (the change in order of "no reduced mobility") produced a small step decrease from 94.2% to 93.2%. All the changes are described in **Table 3.4**.

Table 3.4: Estimated compliance from the segmented linear regression model and equivalent rates of change immediately before and after each intervention and medication switch

Intervention	Estimated compliance			Equivalent rate of change in compliance per 52 weeks		
	Before	*After*	*p value*	*Before*	*After*	*p value*
1. Intervention 1. Introduction of a Junior doctor dashboard	73.2	70.7	0.035	3.4	9.8	<0.001
2. Intervention 2. Introduction of mandatory VTE assessment and prescribing.	82.9	95.4	<0.001	9.8	-0.7	<0.001
3. Intervention 3. Change in order of 'no reduced mobility'	94.2	93.2	0.010 (0.464)	-0.7	-1.0	N/A (0.085)
Medication switches						
1. Enoxaparin to Tinzaparin	91.4	91.2	<0.001	-1.0	1.4	<0.001
2. Tinzaparin back to Enoxaparin	93.3	92.5	0.023	1.4	0.0	0.011

Legend. Figures in parentheses for intervention 3 are p values if a slope change for intervention 3 is included in the model. As this was not significant, it was excluded and as a result the step change for intervention 3 became significant (the p value changing from 0.464 to 0.010). The final model includes five step changes and four slope changes.

VTE= venous thromboembolic event

3.7 Discussion

This study is the first to assess the cumulative impact of a series of interventions to improve full guideline compliant prescribing for VTE prophylaxis over a prolonged (nine-year) period, in a large NHS Trust which already offered a suite of educational tools such as lectures and videos and with high, and target compliant VTE assessment rates. This study highlights several important points.

First, that risk assessments do not automatically convert into an appropriate action following the assessment. Even after the introduction of the EPS system to mandate VTE risk assessment and appropriate prescribing, there was still a difference between completed risk assessments and prophylaxis prescribing. Altering reporting criteria to assess full guideline compliance may be a more effective means to improve patient safety.

Second, the interventions with demonstrable impact (the doctors dashboard clinic and rules based prescribing algorithms) require an EPS which supports dynamic evidence generation and application, enabling rapid learning and improvement based on data flowing from routine patient care. Both of these interventions were based upon the principles of a learning healthcare system, defined by the United States Institute of Medicine (now the National Academy of Medicine) as systems where "science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience"[157].

The most impactful intervention was a systems approach, with an EPS tool which mandated VTE assessment and prescribing as part of the admission process. These improvements were maintained at a higher level than seen following the individual feedback intervention, for the entire follow up period.

Our learning healthcare system included re-evaluating the PICS EPS to see where further improvements could be made. Feedback from prescribers and an assessment using the principles of human factors[158] suggested that the placement of "no reduced mobility" at the top of the risk assessment algorithm potentially suggested that this was true for many patients and an audit of care records suggested that this was being erroneously applied in some instances. In light of this, the EPS was altered to place this option at the end of the list of

contraindications, to ensure the prescriber considered co-morbidities and reason for admission prior to considering this option. This change did not have the impact expected on VTE compliance, and in fact contributed to a small, but significant, step decrease in full compliance. The reason for this is unclear and requires further study.

In this real-world study, there was a change in national LMWH availability, requiring a change in drug and prescribing rules (from enoxaparin to tinzaparin and then back to enoxaparin). These were introduced with traditional education but also necessitated a change in the EPS with a new series of prompts and rules. Despite the changes in prescribing practice, there was no significant change to full VTE guideline compliance, highlighting the resilience of the EPS systems-based approach.

This study did not assess why the systems approach was more effective than other interventions, but there are a number of potential reasons. As the Doctors Clinical Dashboard only identifies statistical outliers, only repeated failures to comply with guidelines will be identified. It is likely that many prescribing errors are made singularly and on an *ad hoc* basis, and these would not necessarily trigger a review. Educational and training events are one -off, and repetition in training has been shown to enhance performance.[159, 160] Healthcare is increasingly complex in terms of organisation and delivery[161] and our ageing population often are multi-morbid and poly-medicated, making healthcare decisions more complex.[162] The

complexity of healthcare and of patients might increase the potential for prescribing errors. A systems-based approach with prescribing support tools, that provides the same support for all prescribers on all occasions, is therefore more likely to impact on practice.

The current paper highlights the difference between VTE assessment compliance and full VTE guideline compliance (an assessment and appropriate prescribing action). While both are important, only the latter will reduce risk from hospital acquired thrombosis, but this information is not nationally collected or reported.

This study highlights the benefit of a paperless system, where real-time prescribing prompts can be given which account for clinical information, as opposed to static prompts, and where analysis includes all records overs a prolonged period. Some quality improvement papers in this field are based on standard audit procedures, where only a proportion of records are reviewed over a short period, leading to a significant risk of bias and making it unclear whether improvements were maintained.[163, 164]

Of note, the systems in place were unable to raise full VTE guideline compliance to 100%, and full VTE guideline compliance plateaued at approximately 92% (with risk assessment completion remaining >95% throughout). The reason for the small but important discordance in VTE risk assessment completion and subsequent correct action are unclear, but a further suite of electronically delivered tools are in development to determine if this can be improved.

This study has many strengths. It includes all patients within the hospital, and thus captures a high number of prescriber events in an unbiased manner. It also describes practices for a sustained period of time (nine years in total) which provides considerable reassurance that the changes in prescriber behaviour were sustained even as the workforce changed.

The paperless EHS deployed at the NHS Trust provides real-time, instantaneous feedback to all prescribers, highlighting the need for a VTE risk assessment, preventing further prescribing until this is completed and the suggested prescription is either approved or deleted. There are then further, automatically generated prompts every 24 hours to review the risk assessment. There are a number of reported interventions which provide retrospective feedback on VTE risk assessment and prescribing practices. These include a mandatory field within the electronic discharge system that record whether a VTE risk assessment on admission took place, the study of hospital coding on discharge or through audit [165]. These provide the opportunity for learning but do not improve compliance or reduce risk for the patient included in the event. Other studies have suggested a VTE nurse specialist can provide real time feedback, reviewing notes in areas of low compliance and high risk.[166] This requires a significant workforce investment to operationalise a twenty-four hours a day, seven days a week service. An EPS solution is available to all, at all times.

This study also has limitations. All prescribing episodes were considered the same, while some guideline-discordant prescribing behaviour may be appropriate depending on the clinical circumstance. The study did not assess whether the improvement in prescribing practices benefited some patient groups or some specialities more than others. Nor did it assess whether the change in prescribing practices was associated with an improvement in patient outcomes (such as a reduction in VTE events) or reduced healthcare costs. Other studies have focused on in-patient HAT events and shown a reduction in the proportion of HAT attributable to inadequate thromboprophylaxis following an intervention with increased guideline compliance [150] suggesting there would be significant clinical benefit from these interventions.

In summary, the use of mandatory assessment rules for VTE prophylaxis within an electronic prescribing system and continuous monitoring and feedback was successful in delivering and sustaining improved concordance between guidelines and prescribing practices in a large secondary and tertiary care hospital. Further work is required to determine whether these methods can be translated to other hospitals and whether these tools can be successfully used to improve performance in other areas. However, the significant and sustained impact demonstrated suggests this learning health systems approach, applied using routine clinical data to inform and refine practice, may demonstrate patient benefit across all areas of prescribing.

Chapter 4: The Impact of Electronic Order Communications on Laboratory Turnaround Times in acute hospital care

This chapter has been published as a pre-print in medRxiv entitled "*The Impact of Electronic Order Communications on Laboratory Turnaround Times in Acute Hospital Care*".[167] The paper is undergoing preparation for consideration to be published with *Health Information Science and Systems*.

S. Gallier[1, 2, 3,4], X. Zou[5], F. Evison[1,6], J. Hodson[1,6,7], J. Atia[6], C, Webster[8], M. Garrick[9], J. Coleman[10,11], T. Pankhurst[12], S. Ball[10], K. Nirantharakumar[13], E. Sapey[1,2,3,4,14]

1. PIONEER Health Data Research Hub in Acute Care, Department of Research Development & Innovation, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK
2. National Institute for Health Research (NIHR) Midlands Applied Research Collaborative, University of Birmingham, B15 2TT, UK.
3. National Institute for Health Research (NIHR) Midlands Patient Safety Research Collaboration, University of Birmingham, B15 2TT, UK.
4. National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, University of Birmingham, B15 2TT, UK.
5. Informatics Department, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK
6. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK.
7. Institute of Translational Medicine, Queen Elizabeth Hospital, Birmingham, UK.
8. Department of Laboratory Medicine, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK
9. Department of Strategy and Quality Development, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK.
10. Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK. MBChB, MA, MD, FRCP.
11. School of Medicine, University of Birmingham, Birmingham, West Midlands, UK.
12. Digital Healthcare and Department of Renal Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK.
13. Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK.
14. Acute Medicine, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK.

Authors' contributions

S Gallier contributed to study design, undertook data curation, performed statistical analysis and wrote the first full draft of manuscript. X Zou, J. Hodson, F Evison, J Atia, J Coleman, T Pankhurst, E Sapey contributed to study design, collated some data, performed some analysis, and contributed to manuscript writing through review. X Zou, J Hodson and F Evison curated some data and supported some statistical analysis. M Garrick supported data collection. All authors amended the manuscript and approved the final version.

4.1 Background

With global health systems under significant pressure, there is considerable interest in increasing the productivity and efficiency of healthcare services. Clinical laboratory services (such as Biochemistry, Haematology, and Immunology) are a vital component of healthcare provision, with up to 70-80% of all healthcare decisions affecting diagnosis or treatment involving a laboratory investigation.[168] The number of laboratory tests requested across both community and hospital healthcare settings is increasing,[169, 170] potentially reflecting the increasing complexity of patients living with multiple long-term conditions.[171, 172] Rapid laboratory test results can facilitate decisions to discharge, treat and admit, including escalation of care decisions. Consequently, the laboratory turnaround time (LTAT) is an important marker of a laboratory service, and is often used as a

key performance indicator in healthcare settings.[173-175] LTAT is usually defined as the time from receiving a specific test request to reporting the result[176].

Digital healthcare technologies have been promoted as a means to improve the efficiency of care, but with recognition that robust clinical validation is necessary prior to widespread adoption.[177] Computerized Provider Order Entry (CPOE) systems are computer-assisted systems that replace a hospital's paper-based ordering system by automating medication, test, and sample ordering processes.[178] Studies assessing the impact of CPOE on medication prescriptions have consistently shown improvements in error rates and adverse drug interactions.[179-184] Studies have also examined the impact of CPOE in rationalising test requests to reduce inappropriate medical investigations.[185, 186] The impact of CPOE on operational processes has been assessed in a limited number of studies across differing clinical settings with mixed results; even fewer focus on emergency departments but those have shown a direct correlation with wait times to medication delivery for high acuity patients and discharge.[187, 188] However, the impact of CPOE on LTAT across a whole hospital system over time and the potential operational efficiency gains have not been assessed.

University Hospitals Birmingham NHS Foundation Trust (UHB) is one of the largest NHS Trusts in England, providing direct acute services and specialist care across four hospital sites including the Queen Elizabeth Hospital Birmingham (QEHB). QEHB uses an Electronic Health Record (EHR) called Prescribing Information and

Communications System (PICS), a rules-based prescription-support system that includes clinical documentation; all physiological and laboratory measurements; provides real-time drug prescribing checks and recommendations; as well as supporting institutional and individual audit of healthcare processes. Over a period of seven years, QEHB progressed from entirely paper laboratory orders to a paperless system. The first ward to go live with electronic blood test ordering via the CPOE system (described below) was on 1st January 2016. The roll-out then continued until the system was live on a total of 39 clinical areas, with the last going live on 5th March 2019.

4.2 Objective

The study aimed to assess the impact of the CPOE system on LTAT within QEHB. Trends in LTAT for processing blood tests were analysed in the two-year period pre- and eighteen-month post-CPOE implementation for each ward. First, trends in changing LTATs were assessed across all in-patient areas, and then subgroup analyses assessed how changes to LTAT varied across differing specialty settings. Finally, a sensitivity analysis was performed for LTAT solely within the laboratory section of the pathway.

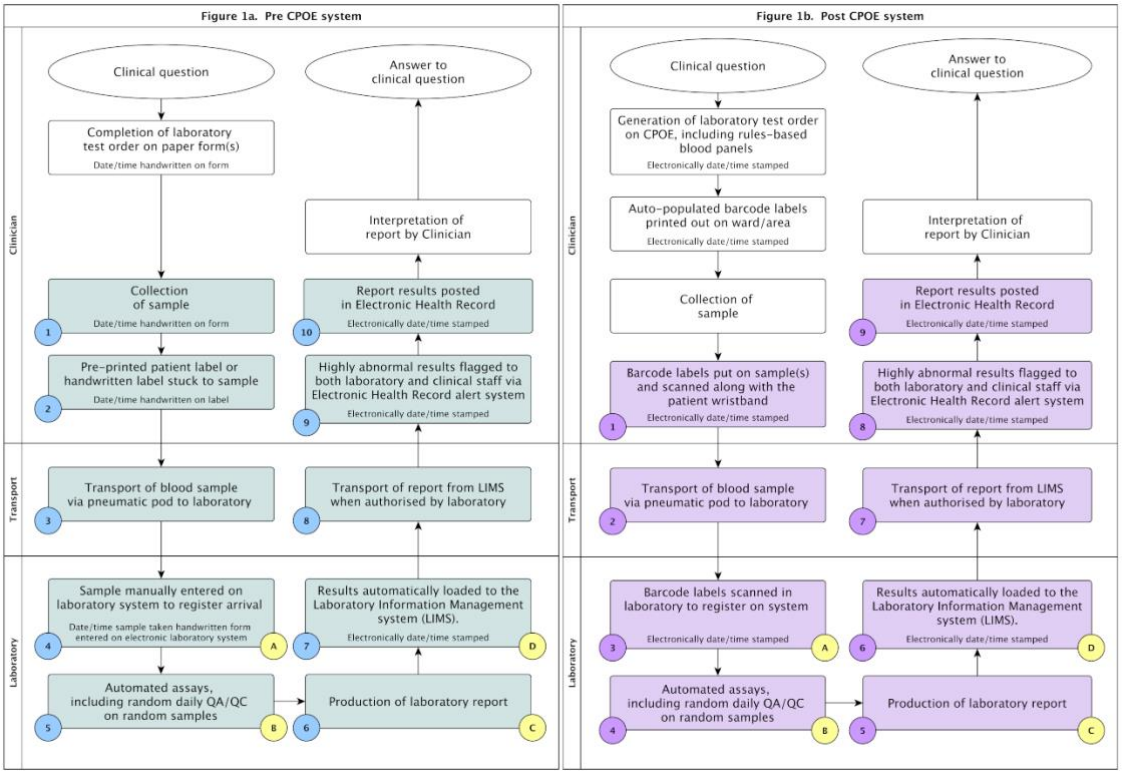
4.3 Materials and methods

The study was supported by PIONEER, a Health Data Research Hub in Acute Care. Ethical approvals for the study were provided by the East Midlands – Derby REC (reference: 20/EM/0158).

4.3.1 Laboratory processing and details of CPOE

The laboratory reporting cycle at QEHB prior to and after the implementation of CPOE is summarised in **Figure 4.1**, with annotation which describes time stamped points included in the current analysis and how the sensitivity analysis was conducted. **Figure 4.1a** represents sample collection and analysis processes pre-CPOE and **Figure 4.1b** post-CPOE implementation.

Figure 4.1: Request report cycle showing the process flows for blood tests ordered at QEHB pre- and post-CPOE.



Legend. *The process is shown from the forming of a clinical question through to the laboratory analysis until the results are provided back to the clinician for interpretation and decision-making. The process chart illustrates where the clock starts and stops for both the full end-to-end Laboratory Turnaround time (LTAT) from, as well as the Lab-LTAT, which comprised the period from the sample being registered into the lab system to results being automatically loaded ready for transport to the clinician. In Figure 4.1a, the pre-CPOE LTAT steps are represented by the blue boxes and circles. In Figure 4.1b the post-CPOE LTAT steps are represented by the purple boxes and circles. The Lab-LTAT sensitivity analysis steps pre- and post-CPOE are represented with yellow circles.*

CPOE=Computerised Order Entry System; LTAT=Laboratory Turnaround time; QA/QC=Quality Assurance/Quality Control.

CPOE was implemented across the hospital in a stepwise fashion from 21st January 2016 to 5th March 2019. CPOE introduced a range of changes to the process of recording the flow of samples through the hospital, as described in **Figure 4.1b**. Specifically, the introduction of wristbands with barcodes, electronic blood order forms that were auto-populated with patient details, rules-based blood panels and labels for blood test tubes. Other than the implementation of CPOE there were no other major changes in laboratory processing (measuring assays, reporting, quality assurance and quality control protocols) during the study period.

4.3.2 Study population

All in-patients attending the QEHB site between 1st January 2014 and 31st December 2019 who had blood samples taken on the premises were initially considered for inclusion in the study population. The end date of the study was selected due to the COVID-19 pandemic, which impacted normal processes at the hospital. Patients were then excluded if: i) they were admitted for dialysis; ii) the blood tests were taken by General Practitioners (GPs) and processed in the UHB pathology laboratories; or iii) the bloods were sent to external laboratories for analysis (send-away samples). Only the first result per sample was included in the analysis, however the number of samples per admission was not limited. Initially, 4,423,417 samples were considered, with 2,212,499 not meeting the exclusion criteria and therefore included in the analysis. A modified consort flowchart diagram provides a summary of how the samples were selected for inclusion in this study (**Supplementary Figure 4.1**).

4.3.3 Data capture

PICS has a comprehensive, time stamped audit database of all actions taken within the system. Data for each laboratory sample request occurring during admissions which met the inclusion criteria were extracted; specifically, the date and time that each request was both generated and reported on the system (recorded to the nearest millisecond), to allow calculation of the LTAT, along with the ward and specialty that made the request. Prior to the implementation of CPOE, the LTAT was defined as the time from the sample being collected, as per the handwritten label on the blood test tube, to the results being reported on the EHR (i.e., from step 1-10 in ***Figure 4.1a***). After CPOE implementation, the LTAT was defined as the time from the barcodes on the sample label/patient wristband being scanned on the ward, to the results being reported on the EHR (i.e., from step 1-9 in ***Figure 4.1b***). In addition to the overall LTAT, the laboratory-specific LTAT (Lab-LTAT) was also assessed as a sensitivity analysis, which was defined as the time from a sample being registered on the system after arrival at the laboratory to the results being reported on the EHR (see yellow step A-D in ***Figure 4.1a/b***).

For the primary analysis, the median LTAT was calculated across all samples collected within monthly intervals. Since the date of CPOE implementation varied by ward, the month numbers were standardised based on the date that CPOE was introduced on the ward that a sample was taken. For example, CPOE was introduced to the first ward on 21st January 2016; hence, “Month 0” for this ward would include samples collected between 21st January 2016 and 20th February

2016, with previous months assigned negative values, and subsequent months assigned positive values. For subgroup analyses, medians were calculated similarly for individual wards, or groups of wards within a specialty.

4.4 Analysis

Trends over time in the monthly median LTAT, and the impact of CPOE were analysed using a segmented linear regression of interrupted time series (ITS) approach.[189] ITS is a quasi-experimental design, intended to evaluate an intervention effect using longitudinal data. This is achieved by quantifying any trends over time in the pre-intervention period, to identify any ongoing baseline trends, and then accounting for these when measuring changes occurring post-implementation. A linear regression model was used, with the median monthly LTAT as the dependent variable and three covariates, which quantified the pre-CPOE gradient, the step-change occurring immediately post-CPOE, and the change in the gradient between the pre- and post-CPOE periods, respectively. A similar approach was also used to assess the changes in the monthly numbers of completed samples over the study period.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY) or R (R Core team, 2020), with $p<0.05$ deemed to be indicative of statistical significance throughout.

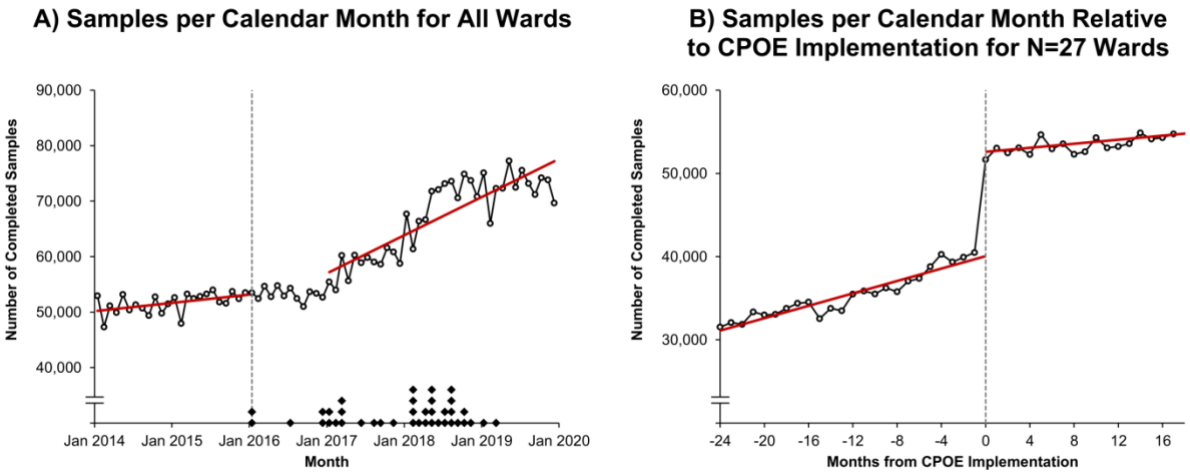
4.5 Results

4.5.1 Numbers of samples

CPOE was introduced to the first two wards on 21st January 2016, with five wards having CPOE by the end of 2016, 15 by the end of 2017, 37 by the end of 2018, and all 39 wards being live by March 2019.

The numbers of blood order samples per month was stable over the two years prior to CPOE being introduced (p=0.160), with 52,934 samples processed in January 2014 and 53,502 in December 2015 (see **Figure 4.2A**). However, after CPOE began to be rolled out, the number of samples per month began to increase progressively (p<0.001). Due to the staggered implementation of CPOE across the wards, it was difficult to identify the direct impact on CPOE on the numbers of bloods samples requested/received. A subsequent analysis considered only N=27 wards with at least 18 months of follow-up post-CPOE implementation, with the calendar months being centred on the date of CPOE implementation at a ward. Here, there was a step-change increase in the number of samples processed immediately after CPOE implementation, with an average increase of 12,541 samples per month (95% CI: 11,481 – 13,602, p<0.001), representing a 31% increase (***Figure 4.2B***). This higher number of samples was then sustained over the 18 months post-CPOE implementation

Figure 4.2: Monthly numbers of completed blood sample orders for inpatients at QEHB



Legend. *In Figure 4.2A, points represent the total numbers of completed blood samples within each calendar month and are plotted at the mid-point of the month. Trend lines are from a segmented regression model; this excluded data for the year after CPOE implementation commenced (i.e., 2016), which was treated as a roll-out period. The broken line represents the commencement of CPOE implementation, with diamonds on the x-axis indicating the month of implementation for each individual ward; points are stacked where implementation occurred at multiple wards in the same month. In Figure 4.2B, points represent the total numbers of completed blood samples, centred at the date of CPOE implementation for each ward. Only those N=27 wards with at least 18 months of follow-up post-CPOE were included in the analysis. Trend lines are from a segmented regression model.*

CPOE=Computerised Order Entry System; QEHB=Queen Elizabeth Hospital Birmingham.

4.6 Laboratory turnaround time (LTAT) analysis

Segmented regression analysis of LTAT only included the N=27 wards with at least 18 months of follow-up after the implementation of CPOE. For these wards, the average LTAT was 209.2 minutes (95% CI: 205.0 – 213.3) 24 months prior to CPOE implementation, and did not change significantly over the period prior to CPOE being implemented (p=0.623, **Table 4.1**, **Figure 4.3**). However, a step-change reduction in LTAT was observed immediately after the CPOE implementation, with a reduction in the median of 31.7 minutes (95% CI: 25.5 – 37.9, p<0.001). The median LTAT then remained stable over the 18 months post-CPOE, with no significant change in the gradient observed (p=0.085).

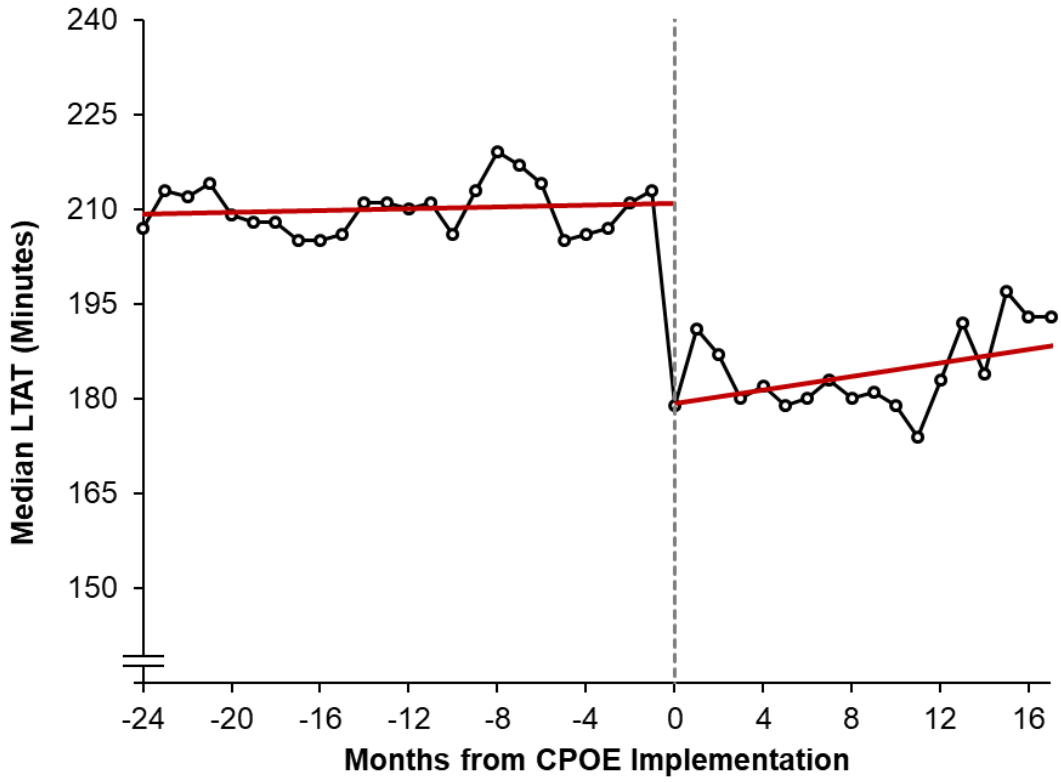
Table 4.1: Segmented regression model of the median LTAT for inpatient blood samples

	Coefficient (Minutes; 95% CI)	**p-Value**
Intercept	209.2 (205.0, 213.3)	**<0.001**
Gradient Pre-CPOE (per Month)	0.1 (-0.2, 0.4)	0.623
Step-Change Post-CPOE	-31.7 (-37.9, -25.5)	**<0.001**
Change in Gradient Post-CPOE (per Month)	0.5 (-0.1, 1.0)	0.085

Legend: *Results are from a segmented linear regression model of the monthly median LTAT over the 24 months pre- and 18 months post-CPOE implementation, as described in the Materials and Methods section. Only those N=27 wards with at least 18 months of post-CPOE follow-up were included, to maintain a consistent cohort. Coefficients are reported in minutes, and gradients are reported per calendar month. Bold p-values are significant at p<0.05.*

CI=Confidence Interval; CPOE= Computerised Order Entry System; LTAT=laboratory turnaround time.

Figure 4.3: Segmented regression model of the median LTAT for inpatient blood samples



***Legend**. Points represent the median LTAT within each calendar month, with Month 0 (and the broken line) designating the month in which CPOE was implemented. Only those N=27 wards with at least 18 months of post-CPOE follow-up were included, to maintain a consistent cohort. Trend lines are from a segmented regression model, as described in **Table 4.1**.*

CPOE= Computerised Order Entry System; LTAT=laboratory turnaround time

Previous publications have shown reduced impacts of CPOE in acute care environments [187]. To review whether changes in LTAT varied across clinical settings with the hospital, subgroup analyses were then performed within different groupings of wards (**Table 4.2** and **Figure 4.4**). Whilst there was variability in the impact of CPOE across these subgroups of wards, significant step-change improvements were still observed in the groups of medicine, surgery and non-critical care wards. CPOE was not found to be associated with a step-change in the median LTAT for the subgroup of critical care wards (p=0.185, **Figure 4.4a**). However, a significant reduction in the gradient (p<0.001) was instead seen, indicating that improvements in LTAT in the critical care wards were gradual, rather than occurring immediately post-CPOE implementation.

Analysis of individual wards identified a different effect of CPOE implementation in one acute clinical setting, namely the Acute Medical Unit (AMU). The LTAT at this ward was considerably shorter than the remainder of wards, with a median of 92.8 minutes (95% CI: 86.3 – 99.4) at 24 months prior to CPOE implementation, compared to 209.2 minutes (95% CI: 205.0 – 213.0) for the cohort as a whole. The implementation of CPOE within AMU was associated with a step-change increase in the median LTAT of 17.0 minutes (95% CI: 7.2 – 26.8, p=0.001, ***Figure 4.4e***). However, this was followed by a significantly more negative rate of change in LTAT (p=0.020), such that the estimated LTAT at 18 months post-CPOE implementation was lower than it had been immediately prior to CPOE implementation (77.1 vs. 87.9 minutes).

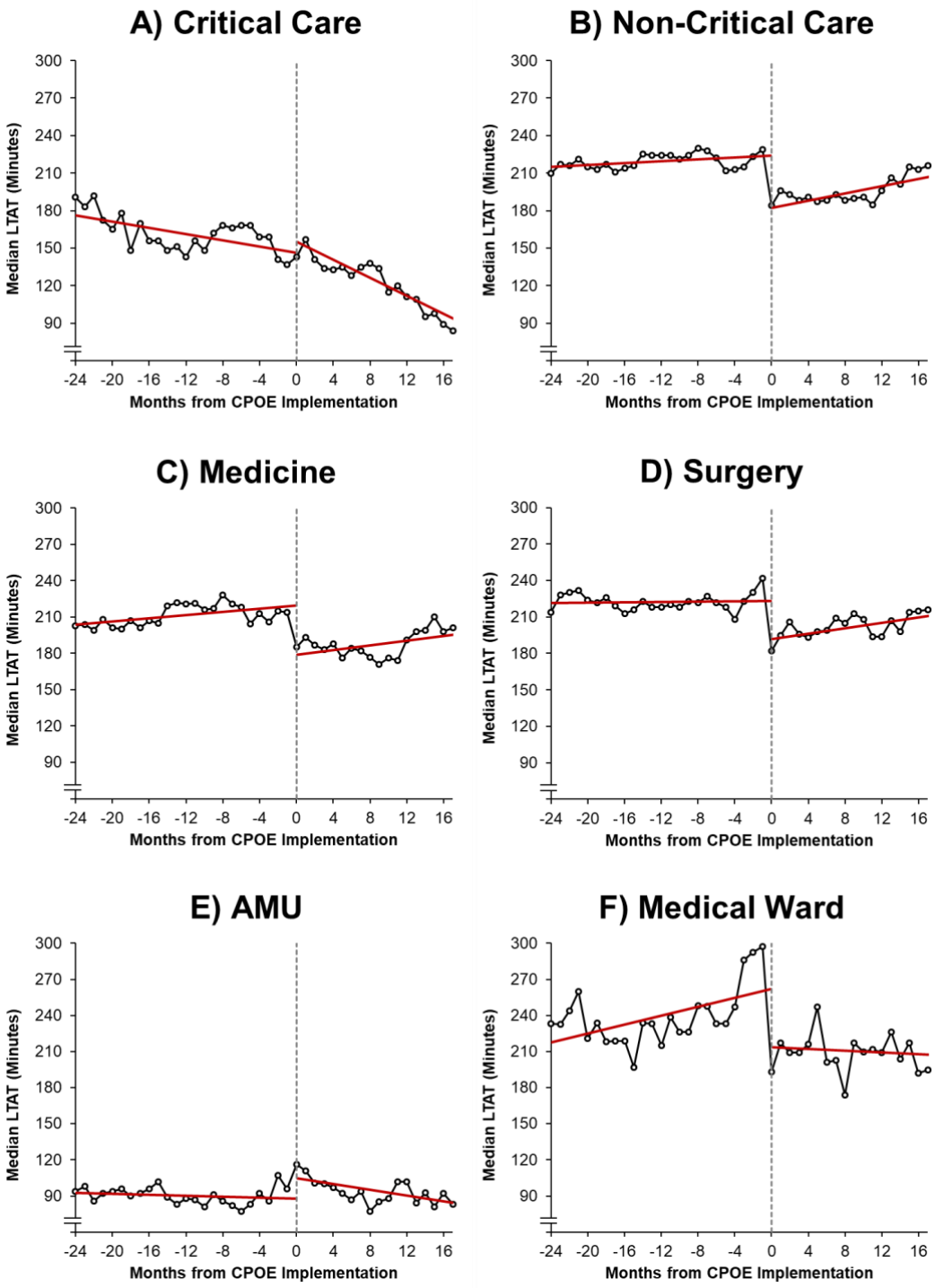
Table 4.2. Segmented regression models of the median LTAT for inpatient blood samples by specialty/area

	Coefficient (Minutes; 95% CI)	**p-Value**	**Coefficient (Minutes; 95% CI)**	**p-Value**
	Group 1 Critical Care		Non-Critical Care	
Intercept	177.5 (168.6, 186.4)	<0.001	214.6 (209.3, 219.9)	<0.001
Gradient Pre-CPOE	-1.2 (-1.9, -0.6)	<0.001	0.4 (0.0, 0.7)	0.047
Step-Change Post-CPOE	8.9 (-4.4, 22.3)	0.185	-41.8 (-49.8, -33.9)	<0.001
Change in Gradient Post-CPOE	-2.4 (-3.5, -1.2)	<0.001	1.1 (0.4, 1.8)	0.003
	Group 2 Medicine		Surgery	
Intercept	203.0 (195.9, 210.2)	<0.001	221.4 (215.2, 227.7)	<0.001
Gradient Pre-CPOE	0.7 (0.2, 1.2)	0.011	0.1 (-0.4, 0.5)	0.744
Step-Change Post-CPOE	-40.7 (-51.4, -30.0)	<0.001	-31.4 (-40.8, -22.0)	<0.001
Change in Gradient Post-CPOE	0.3 (-0.6, 1.2)	0.494	1.0 (0.2, 1.9)	0.012
	Group 3 AMU		Medical Ward	
Intercept	92.8 (86.3, 99.4)	<0.001	215.8 (199.6, 232.0)	<0.001
Gradient Pre-CPOE	-0.2 (-0.7, 0.3)	0.381	1.9 (0.7, 3.0)	0.002
Step-Change Post-CPOE	17.0 (7.2, 26.8)	0.001	-48.5 (-72.7, -24.2)	<0.001
Change in Gradient Post-CPOE	-1.0 (-1.8, -0.2)	0.020	-2.2 (-4.3, -0.1)	0.038

***Legend**. Results are from segmented linear regression models of the monthly median LTAT times over the 24 months pre- and 18 months post-CPOE implementation, as described in the Materials and Methods section. Separate models were produced for each of the specialty groups/areas. Analyses of Group 1 and 2 include only those N=27 wards with at least 18 months of post-CPOE follow-up, to maintain a consistent cohort; analysis of Group 3 is based on individual wards. Coefficients are reported in minutes, and gradients are reported per calendar month. Bold p-values are significant at p<0.05.*

CI=Confidence Interval; CPOE= Computerised Order Entry System; LTAT=laboratory turnaround time.

Figure 4.4. Segmented regression models of the median LTAT for inpatient blood samples by specialty/area



Legend. *Points represent the median LTAT within each calendar month, with Month 0 (and the broken line) designating the month in which CPOE was implemented. Figures A-D include only those wards with at least 18 months of follow-up post-CPOE implementation, to maintain a consistent cohort; Figures E-F represent data for individual wards. Trend lines are from a segmented regression model on the stated specialty/area, as described in Table 4.2.*

AMU=Acute Medical Unit; CPOE= Computerised Order Entry System; LTAT=laboratory turnaround time.

4.7 Sub-section sensitivity analysis - Laboratory turnaround time (Lab-LTAT)

A sub-section analysis was completed, which only assessed the turnaround time within the laboratory, namely the Lab-LTAT. The median Lab-LTAT was found to show a greater improvement than the overall LTAT after the implementation of CPOE, with a step-change reduction of 52.5 minutes (95% CI: 47.9 - 57.0, p<0.001, **Table 4.3** and **Figure 4.5**). Supplementary Lab-LTAT analyses were conducted on the specialty/areas explored in **Table 4.2** (**Supplementary Table 4.1** and **Supplementary Figure 4.2**). These analyses consistently found step-changes were in Lab-LTAT to be larger than those identified in the analysis of the overall LTAT. Interestingly, analysis of AMU did not find a significant step-change increase in Lab-LTAT (p=0.285), with the median Lab-LTAT remaining consistent over the whole study period for this ward.

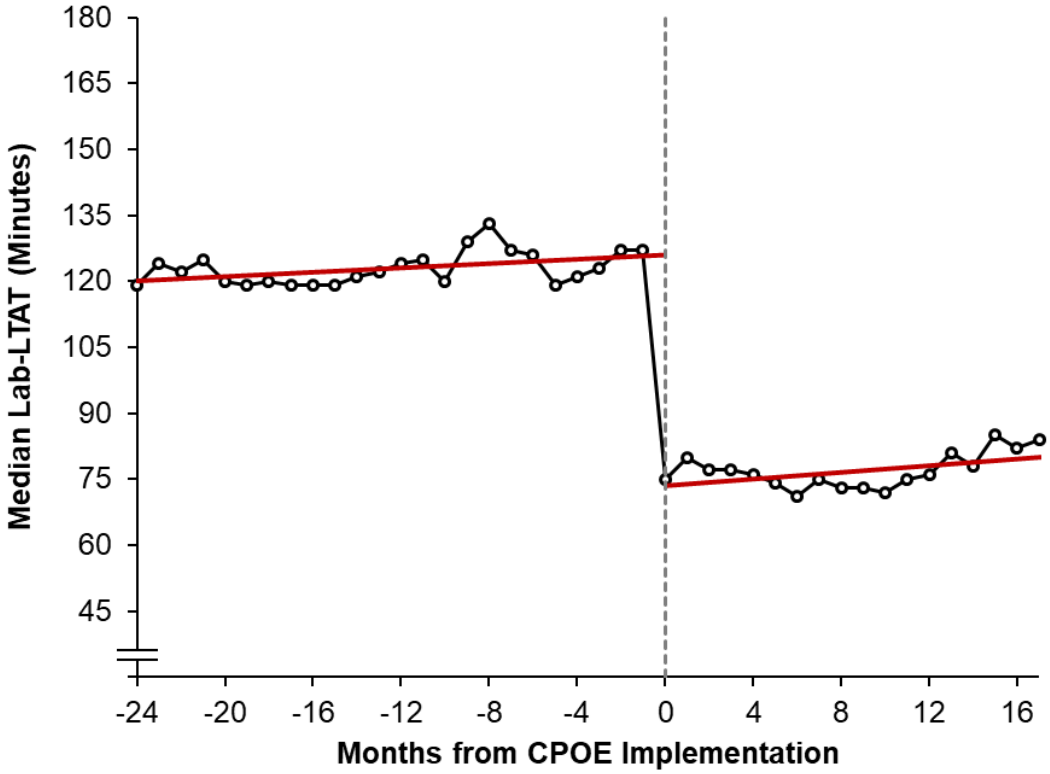
Table 4.3. Segmented regression model of the median turnaround times for inpatient blood samples solely within the laboratory (Lab-LTAT).

	Coefficient (Minutes; 95% CI)	**p-Value**
Intercept	119.8 (116.8, 122.9)	<0.001
Gradient Pre-CPOE (per Month)	0.2 (0.0, 0.5)	0.024
Step-Change Post-CPOE	-52.5 (-57.0, -47.9)	<0.001
Change in Gradient Post-CPOE (per Month)	0.1 (-0.3, 0.5)	0.490

***Legend**. Results are from a segmented linear regression model of the monthly median Lab-LTAT over the 24 months pre- and 18 months post-CPOE, as described in the Materials and Methods section. Only those N=27 wards with at least 18 months of follow-up post-CPOE implementation were included, to maintain a consistent cohort. Coefficients are reported in minutes, and gradients are reported per calendar month. Bold p-values are significant at p<0.05.*

CI=Confidence Interval; CPOE= Computerised Order Entry System; LTAT=laboratory turnaround time

Figure 4.5. Segmented regression model of the median turnaround times for inpatient blood samples solely within the laboratory (Lab-LTAT).



Legend. *Points represent the median Lab-LTAT within each calendar month, with Month 0 (and the broken line) designating the month in which CPOE was implemented. Only those N=27 wards with at least 18 months of follow-up post-CPOE implementation were included, to maintain a consistent cohort. Trend lines are from a segmented regression model, as described in Table 4.3.*

CPOE= Computerised Order Entry System; LTAT=laboratory turnaround time

4.8 Discussion

To our knowledge, this is the first study documenting the change in LTAT after the implementation of CPOE for laboratory tests across all clinical areas within a large acute hospital. In summary, this retrospective real-world patient data study demonstrated that CPOE implementation was associated with an overall step-change reduction in the median LTAT of 31.7 minutes, which was sustained over the 18 months post implementation. Although this varied by broad clinical specialty, most clinical areas either demonstrated a step-change reduction in

median LTAT or a change in the gradient of LTATs post CPOE, favouring faster reporting of results.

Potential reasons for the reduction in LTAT include the operational efficiency gains from replacing paper-based orders with computerised ordering systems. As orders are communicated effectively and there is less need for clarification due to illegibility, workflow is maximised. Barcodes interface with the CPOE system and speed up patient identification. Perhaps more significantly, barcodes streamline workflows in the laboratory by eliminating the time previously taken to manually load and enter the sample data prior to commencing the analysis. The clinical impact of a reduction in LTAT has not been explored here. However, potential impacts may include faster clinical decision making and reduced error rates. For example, if discharge is dependent on a single blood test the decision can be expedited by the timelier provision of the result.

Subgroup analyses by area generally found similar step-change improvements in LTAT after implementation of CPOE. However, no such improvement was observed for the Acute and Critical Care wards, with AMU specifically demonstrating a significant increase in LTAT immediately after CPOE was introduced. There are two potential factors that may have influenced this finding. Firstly, AMU already had an expediated process for blood sample testing prior to the implementation of CPOE, resulting in the median LTAT at the start of the period being less than half that of the remainder of the hospital (92.8 vs. 209.2 minutes). As such, there was less

scope for improvement in efficiency, compared to wards with a longer average LTAT. Secondly, for the hospital as a whole, the step-change reduction in Lab-LTAT was found to be larger than the overall LTAT, at 52.5 minutes and 31.7 minutes, respectively. This implies that the majority of the benefit of CPOE on LTAT occurred in the period after the sample arrived at the laboratory, and that the period between the sample being collected and arriving at the laboratory may actually have been increased when CPOE was introduced. This is in keeping with in other studies of CPOE in acute care settings, with a study by Syed et al. demonstrating turnaround times increasing in the Emergency Department (ED) following the implementation of CPOE,[187] whilst Fernando et al, in a qualitative study of CPOE, suggested that the complexity of the acute environment made it vulnerable to disruption following the introduction of any new service.[190] Since the Lab-LTAT for AMU was not significantly impacted by the implementation of CPOE, likely since it was already at near-peak efficiency, this did not offset the increase in the time taken on the ward, resulting in the step-change increase in LTAT occurring after CPOE was introduced. However, despite this, a significantly increased rate of progressive improvement in LTAT was observed after CPOE implementation at both AMU, and Critical Care as a whole. Consequently, the median LTAT at 18 months after CPOE implementation was lower than it had in the prior period suggesting that, whilst this had an initial negative impact, CPOE was beneficial in the long-term.

As there were no other major changes to the conveyance, processing, reporting or QA of samples, the reduction in LTAT is most likely to reflect the impact of CPOE. The sensitivity analysis that focussed solely on processing within the laboratory (Lab-LTAT) supports this, as this excluded all other process steps except those within the laboratory. The Lab-LTAT results indicated a larger step-change reduction of 52.5 minutes (vs. 31.7 minutes for overall LTAT), indicating this element of the request cycle benefitted significantly from CPOE implementation. There is relatively little research into the impact of CPOE on hospital pathology services; however, this study suggests improvements in efficiencies. This is probably due to the automation enabled through the introduction of barcodes and orders being available electronically, although the study did not examine the potential new challenges this system created. An additional finding of this study was, a significant increase in the number of samples processed following the implementation of CPOE to a ward, equivalent to an additional 12,541 samples per week across the hospital as a whole, representing a 31% increase. That the LTAT did not lengthen, and rather was shortened significantly, despite this substantial increase in sample processing suggests the benefits of CPOE are resilient to service change.

The reasons for, and implications of the significant increase in the number of samples following the implementation of CPOE were not explored here. A report reviewing the Diagnostic Services for NHS England [191] and a Primary Care study [192] over a comparable period described an increase in clinical test ordering, so this

increase has been noted elsewhere in the NHS. However, the fact that the increase occurred directly after CPOE was introduced to a ward would imply that this change likely had an impact. A potential reason for this may be the CPOE system making it easier for samples to be ordered. The introduction of blood-panels within the system again may have contributed to this increase, as the electronic system could include additional tests than previously requested. Another factor might be the automatic ordering of daily blood tests without a clinical review.

The study demonstrates a reduction in LTAT in all clinical in-patient areas and specialities, however the time to the realisation of that impact from implementation varies significantly across the specialty areas. Although results were heterogeneous across the specialities and settings assessed, most areas saw a median reduction in LTAT of approximately 30 minutes occurring directly after CPOE implementation. This would provide an opportunity for expedited clinical decision making, and could improve patient flow, where results determined suitability for discharge.

This study has limitations. This is a single centre study, albeit a large hospital which cares for a diverse case mix of patients. No additional quantitative or qualitative evidence about the order entry system was collected as part of this study. This study did not examine the reasons for changes in LTAT across the clinical settings. This study was not undertaken as a prospective evaluation, but

rather takes retrospective data on the use of the computerised order entry system; however it does represent a naturalistic view of the diversity across numerous clinical settings over several years.

This study has considerable strengths. The QEHB is a large and complex hospital environment. All patients treated over a five-year period were included, with data comprising over two million samples. This supports the generalisability of these findings. Many studies evaluate shorter term results following intervention introduction. The longer-term evaluation presented here should help inform health care settings when making decisions to purchase CPOE systems.

4.9 Conclusion

This study demonstrates that the implementation of CPOE within an acute hospital improves efficiencies of care delivery where expedited blood results can enhance clinical decision-making including the determination of suitability for discharge. LTAT in acute care settings were initially adversely affected, but did improve subsequently, suggesting that the system changes in these complex settings need time for clinicians to establish new processes.

Establishing and implementing a hospital-wide CPOE has been a complex transformation affected by multiple differing factors. However, this study shows the operational efficiencies associated with such a system, with the potential for this to translate to improved patient flows. Understanding the likely reduction in

LTAT also provides information to support an economic evaluation of the implementation of such a system into a new setting.

Chapter 5: Applying a COVID Virtual Ward model, assessing patient outcomes and staff workload

This chapter has been published in Acute Medicine entitled "*Applying a COVID Virtual Ward model, assessing patient outcomes and staff workload*" [193] (see **Appendices for Chapter 5**, **Supplementary File 5.1**).

S Gallier[1], C Atkin[2], V Reddy-Kolanu[3], D Parekh[4], X Zou[5], F Evison[6], S Ball[7] & E Sapey[8]

1. PIONEER Technical Director, Lead for Research Analytics, Department of Health Informatics, Department of Research Development & Innovation, University Hospitals Birmingham NHS Foundation Trust.
2. NIHR Lecturer in Acute Medicine, Institute of Inflammation and Ageing, University of Birmingham.
3. Consultant in Acute Medicine, University Hospitals Birmingham NHS Foundation Trust.
4. Senior Lecturer in Acute Care, Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham.
5. Research Analytics, Health Informatics, University Hospitals Birmingham, NHS Foundation Trust.
6. Senior Research Analysis, Health Informatics, University Hospitals Birmingham NHS Foundation Trust.
7. Chief Medical Officer, Director of Better Care Programme, University Hospitals Birmingham NHS Foundation Trust.
8. University of Birmingham.

Authors' contributions

S Gallier contributed to study design, undertook data curation, data analysis and wrote the first full version of the manuscript. C Atkin, V Reddy-Kolanu and D Parekh assisted with clinical data insights, F Evison and X Zou analysed some the data. S Ball and E Sapey contributed to study design and contributed to manuscript writing through review. All authors approved the final manuscript.

5.1 Introduction

The global pandemic caused by SARS-CoV-2 continues to provide health challenges worldwide. During infection 'waves', affected areas experience a high number of hospital presentations and admissions[194], requiring significant reconfiguration of staff and health services to meet the demands for care.

On 13th January 2021, National Health Service England (NHSE) published a document which provided a standard operating procedure for a 'COVID Virtual Ward' (CVW), with an aim of enabling the safe discharge of patients with COVID-19 from the hospital setting to the community early upon presentation to hospital, with daily contact and safety netting. NHSE recommended that all areas should pursue the roll out of a COVID virtual ward model to reduce pressures on acute hospital services, and that the CVW should be delivered by the acute hospital.[195]

The recommended CVW model was as follows[195]: Subject to completion of a satisfactory exercise test, patients with oxygen saturations of 95-100% and low NEWS2 (< 3) and improving clinical trajectories could be discharged to a COVID virtual ward where clinically appropriate. Patients with saturations of 93-94% with improving clinical trajectories (symptoms, signs, blood results, chest x-rays), could also be considered for the COVID virtual ward where clinically appropriate. Patients with oxygen saturations of 92% or lower or experiencing moderate/severe shortness of breath would generally be unsuitable for early supported discharge,

unless the patient was stable and this represented their usual baseline oxygen saturation.

In the CVW model, patients are discharged home with an oximeter and asked to take three readings each day and to call a staffed hospital number immediately if they note a reading of less than 92%, or they should attend their nearest emergency department within an hour or call 999. The patient would be proactively contacted by phone every day (seven days a week, as they would be for a hospital-based ward round). At 14 days (or before if deemed clinically appropriate) patients would either be discharged from the CVW or receive a further clinical assessment if symptomatic. A friend or family member, or an NHS Volunteer Responder, would then return the oximeter for decontamination and reuse.

To deliver this model, the CVW telephone line requires staffing for at least 12 hours a day (8am–8pm) seven days a week with locally arranged provision of out of hours cover. These staff should be supervised by an experienced, clinically registered professional who is also responsible for making the proactive daily calls, i.e. virtual ward round. The CVW should have a named medical consultant or senior trainee (ST3+ doctor), usually an acute or respiratory physician.

This model, or similar, have been applied in a number of care settings. In June 2020, an article reported that of 200 patients managed on a CVW in a UK secondary care hospital, 13% of all cases re-presented to hospital, and 10% of all cases were readmitted.[196] In November 2020, a retrospective study of 273 COVID-

19 was published assessing a similar system, but with 5 days of virtual follow up rather than the 14 days described by NHSE, and an option for discharge without enrolment to the CVW for those at lowest risk.[197] The authors describe an 11% readmission rate and one death. A multi-site mixed methods study assessing clinical sites which had implemented a similar service suggested the cost of implementing such a service was approximately £400 to £553 per patient.[198]

These studies support the safety of the CVW system. However, there are implied assumptions; first that all patients would otherwise be admitted to hospital and second, that the provision of the CVW impacts positively on re-presentations (either reducing unnecessary readmissions or identifying where re-assessment is needed). Also, there are no descriptions of the patients who did not meet the CVW criteria, to understand the volume of patients who still required in-patient care. Implementation of such a system as the CVW has an opportunity cost, as staff have to be redeployed from other clinical areas and the reliance on acute or respiratory physicians to deliver the CVW may re-direct care from high intensity clinical environments during pandemic waves. Traditionally these care pathways would be assessed in randomised control trials with health economic reviews. In the absence of such trials, understanding both the "natural history" of those discharged who meet the CVW criteria and the care burden which remains in the hospital is important to place the staffing needs of the CVW in context.

Birmingham is one of the most ethnically diverse cities in the UK with a high burden of COVID-19 cases and COVID-19 associated mortality in all the UK COVID-19 waves.[199, 200]

The study was conducted to understand the potential impact of a CVW. The study hypothesis was that introducing a CVW system was would a significant burden to staff workload, without improving hard outcomes such as death and readmission.

The study objectives were:

- To retrospectively assess the proportion of patients who would have met criteria for a potential virtual ward
- To evaluate outcomes in patients with COVID-19 who were discharged within 24 hours of admission without the support of a CVW
- To assess the proportion of admitted patients meeting potential CVW criteria who required hospital level intervention, and their outcomes
- To estimate the additional time required to deliver a CVW service for patients who would have met criteria for management through CVW

Retrospectively, patients were labelled as either meeting or not meeting the criteria for inclusion in a putative CVW, based on reported criteria. Their outcomes and clinical pathways were assessed and the potential time and staffing levels needed to deliver such a system calculated in a hospital trust with a high burden of COVID-19 presentations.

5.2 Methods

This data study was supported by PIONEER, a Health Data Research Hub in Acute Care. All study activities complied with the ethical approvals provided by the East Midlands – Derby REC (reference: 20/EM/0158).

University Hospitals Birmingham NHS Foundation Trust (UHB), UK is one of the largest Trusts nationally, covering 4 NHS hospital sites, treating over 2.2 million patients per year and housing the largest single intensive care unit (ICU) in Europe. The Queen Elizabeth Hospital Birmingham (QEHB) is the largest hospital within UHB. UHB saw the highest number of COVID admissions in the UK (>10,000 confirmed cases by March 2021) and the highest number of patients ventilated, with an expanded ICU capacity of >200 beds.

5.2.1 Study population

Health data from all adults with a confirmed positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) swab result between 1st June 2020 and 31st January 2021 who attended the Emergency Department or Acute Medical Unit at QEHB at the time of or up to two weeks following a positive SARS-CoV-2 swab test were included. COVID cases were confirmed following a nasopharyngeal and oropharyngeal swab in all cases[201],processed in accordance with NHS guidance within UHB NHS laboratories [202].

UHB has built and runs its own electronic health record (EHR) and developed a structured electronic clerking proforma where all patients with suspected COVID-

19 could be identified on admission. For all patients, the results of the first positive swab were included but patient records were checked for subsequent positive swab results if associated with a subsequent admission. Mortality and patient admission status (discharged and alive, continued admission and alive) were assessed 28 days after the first positive swab result.

5.2.2 Data collection and variable definitions

Patient demographics and clinical data were collected from the QEHB EHR. Clinician confirmed co-morbidities were available from the EHR, the summary primary care record (Your Care Connected) and diagnostic codes derived from previous hospital episodes, including NHS Digital SNOMED CT coding[203], mapped to historically entered ICD-10 codes[204].

English Indices of Deprivation scores were calculated using postcodes [129]. Ethnicity was self-reported by the patient or their family members on admission, grouped as per national guidelines[205].

All patients with a positive COVID-19 swab admitted during the time period were included with no exceptions. No patients under the age of 16 are admitted to QEHB.

Results of exercise tests (40 step walk test which consisted of patients taking 40 steps around their assessment area (of any step length) and oxygen saturations were measured both before and after the 40 steps), physiological assessments,

chest radiograph reports and acuity scores were used to retrospectively determine whether a patient could have been suitable for a COVID virtual ward. Clinical trajectories were considered using the same parameters over the first 24 hours of admission. For the purposes of this study, patients with either oxygen saturations of 95-100% and low NEWS2 (<3) or with saturations of 93-94% with improving clinical trajectories over the first 24 hours of admission were considered suitable for a potential COVID virtual ward if they did not desaturate after completing a 40 step walk test below levels described above. Trajectories had to include oxygen saturations improving to >94% on room air without deterioration in NEWS2 scores to meet the CVW criteria, except where oxygen saturations of 92% or lower were compatible with baseline levels as demonstrated through previous monitoring. Decisions as to whether a patient would have met the criteria for a CVW were made against objective parameters by one clinically qualified person and ratified by another (both acute medicine trained), with blinding to all patient outcomes.

In all admitted cases, clinical note reviews were undertaken to assess whether any assessments or treatments were delivered which would preclude discharge and could not be given at home – these included intravenous therapies, supplemental oxygen or other respiratory support, initiation of treatment dose anti-coagulation subcutaneously or requirement for increased social care.

5.3 Outcomes

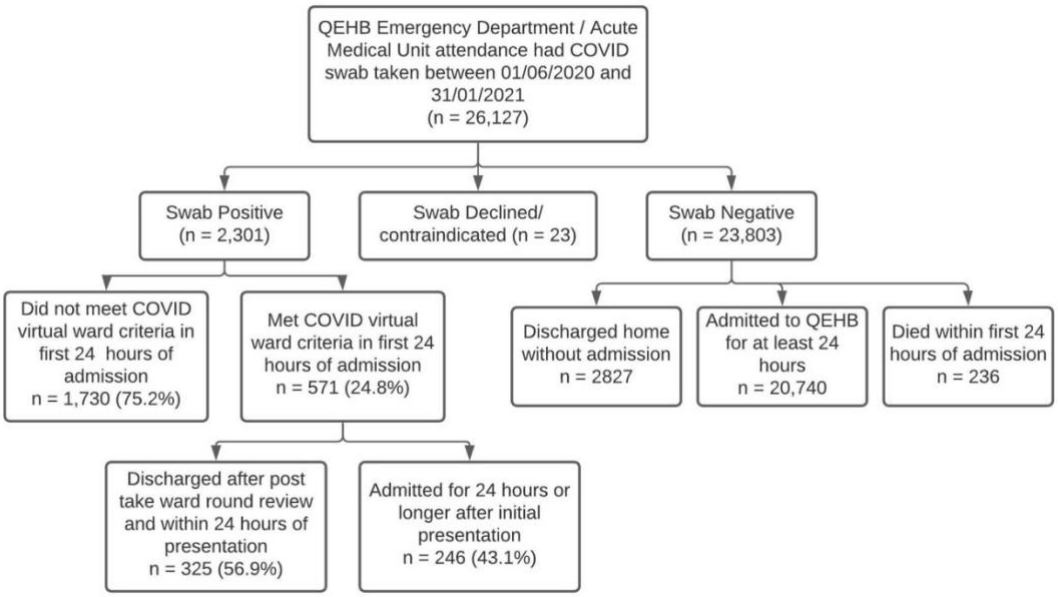
Primary outcome was re-presentation to QEHB (via the Emergency Department or Acute Medical Unit) for any cause, or death within 28 days of discharge, as per national reporting.[206] For those patients discharged from hospital, primary care records were reviewed and any patients who had died in the community within the censor period were noted. Those with an on-going admission were censored 28 days after a positive swab result.

5.4 Statistics

Statistical analysis was performed using STATA (SE) version 15 (StataCorp LLC, Texas, USA). Baseline characteristics for the total population are presented as mean (standard deviation) or median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. Continuous variables were compared between datasets using Mann-Whitney U tests. Categorical variables were compared using Fisher's exact and Chi-Square tests. Results were considered significant if the p-value was <0.05. There was no adjustment for multiple comparisons but exact p values are given.

5.5 Results

Figure 5.1: Modified consort diagram of patients presenting to the Emergency Department or Acute Medical Unit at Queen Elizabeth Hospital Birmingham



Legend. *Presentations were all presentations for the time period stated. Only those with a confirmed positive PCR SARS-CoV-2 Swab were included in pathway mapping. Those with no swab results (23 individuals where swabs were declined or contraindicated due to facial injury) were not included in the pathway analysis. Patients were divided into those retrospectively meeting potential COVID Virtual Ward criteria as described in the methods.*

QEHB=Queen Elizabeth Hospital Birmingham

Patient demographics

Overall demographics of all patients presenting with COVID-19 during the time period criteria are given in **Table 5.1**, divided by whether they would have met the criteria for a CVW. **Table 5.2** compares the demographics of patients who retrospectively met potential CVW criteria, comparing those discharged within 24 hours of presentation and those admitted for ≥24 hours. In general, patients admitted for ≥24 hours were more likely to be older, with 14.5% of patients aged >65 years in the discharged group, compared to 44.8% in the admitted group.

Those admitted were more likely to have significant comorbidities, including dementia, stroke, active malignancies and heart disease.

Table 5.1: Demographics of all swab positive patients, comparing patients who would or would not have met potential COVID virtual ward criteria

		Would have met the COVID virtual ward criteria	Would not have met COVID virtual ward criteria	**p-value**
	Overall Count	571 (24.8%)	1730 (75.2%)	
Sex	Female	309 (54.1%)	803 (46.4%)	**p = 0.001**
	Male	262 (45.9%)	926 (53.5%)	
Age	Median (IQR)	51 (37-68)	62 (50-78)	
	50 and Under	285 (49.9%)	445 (25.7%)	**p<0.001**
	51-65	129 (22.6%)	525 (30.3%)	
	66-75	52 (9.1%)	267 (15.4%)	
	76-85	54 (9.5%)	280 (16.2%)	
	Over 85	51 (8.9%)	213 (12.3%)	
Ethnicity	White	238 (41.7%)	823 (47.6%)	p = 0.124
	Black	30 (5.3%)	79 (4.6%)	
	South Asian	141 (24.7%)	425 (24.6%)	
	Mixed	14 (2.5%)	34 (2%)	
	Chinese	3 (0.5%)	9 (0.5%)	
	Any Other Ethnic Group	18 (3.2%)	61 (3.5%)	
	Unknown or declined to self-report	127 (22.2%)	299 (17.3%)	
IMD Quintile	1 (Most Deprived)	308 (53.9%)	943 (54.5%)	p = 0.765
	2	127 (22.2%)	351 (20.3%)	
	3	79 (13.8%)	266 (15.4%)	
	4	40 (7%)	108 (6.2%)	
	5 (Least Deprived)	16 (2.8%)	60 (3.5%)	
	Unknown	1 (0.2%)	2 (0.1%)	
Co-morbidities*	Chronic Kidney Disease	69 (12.1%)	259 (15%)	p = 0.087
	Dementia	38 (6.7%)	170 (9.8%)	**p = 0.022**
	Interstitial Lung Disease	5 (0.9%)	29 (1.7%)	p = 0.169
	Stroke or cerebrovascular	65 (11.4%)	243 (14%)	p = 0.105
	Ischaemic heart disease	108 (18.9%)	364 (21%)	p = 0.275
	Asthma	101 (17.7%)	343 (19.8%)	p = 0.262
	Hypertension	205 (35.9%)	903 (52.2%)	**p < 0.001**
	Diabetes	132 (23.1%)	586 (33.9%)	**p < 0.001**
	Any active malignancy	91 (15.9%)	334 (19.3%)	p = 0.072
	COPD	28 (4.9%)	224 (12.9%)	**p < 0.001**
	Atrial fibrillation	63 (11%)	236 (13.6%)	p = 0.108
BMI	Underweight	13 (2.3%)	40 (2.3%)	**p = 0.003**
	Normal weight	93 (16.3%)	338 (19.5%)	
	Overweight	91 (15.9%)	463 (26.8%)	
	Obese	78 (13.7%)	508 (29.4%)	
	Morbid obesity	21 (3.7%)	136 (7.9%)	
	Unknown	275 (48.2%)	245 (14.2%)	

***Legend**. Data is number (percentage) unless otherwise stated. Ethnicity was self-reported (see Methods). English Indices of deprivation (IMD) were calculated using postcode. Diabetes includes type 1 and type 2 diabetes.*

*COPD= Chronic Obstructive Pulmonary Disease. Patients could (and often did) have more than one co-morbid condition**

Table 5.2: Comparison of demographics between swab positive patients who met the potential COVID virtual ward criteria who were either discharged within 24 hours of attendance or admitted to hospital for > 24 hours

		Discharged within 24 hours	Admitted for > 24 hours	p-value
	Overall Count	325 (56.9%)	246 (43.1%)	
Sex	Female	185 (56.9%)	124 (50.4%)	p = 0.122
	Male	140 (43.1%)	122 (49.6%)	
Age	Median (IQR)	45 (34-57)	63 (44-80)	
	50 and Under	202 (62.2%)	83 (33.7%)	**p < 0.001**
	51-65	76 (23.4%)	53 (21.5%)	
	66-75	25 (7.7%)	27 (11%)	
	76-85	12 (3.7%)	42 (17.1%)	
	Over 85	10 (3.1%)	41 (16.7%)	
Ethnicity	White	114 (35.1%)	124 (50.4%)	**p = 0.010**
	Black	16 (4.9%)	14 (5.7%)	
	South Asian	90 (27.7%)	51 (20.7%)	
	Mixed	10 (3.1%)	4 (1.6%)	
	Chinese	1 (0.3%)	2 (0.8%)	
	Any Other Ethnic Group	13 (4%)	5 (2%)	
	Unknown	81 (24.9%)	46 (18.7%)	
IMD Quintile	1 (Most Deprived)	175 (53.8%)	133 (54.1%)	**p = 0.012**
	2	76 (23.4%)	51 (20.7%)	
	3	48 (14.8%)	31 (12.6%)	
	4	23 (7.1%)	17 (6.9%)	
	5 (Least Deprived)	2 (0.6%)	14 (5.7%)	
	Unknown	1 (0.3%)	0 (0%)	
Co-morbidities*	Chronic Kidney Disease	14 (4.3%)	55 (22.4%)	**p < 0.001**
	Dementia	6 (1.8%)	32 (13%)	**p < 0.001**
	Interstitial Lung Disease	2 (0.6%)	3 (1.2%)	p = 0.443
	Stroke or cerebrovascular	9 (2.8%)	56 (22.8%)	**p < 0.001**
	Ischaemic heart disease	32 (9.8%)	76 (30.9%)	**p < 0.001**
	Asthma	50 (15.4%)	51 (20.7%)	p = 0.097
	Hypertension	66 (20.3%)	139 (56.5%)	**p < 0.001**
	Diabetes	41 (12.6%)	91 (37%)	**p < 0.001**
	Any active malignancy	20 (6.2%)	71 (28.9%)	**p < 0.001**
	COPD	13 (4%)	15 (6.1%)	p = 0.250
	Atrial fibrillation	15 (4.6%)	48 (19.5%)	**p < 0.001**
BMI	Underweight	2 (0.6%)	11 (4.5%)	p = 0.436
	Normal weight	19 (5.8%)	74 (30.1%)	
	Overweight	22 (6.8%)	69 (28%)	
	Obese	21 (6.5%)	57 (23.2%)	
	Morbid obesity	8 (2.5%)	13 (5.3%)	
	Unknown	253 (77.8%)	22 (8.9%)	

Legend. *Data is number (percentage) unless otherwise stated. Ethnicity was self-reported (see Methods). English Indices of deprivation (IMD) were calculated using postcode. Diabetes includes type 1 and type 2 diabetes. COPD= Chronic Obstructive Pulmonary Disease. Patients could (and often did) have more than one co-morbid condition*

5.5.1 Outcomes for those discharged from hospital after initial review

Outcomes at 28 days for the 325 swab positive patients who would have met the COVID virtual ward criteria and were discharged within 24 hours were assessed.

281 patients (86.4%) were not readmitted and were still alive at 28 days post initial presentation. 44 patients (13.5%) re-presented within 28 days, 30 due to COVID-related symptoms (68.2% of re-presentations or 9.2% of those meeting CVW criteria) and 14 with a diverse list of conditions (**Table 5.3**). The median length of time at home prior to re-presentation was 2.5 days (IQR 1.5 – 5 days).

Table 5.3. Reasons for COVID-positive patients re-presenting to hospital within 28 days after initial discharge.

Readmission diagnosis	Number	Percentage of readmissions
COVID- associated re-presentation	30	68.20%
Poisoning	3	6.82%
Musculoskeletal / limb pain	3	6.82%
Fractured bone	2	4.55%
Congestive heart failure	1	2.30%
Epilepsy, unspecified	1	2.30%
Headache	1	2.30%
Pilonidal cyst with abscess	1	2.30%
Pulmonary embolism	1	2.30%
Syncope and collapse	1	2.30%
Total	44	

***Legend**. Data was collected via routine clinical coding but individual notes were checked to confirm medical reason for re-presentation by a consultant physician.*

Nine (20.5%) of the 44 patients were discharged within 24 hours of this second presentation. Of the COVID-associated re-presentations, the overall median length of stay in hospital was 4 days (IQR 1 – 7.5 days). Of the 44 re-presenting patients, 5 (11.4%) were transferred to ITU. One (2.3%) patient died within 28 days.

5.5.2 Outcomes for those who were admitted to hospital after initial review

Treatment pathways and outcomes for the 246 swab positive patients who met the potential COVID virtual ward and were admitted to hospital for ≥24 hours were assessed. 191 patients (77.6%) received an intravenous infusion including fluids or

antibiotics, and 94 patients (38.2%) required oxygen therapy after the first 24 hours of admission. 14 patients (5.7%) received therapeutic dose anticoagulation. 47 (19.1%) patients did not require intravenous treatment, supplemental oxygen or a community care assessment in hospital.

For these 246 patients, the median length of hospital stay was 4 days (IQR 2 – 9 days). 9 patients (3.7%) were transferred to intensive care. 26 patients (10.6%) died within 28 days of presentation. Of those 26 who died, 18 died during the inpatient stay.

Of those who survived to discharge, 215 (87.4%) patients were discharged to their own home (204 patients) or to their usual care home (11patients). 12 (4.8%) were discharged to a community hospital.

For the 47 patients who did not require intravenous therapies, oxygen or community care review, the median length of stay was 34 hours (IQR 28 – 40 hours). None of these patients were readmitted during the follow-up period. They were younger (median age 47 years (35-59), p=0.002) but with co-morbidities. A notes review revealed that these patients were not reviewed by an Acute Medicine or Respiratory consultant within the first 24 hours of their admission.

5.5.3 Comparing reported outcomes

Outcomes for patients discharged from hospital within the current study were compared to previous studies assessing CVW services (**Table 5.4**). No difference

was demonstrated in the proportion of patients re-presenting to hospital, or the proportion who re-presented who required ITU care or who died.

Table 5.4: Comparing outcomes in patients managed without CVW at Queen Elizabeth Hospital Birmingham to outcomes from published evaluations of CVW services

	Total number	Re-presented to hospital n (%)	Did not re-present n (%)	p-value	Admitted to ITU n (%)	p -value	Died n (%)	p value
UHB	325	44 (13.5%)	281(86.5%)		5 (1.5%)		1 (0.3%)	
Nunan et al[197]	273	31 (11.4%)	242 (88.6%)	p=0.458*	2 (0.7%)	p=0.693	1 (0.4%)	p=0.999
Thornton[196]	200	26 (13.0%)	174 (87.0%)	p=0.895**	*Not reported*			

Legend. *UHB numbers are those who retrospectively met the criteria for potential management through CVW and were discharged without CVW service, compared to those who were discharged to a CVW in Thornton and Nunan studies. Re-presentation is defined as reattendance at the Emergency Department or acute medical unit. Figures are compared using Fisher's Exact tests. * = comparing reported Nunan at el[197] and UHB re-presentation rates.**= comparing reported Thornton[196] and UHB reported re-presentation rates.*

5.5.4 Time required for service provision

If modelling virtual care requirements of the 325 patients sent home within 24 hours, assuming 14 days of follow-up (as per NHSE guidance) and a steady admission rate during the assessed time period, 4550 telephone calls would be required in the 245 days of the study period plus 14 days to allow for follow-up (259 days), an average of 18 calls per day. If each telephone contact required 25 minutes (5 minutes preparation/5 minutes note making and 15 minutes conversation with the patient), the daily workload would be 450 minutes/7.5 hours each day (without break), or 52.5 hours per week, for every week of the study period. While it is unlikely that all patients who met the CVW criteria within the first 24 hours of presentation would have been deemed medically fit for discharge to the virtual ward, the same modelling for the 571 cohort who met the CVW criteria would require 7994 telephone calls over the study period plus follow-up period of

14 days, which equates to 31 calls per day, taking 775 minutes or 13 hours per day. This excludes the provision of a manned telephone service that patients could call if concerned. This would require at least 2 or 3 staff members each day, as well as senior medical oversight and out of hours cover.

5.6 Discussion

This retrospective analysis of health data for patients admitted to hospital with a positive COVID-19 swab result found that 24.8% of patients would have met criteria for management via a Covid virtual ward. Of these patients, 56.9% were discharged from hospital, and received usual care. In this cohort, only 13% re-presented to hospital and 10% were readmitted. These outcomes are similar to reported outcomes from CVWs, without the additional considerable time and staffing commitment required to deliver a CVW service.

Of the 246 patients who would have met criteria for management via a CVW and were admitted to hospital, 80.9% required other management necessitating hospital admission, such as intravenous treatment, suggesting other factors play a larger role in assessment of suitability for CVW management than the criteria used in this analysis alone.

The NHSE CVW was developed to facilitate the care of COVID-19 patients who had presented to hospital, but who could be cared for at home. Thrice daily oxygenation saturations and daily contact by trained hospital staff were provided for appropriate safety netting. The hope for the service was that it would free

hospital beds, enable staff to focus on the most unwell patients with COVID-19, while providing a safe clinical service for patients.

To date, the CVW has not been evaluated in a gold standard, robust randomised clinical trial. Instead, CVWs have been reported in a series of observational studies and summarised in a recent systematic review[207]. These studies present some evidence of the safety of the CVW service, but have not described the burden of COVID where criteria were not met, nor described the natural history of discharged patients without this service, to enable a comparison of opportunity costs as well as gains.

This study presents retrospectively analysed, routinely collected health data for all patients admitted to QEHB with a positive COVID-19 swab result. Patients were assessed as to whether they met the criteria for the CVW parameters as presented by NHSE[195] either on initial presentation or during the first 24 hours, using time-stamped data available in the clinical record.

Of note, 75.2% (1730) of patients presenting to hospital during this period did not meet the CVW criteria, suggesting that during a wave of COVID-19, the CVW would only be suitable for a proportion of patients. In the 24.8% (571) who did meet the CVW criteria, 325 (56.9%) patients were discharged, and of those discharged, only 13% re-presented and 10% were admitted. Patient outcomes for those discharged within 24 hours in this study were compared to those discharged with CVW support in published evaluations of CVW services, to determine whether any

difference in outcome was seen in this cohort discharged without CVW support. No difference in outcome was demonstrated (**Table 5.4**).

The percentage of patients who re-presented was the same as reported in those discharged on a CVW, suggesting the CVW may not reduce re-presentation or re-admission rates. Further, the proportion of re-presenting patients who required ITU care or who died were the same as those reported in one CVW observational study[197], suggesting the CVW may not be safer in practice than discharge without the CVW. In this study, the patient death following re-presentation and re-admission was due to pneumonia, and has been classified as a COVID-19 related death in line with national reporting criteria for deaths occurring within 28 days of a positive swab result.

This study does not include a health economic analysis of service provision, but during COVID-19 waves, the CVW requires substantial staffing to operate. It is unclear whether there is the capacity to redeploy these skilled staff members from caring for the 75% of patients who did not meet CVW criteria to the 25%, especially if this does not confer improvements in hard outcomes such as mortality, ITU provision or re-presentation and admission. Previous studies have reported patient satisfaction with the CVW, reducing the potential anxiety of being discharged[197]. The current study does not assess this important factor.

Of note, a number of studies have reported remote monitoring for COVID-19 patients either initially in the community for positive patients as part of a triage

system with lower presentations to hospital,[198] such as 4%,[208] which probably reflects the screening of milder cases, less likely to present to hospital in the current study. However, where focusing on a secondary care delivered CVW, a re-presentation rate of approximately 13% has been reported.[209]

In this study, those who were admitted to hospital for >24 hours were more likely to have several comorbidities, including chronic kidney disease, ischaemic heart disease, diabetes and active malignancy. This may be reflective of the association between these comorbidities and severe manifestations of COVID-19, with poorer outcomes previously demonstrated in patients with these conditions.[4, 210]

This study has limitations. First, by comparing outcomes across studies, there is an assumption that patient populations including demography, burden of disease and impact of COVID-19, are similar across published studies. Most studies to date have not presented in depth demography and therefore these direct comparisons should be reviewed with caution. Second, in the current paper, the objective criteria for the CVW were applied using the granular electronic health record at QEHB without the benefit of seeing the patient or considering the time of the initial presentation, and all these factors are important when making the decision to admit or discharge. Third, it is possible that more of the patients who met the CVW criteria might have been discharged were the CVW in place. Fourth, when assessing staffing needs it has been assumed that all patients will require follow up for 14 days, as described in the NHSE SOP. It is highly likely that some

would require much less follow up prior to discharge. Fifth, this is not a formal health economic review, which would form part of the evaluation of any new service. Although we have included an estimate of the additional time that would be required to staff a CVW service based on the number of patients meeting CVW criteria in this analysis, there is no clear guidance for the staffing levels that would be needed to safely and effectively deliver a CVW service 7 days a week, and this may well vary from centre to centre, dependent on other factors including local population demographics. To fully assess the cost of a CVW service would require prospective measurement of service utilisation and health-related Quality of Life data, which was outside the scope of the current analysis.

The study has significant strengths. Decisions as to whether the patient met the CVW criteria were made independently by two researchers, without knowledge of outcomes, thus reducing bias. All patients were included in the study, reducing the population bias which can hinder consented studies. As data includes all medications and electronic noting, reasons for continued admission could be assessed.

In summary, this study reports similar percentage re-presentations, admissions, escalations to ITU and deaths in patients who were discharged without a CVW compared to studies where a CVW was implemented. The study also highlights that only 25% of COVID-19 admissions were suitable for the CVW based on objective criteria, and the potential intensity of work created by implementing a

CVW. The study begins to explore the potential opportunity costs of the CVW system, but does not consider patient factors, such as the reassurance potentially given by discharge to a CVW setting.

Any new care pathways or initiatives have opportunity gains and costs, and in usual times, processes are often assessed using rigorous randomised control trials which often include quantitative, qualitative and health economic analyses. While the CVW was established to enhance patient safety and reduce unneeded hospitalisation, it is important to assess whether the service achieves this compares to usual care. More research is needed before this service is fully implemented.

Chapter 6: The variability and performance of NHS England's "Reason to Reside" criteria in predicting hospital discharge in acute hospitals in England. An observational study.

This chapter has been published in BMJ Open entitled "*Variability and performance of NHS England's 'reason to reside' criteria in predicting hospital discharge in acute hospitals in England: a retrospective, observational cohort study*" [(211)] (**Appendices for Chapter 6**, **Supplementary File 6.1**).

Elizabeth Sapey[1,2], Suzy Gallier[2,3], Felicity Evison[4], David McNulty[5], Katherine Reeves[6], Simon Ball[7]

1a. PIONEER, HDRUK Health Data Hub in Acute Care, Birmingham, UK. University of Birmingham, Birmingham, UK. ORCiD ID: 0000-0003-3454-5482. [redacted]
1b. Acute Medicine, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK.
2. University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK. [redacted]
3. Joint first authors.
4. University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK. [redacted]
5. University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK. [redacted]
6. University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK. [redacted]
7a. Health Data Research UK (HDR-UK) Midland's Physical Site. University of Birmingham, Edgbaston, Birmingham, UK. Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK.
7b. Chief Medical Officer, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, UK. [redacted]

Authors' contributions

Suzy Gallier contributed to study design, undertook data curation, data analysis and wrote the first full version of the manuscript. Simon Ball and Elizabeth Sapey conceived the study, and Felicity Evison, David McNulty, Katherine Reeves conducted some of the data analysis. Elizabeth Sapey and Suzy Gallier wrote the first draft of the study. All authors read and approved the study manuscript. Simon Ball is senior author and manuscript guarantor.

6.1 Introduction

In 2021 the UK Government published its policy and operating model for hospital discharge and community support within the National Health Service in England (NHSE).[212] This policy responded to concerns about bed capacity during the COVID-19 pandemic.

A National Audit Office report recognised the potential to release acute hospital beds in 2016, finding that older patients no longer needing acute treatment accounted for 2.7 million NHS hospital bed days per year.[213] The report concluded that a lack of planning delayed discharge, recognising research which highlighted adverse outcomes during prolonged hospital stay.[214, 215]

The aforementioned policy mandates using set criteria to identify in-patients in whom discharge home, or to a less acute setting, should be considered. These criteria have been referred to interchangeably, as “reasons to reside” (R2R), “right to remain” or “criteria to reside” (See **Table 6.1**). Since April 2020, NHS hospitals have been required to provide daily reports on the numbers of people leaving hospital, to where, and the reasons for those remaining in hospital. The proportion of in-patients not meeting R2R criteria, and the proportion of patients without R2R discharged that day, are also reported. These metrics are considered to be measures of organisational efficiency.

Table 6.1: Reason to Reside (R2R)

1	Requiring ITU or HDU care
2	Requiring oxygen therapy / NIV
3	Requiring intravenous fluids
4	NEWS2 > 3 (clinical judgement required in persons with AF and/or chronic respiratory disease)
5	Diminished level of consciousness where recovery realistic
6	Acute functional impairment in excess of home/community care provision
7	Last hours of life
8	Requiring intravenous medication > bd (including analgesia)
9	Undergone lower limb surgery within 48 hours
10	Undergone thorax-abdominal/pelvic surgery within 72 hours
11	Within 24 hours of an invasive procedure? (with attendant risk of acute life-threatening deterioration)

***Legend**. The policy and operating model for hospital discharge and community support within the National Health Service in England states that every person on every general ward should be reviewed on a twice daily ward round to determine whether they meet R2R. If the answer to each question is 'no', the policy states that active consideration for discharge to a less acute setting must be made [(212)].*

AF=Atrial Fibrillation; bd=twice daily; HDU=High Dependency Unit; ITU=Intensive Care Unit; NEWS2=National Early Warning Score; NIV=Non-Invasive Ventilation; R2R=Reason to Reside.

R2R appears to have emerged heuristically from the clinical experience of those involved in its development. A series of questions are posed that might prompt consideration of individual patients for discharge. However, there are no standardised data definitions, there has been no validation of R2R, no investigation of its role as a clinical decision support tool, or of its value in evaluating hospital performance. A further barrier to evaluating the performance of R2R is that there is no gold standard definition which identifies patients who could be discharged from hospital against which to compare R2R performance. This lack of a reference standard limits, but does not preclude assessment of the validity of a clinical test, provided a 'fair' measure of performance can be defined.[(216)] The set of patients actually discharged in the subsequent 24 hours is one potentially 'fair' test of performance of R2R.

In the current study, we show the degree of variation in R2R associated metrics reported across centres in England. Secondly, we propose precisely defined, inter-

operable, data definitions corresponding to the elements of R2R. This allows for consistent, generalisable analysis. Thirdly, we evaluate the performance of R2R to predict discharge over the subsequent 24 hours.

6.2 Methods

This study used unconsented, anonymous health data and all study activity was approved by the East Midlands–Derby REC (reference: 20/EM/0158) and was supported by PIONEER, the Health Data Hub in acute care. All studies activities followed the World Medical Association's Declaration of Helsinki. The R2R criteria are as described[212] and are also provided in **Table 6.1**.

6.2.1 National Data

National NHS England data were accessed via The UK Health Facts and Dimensions database[217] for all reporting Trusts in England. Assessment of variability in national R2R reporting included data from 29 November 2021 to 20 February 2022. **Supplementary Table 6.1** provides the names of the Trusts whose data are presented anonymously. Data were collected daily during the censor period for 121 centres, yielding a total of 10 164 potential data points (centre-days). For each of these, the total number of occupied and unoccupied beds, and the number of patients with no right to reside were extracted. The number of patients with no right to reside were submitted once a day by each NHS trust, based on the local hospital interpretation of the definition provided by NHSE.[217] This required none of the criteria to be met at the time of local data collection. The

numbers of patients with right to reside were then calculated by subtracting the number with no right to reside from the total number of occupied beds on that day. The number of general and acute beds occupied in any given centre, on any given day (in-patients), was used as a surrogate for the number of patients eligible for evaluation using the R2R criteria. Review of the dataset found some missing and potentially spurious data, which were excluded prior to analysis. This included instances where R2R data were not recorded (n=184 data points), where the total numbers of beds were either zero, missing or clearly spurious (n=37 data points) or where there were more patients with no R2R than the total number of beds (n=3 data points). The national data are shown for the other n=121 centres, excluding UHB.

6.2.2 Local Data

In-depth analysis of R2R criteria were performed using data from the Queen Elizabeth Hospital Birmingham (QEHB). QEHB is a National Health Service (NHS), urban, adult, acute hospital in England which in 2019 had 1269 beds including 80 level 2/3 intensive care (ICU) beds, an Emergency Department that assesses >300 patients per day, and a mixed secondary and tertiary practice that includes all major adult specialities except for obstetrics and gynaecology. The electronic healthcare record (EHR) at QEHB (PICS, Birmingham Systems) contains time-stamped, structured records that include demography, location, admission and discharge, co-morbidities, physiological measurements supporting NEWS2 and Glasgow Coma Scale, operation noting, prescribing and investigations.

The R2R criteria in **Table 6.1** were mapped to computable definitions derived from the EHR (See **Table 6.2**), to generate an electronic R2R (eR2R). The OPCS Classification of Interventions and Procedures codes mapped to criterion 9-11 are described in **Supplementary Table 6.2**. The concept 'acute functional impairment in excess of home/community care provision', had no direct correlate. Safer Nursing Care Tool (SNCT) levels of care were however available.[218] SNCT level 2 and 3 correspond closely with the requirement for HDU or ICU[219]. Level 1a identifies patients requiring enhanced nursing reflecting acuity of illness and Level 1b identifies a group with increased nursing dependency. Level 1b is likely to include those who would and would not be considered to require ongoing care in acute hospital. SNCT level 1 was included in the definition of eR2R in two ways, including (eR2Rab) and excluding (eR2Ra) level 1b, to determine if this affected performance.

Table 6.2: Data definitions used to operationalise R2R for EHR

	Flag if…	R2R criterion number
On ITU HDU	listed as being in ITU or HDU ward	1
SNCT Level ≥ 2	Most recent SNCT level in previous 48 hours ≥ 2	1
SNCT Level 1a	Most recent SNCT level in previous 48 hours = 1a	6
SNCT Level 1b	Most recent SNCT level in previous 48 hours = 1b	6
Oxygen therapy/ NIV	oxygen administration or NIV documented in observation chart within previous 24 hours	2
Intravenous fluids	iv fluid administration initiated in previous 24 hours or variable rate insulin infusion administered in previous 24 hours	3
NEWS2	if NEWS2 > 3 within last 24 hrs	4
Diminished consciousness	Glasgow Coma Scale value ≤ 12 in last 24 hours	5
Last hours of life	comfort observation completed current OR End of Life medication bundle administered within last 24 hours	7
Intravenous prescription [3] tds current (regular not prn)	IV medication prescribed within last 24 hours and frequency ≥ 3 times per day for regular medication only	8
Intravenous medication administration [3] tds within 24 hrs	IV medication administered ≥ 3 times within last 24 hours	8
Lower limb surgery within 48hrs	Procedure with relevant OPCS codes in previous 48 hours	9
Thorax-abdominal-pelvic surgery with 72hrs	Procedure with OPCS relevant codes in previous 72 hours	10
Invasive procedure within 24hrs	Procedure with OPCS relevant codes in previous 24 hours	11

***Legend**. The table describes the data definitions used and the R2R criteria they map to.*
*All OPCS codes used to identify procedures are listed in **Supplementary Table 6.2**.*

EHR=electronic healthcare record; HDU=high dependency unit; ITU=intensive care; NEWS2=National Early Warning Score 2; OPCS= OPCS Classification of Interventions and Procedures code, which is used to identify the coded clinical entry; prn=pro re nata (as required administration of medication); R2R=reason to reside; SNCT=Safer Nursing Care Tool; tds=three times a day.

The primary analysis of eR2R was for patients who had been in hospital for more than twenty-four hours at midnight. Discharge over the course of the subsequent twenty-four hours was evaluated. Secondary analyses were undertaken for the set of patients in a bed at 08:00 and at 16.00 to define any change in eR2R performance in these different cross sections of the in-patient population. Three calendar years were analysed separately, to assess the effects of the COVID19 pandemic.

6.2.3 Statistics

Initially, daily numbers of patients with R2R quantified both as absolute numbers and a proportion of the total number of beds were plotted for national centres and used to calculate between-centre and within-centre variation. These data are analysed as beds occupied at the specified time of day, where the bed inherits the demographics, comorbidities and other qualities of the occupying patient. This represents the in-patient population in cross-section.

For the local analysis of eR2R: the term patient-day was used to refer to a bed with the qualities of the occupying patient at the time of the analysis. The in-patient population is described as means of patient-days thereby representing a cross-section of the group. The performance of eR2R as a predictor of remaining in hospital (or absence of eR2R as a predictor of discharge) was reported as a true positive rate (TPR) and true negative rate (TNR), positive predictive value (PPV), negative predictive value (NPV) and Youden's J statistic (TPR+TNR-1), where positive is remains in hospital and negative is discharge from hospital within 24 hours.

Normally distributed variables are reported as arithmetic means ± standard deviations, with medians and ranges used otherwise. Between-centre variation was assessed by ANOVA. This included a model accounting for day of the week as a fixed effect and the centre as a random effect. All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY), with $p<0.05$ deemed to be indicative of statistical significance throughout

6.2.4 Patient and public involvement

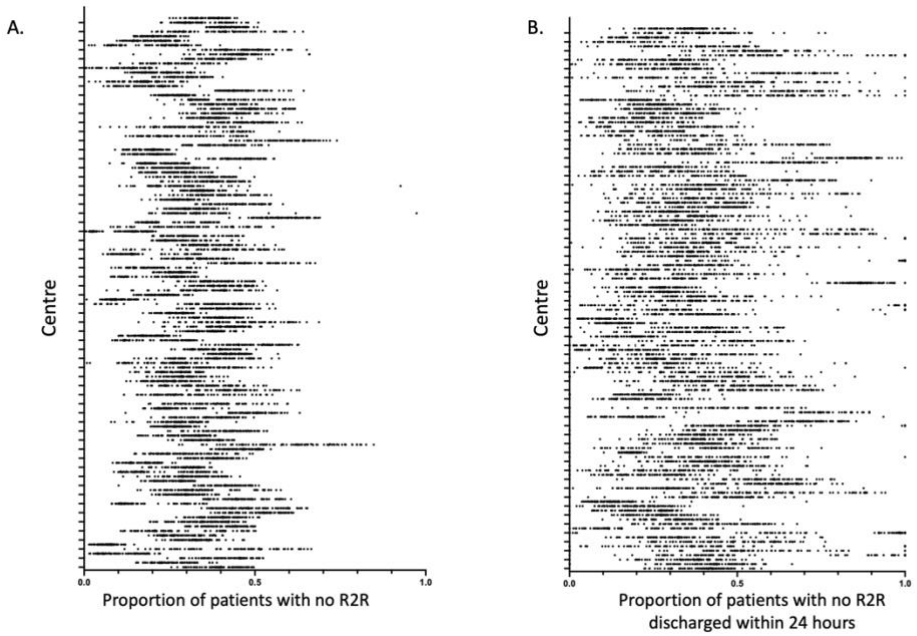
The research question and topic were agreed following patient/public discussion groups about NHSE discharge policies. Patients/public reviewed the data fields included in the study, with the PIONEER Data Trust Committee providing support for the project (a group of patient/public members who review studies using health data).[220] A patient/public group have reviewed the results and have written a lay summary for study dissemination to patient groups

6.3 Results

6.3.1 R2R reporting in England November 20-February 21

Across 10,164 available centre-days, accounting for 6,602,706 patient-days, the number of patients reported without R2R as a proportion of in-patients varied significantly between centres (p<0.0001). Individual centre means ranged from 6.7%±2.5% to 59.9%±13.8% (**figure 6.1A**). There was also marked within-centre Variation (**figure 6.1A**), with coefficients of variation (CV) ranging from 8.2% up to 59.3%. Of patients not meeting R2R criteria, the proportion discharged over the following 24 hours, varied significantly between centres (p<0.0001). Individual centre means ranged from 14.0%±7.4% to 85.8%±25.2% (**figure 6.1B**). There was also marked within centre variation, with CV ranging from 6.4% up to 83.2%. These data are shown as median and IQR in **Supplementary Figure 6.1A, 6.1B**). The proportion of patients without R2R and the proportion of that group discharged within 24 hours were only weakly correlated (R2=0.12; **Supplementary Figure 6.2**).

Figure 6.1: National reporting of R2R criteria



***Legend**. The proportion of patients with no R2R (A) and of that group the proportion of patients discharged within 24 hours (B) reported to Strategic Data Collection Service (SDCS) NHS Digital, UK from 29 November 2021 to 20 February 2022 across 121 centres. Each dot represents result for a single centre-day. We have ordered centres in both A and B according to the median value of proportion of patients with R2R (see **Supplementary Figure 6.3** for median and IQRs).*

IQRs=Interquartile ranges; NHS=National Health Service; R2R=reason to reside; UK=United Kingdom

6.3.2 Performance of eR2R at QEHB

Patients and admissions

Standardised definitions corresponding to the elements of R2R (**Table 6.2**) were used to analyse data from QEHB, on 1,214,480 in-patient days, between 01 Jan 2019 – 31 Dec 2021. The demographic and clinical details of that population are summarised in **Table 6.3** which also shows that those meeting the definition of eR2Rab were older and more likely to have one or more co-morbidities than those who did not. Variation in the daily number of patients with or without an eR2R is shown in **Supplementary Figure 6.3**.

Table 6.3. Demographics of patients meeting and not meeting R2R criteria on presentation to QEHB in the censor period

	All QEHB patient days	Meeting eR2Rab	Not meeting eR2Rab
n	1039592	919751 (88.5%)	119841 (11.5%)
Age in years*: median (IQR)	68 (53-80)	69 (54-81)	63 (48-76)
Sex* (n, %)			
Female	488120 (47.0%)	434418 (47.2%)	53702 (44.8%)
Male	546061 (52.5%)	484816 (52.7%)	61245 (51.1%)
Not recorded	5411 (0.5%)	517 (0.1%)	4894 (4.1%)
Self-reported ethnicity* (n, %)			
White	784528 (75.5%)	698573 (76.0%)	85955 (71.7%)
Mixed/ Multiple	12983 (1.2%)	11023 (1.2%)	1960 (1.6%)
South Asian/ Asian British	114049 (11.0%)	98903 (10.8%)	15146 (12.6%)
Black/ African/ Caribbean/ Black British	51122 (4.9%)	43991 (4.8%)	7131 (6.0%)
Other ethnic group	19475 (1.9%)	16623 (1.8%)	2852 (2.4%)
Not known	57435 (5.5%)	50638 (5.5%)	6797 (5.7%)
Co-morbidity count* (n, %)			
None	196121 (18.9%)	164704 (17.9%)	31417 (26.2%)
1-2	474922 (45.7%)	423200 (46.0%)	51722 (43.2%)
3 or more	368549 (35.5%)	331847 (36.1%)	36702 (30.6%)
Morbidities (n, %)			
Hypertension*	492160 (47.3%)	439930 (47.8%)	52230 (43.6%)
Cerebrovascular disease*	159316 (15.3%)	147676 (16.1%)	11640 (9.7%)
Atrial fibrillation*	224501 (21.6%)	204458 (22.2%)	20043 (16.7%)
Ischaemic heart disease, angina, myocardial infarct*	198480 (19.1%)	173708 (18.9%)	24772 (20.7%)
Diabetes (type 1 and 2)*	271505 (26.1%)	242328 (26.3%)	29177 (24.3%)
Asthma*	103679 (10.0%)	91136 (9.9%)	12543 (10.5%)
COPD*	112731 (10.8%)	103882 (11.3%)	8849 (7.4%)
Interstitial Lung Disease*	2533 (0.2%)	2380 (0.3%)	153 (0.1%)
Chronic Kidney Disease*	198052 (19.1%)	178284 (19.4%)	19768 (16.5%)
Any active Malignancy *	215959 (20.8%)	194419 (21.1%)	21540 (18.0%)
Dementia (all types)*	65272 (6.3%)	61324 (6.7%)	3948 (3.3%)
English Indices of deprivation			
1	430114 (41.4%)	382132 (41.5%)	47982 (40.0%)
2	222478 (21.4%)	197999 (21.5%)	24479 (20.4%)
3	178565 (17.2%)	158047 (17.2%)	20518 (17.1%)
4	107747 (10.4%)	96115 (10.5%)	11632 (9.7%)
5	75854 (7.3%)	67296 (7.3%)	8558 (7.1%)
Not recorded	24834 (2.4%)	18162 (2.0%)	6672 (5.6%)
Care escalation to ITU (n, %)	101017 (9.7%)	93080 (10.1%)	7937 (6.6%)

***Legend**. Data is number (percentage) of patients in a bed at 00:00. Ethnicity was self-reported. Medical conditions were physician confirmed and checked against admission and linked primary care notes. English Indices of deprivation were calculated using postcode. *Significant difference between meeting and not meeting eR2Rab (p<0.05 in univariate analysis)*

COPD=Chronic Obstructive Pulmonary Disorder; IQRs=Interquartile ranges; ITU=Intensive Care Unit; NHS=National Health Service; R2R=reason to reside; UK=United Kingdom

6.3.3 Criteria contributing to eR2R

Given the potential for the COVID19 pandemic to affect R2R, calendar years were analysed separately. The number of patients meeting any given eR2R criterion are

shown in **Table 6.4a**. The progressive contribution of different elements of the definition of eR2R assessed daily in a modified Consort table, are summarised in **Table 6.4b**. The proportion of patients not meeting eR2R criteria exhibited relatively little day to day variation in 2019 (eR2Rab, CV = 11.2%; eR2Ra, CV = 6.3%), although somewhat higher in the context of case mix variation consequent upon peaks of patients admitted with COVID-19 in 2020 (eR2Rab, CV = 23.3%; eR2Ra, CV = 14.4%) and 2021 (eR2Rab, CV=17.1%; eR2Ra, CV = 9.9%). The criteria contributing most to eR2R status included acuity level (NEWS2 >3), SNCT level nursing requirement, being on intensive care and requiring intravenous medications or fluids.

Table 6.4a: The number (percentage) of patient-days on which each eR2R data definition was met

Year	2019	2020	2021
Criterion	n (%)	n (%)	n (%)
ICU	22899 (6.1)	20326 (6.7)	21305
TAP surgery 72Hrs	3783 (1.0)	3010 (1.0)	3974
Lower limb surgery 48Hrs	285 (0.1)	252 (0.1)	221 (0.1)
Invasive surgery 24Hrs	1861 (0.5)	1613 (0.5)	1988 (0.6)
NEWS2 > 3 24hrs	93501 (24.8)	85123 (27.9)	97722 (27.3)
O2 Treatment 24Hrs	77949 (20.7)	69355 (22.7)	77202 (21.6)
Insulin Infusion 24Hrs	10951 (2.9)	10860 (3.6)	12496 (3.5)
IV Fluids 24Hrs	79802 (21.2)	71376 (23.4)	80246 (22.4)
IV medication administered in last 24hrs >= tds	95034 (25.2)	81174 (26.6)	91573 (25.6)
IV medication prescribed in last 24Hrs >= tds	21543 (5.7)	17866 (5.9)	19249 (5.4)
SNCT Dependency 1a, 2, 3	99139 (26.3)	72226 (23.7)	88832 (54.8)
COMA Score <=12 in last 24Hrs	6594 (1.8)	6448 (2.1)	6664 (1.9)
End of Life care definition met in last 24Hrs	5359 (1.4)	4747 (1.6)	5075 (1.4)
SNCT Dependency 1b	172659 (45.8)	160380 (52.5)	179527 (50.2)
Total number of patient days	376684	305254	357654

***Legend**. The number (percentage) of patient days on which each eR2R definition was met. The population was in-patients at 24.00 with length of stay ^{3}24 hours.*

Hrs=Hours; ICU=Intensive Care Unit; IV=Intra-venous; NEWS2=National Early Warning Score 2; R2R=reason to reside; SNCT=Safer Nursing Care Tool; tds=three times a day;

Table 6.4b: Daily mean contribution of each eR2R data definition in a phased analysis (modified Consort diagram)

Year	**2019**	**2020**	**2021**
Criterion	**Mean % (SD)**	**Mean % (SD)**	**Mean % (SD)**
TAP surgery 72Hrs	0.7% (0.35)	0.7% (0.37)	0.8% (0.45)
Lower limb surgery 48Hrs	0.1% (0.07)	0.1% (0.11)	0.1% (0.08)
Invasive surgery 24Hrs	0.2% (0.15)	0.2% (0.18)	0.2% (0.15)
NEWS2 > 3 24hrs	24.2% (2.28)	27.5% (3.82)	26.6% (3.64)
O2 Treatment 24Hrs	4.0% (0.61)	3.9% (0.72)	3.6% (0.68)
Insulin Infusion 24Hrs	0.5% (0.24)	0.6% (0.28)	0.5% (0.23)
IV Fluids 24Hrs	8.8% (1.09)	9.5% (1.37)	9.6% (1.24)
IV Medication Admin 24Hrs >= tds	7.7% (1.05)	7.4% (1.29)	7.5% (1.17)
IV Medication Prescribed 24Hrs	0.7% (0.28)	0.6% (0.29)	0.6% (0.27)
Dependency 1a, 2, 3	8.8% (1.42)	6.7% (1.21)	7.8% (1.12)
COMA Score <=12 24Hrs	0.0% (0.05)	0.0% (0.08)	0.0% (0.06)
End of Life 24Hrs	0.5% (0.24)	0.4% (0.27)	0.4% (0.19)
Dependency 1b	24.5% (1.88)	25.5% (3.53)	25.3% (2.59)
Criterion	**Mean % (SD)**	**Mean % (SD)**	**Mean % (SD)**
ICU	6.1% (0.44)	7.1% (3.10)	6.0% (2.16)
TAP surgery 72Hrs	0.7% (0.35)	0.7% (0.37)	0.8% (0.45)
Lower limb surgery 48Hrs	0.1% (0.07)	0.1% (0.11)	0.1% (0.08)

***Legend**. A phased analysis undertaken for each day and presented as a modified Consort Diagram. The progressive contribution of each element to the definition of eR2R was calculated as proportion of the whole population and then averaged across each calendar year. The order of the phased analysis was determined by the researchers to be that which was most informative. SNCT dependency is a global nursing assessment and therefore was placed last.*

Hrs=Hours; ICU=Intensive Care Unit; IV=Intra-venous; NEWS2=National Early Warning Score 2; R2R=reason to reside; SNCT=Safer Nursing Care Tool; tds=three times a day;

6.3.4 Informedness of eR2R for discharge in the next 24 hours

For the outcome discharge (remain -) / no discharge (remain +) within 24 hours, across the 3 different years, the eR2Ra TPR lay between 0.63 and 0.65, TNR between 0.46 and 0.47, the PPV was 0.91 and NPV between 0.12 and 0.15; the eR2Rab TPR lay between 0.88 and 0.91, TNR between 0.18 and 0.24, the PPV between 0.90 and 0.91 and NPV between 0.18 and 0.20 (**Table 6.5**). The J statistic for both definitions lay between 0.09-0.12. In secondary analyses based upon the in-patient population at 08.00 and at 16.00 the J-statistic ranged between 0.10-0.14 and 0.10-0.15 respectively (**Supplementary Tables 6.3a and 6.3b**).

Table 6.5: Contingency tables showing the number of patients meeting criteria for (A) eR2Ra and (B) eR2ab

A.

	2019	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	213,382	20,845	234,227
	No (-)	124,874	17,583	142,457
	Total	338,256	38,428	376,684
	2020	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	177,065	18,292	195,357
	No (-)	93,947	15,950	109,897
	Total	271,012	34,242	305,254
	2021	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	208,068	20,084	228,152
	No (-)	112,007	17,495	129,502
	Total	320,075	37,579	357,654

B.

	2019	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	297,172	29,372	326,544
	No (-)	41,084	9,056	50,140
	Total	338,256	38,428	376,684
	2020	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	246,461	28,026	274,487
	No (-)	24,551	6,216	30,767
	Total	271,012	34,242	305,254
	2021	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	288,384	30,336	318,720
	No (-)	31,691	7,243	38,934
	Total	320,075	37,579	357,654

***Legend**. The tables show numbers of patients meeting R2R criteria and the corresponding number of patients who remain in hospital over the next 24 hours or do not (were discharged), for the in-patient population at 00:00. For eR2Ra, the TPR varied between 0.62-0.65 and TNR 0.46-0.51, across 3 different years and 3 different time points. For eR2Ra, the TPR varied between 0.87-0.91 and TNR 0.18-0.25, across 3 different years and 3 different time points. **Supplementary Table 6.3b** shows the same data for the in-patient population at 16:00. See **Supplementary Table 6.4** for all sensitivity and specificity analysis.*

TPR=True positive rate; TNR=true negative rate

6.3.5 In-patients not meeting eR2R

The demographic and clinical details of patient who did not meet the eR2Rab definition, stratified by discharge in the subsequent 24 hours are shown in **Supplementary Table 6.5**. For patient-days on which discharge occurred within 24 hours, there was significantly higher representation of those with no documented co-morbidities 29.2% vs 24.0% ($p<0.0001$). In those that remained in hospital, 61.2% met eR2R criteria on subsequent days (76% within the next 24 hours). Of all those that remained, 21.9% acquired a NEWS2 > 3, 32.8% received iv fluids or drugs > 3 times / day and 1.9% were admitted to ICU.

6.4 Discussion

Assessment of an individual patient's R2R has been promoted as a tool to improve the identification of those who could be discharged from acute hospitals in England. The proportion of in-patients with R2R and their rate of discharge has then been used to evaluate the operational efficiency of acute hospitals and their adjacent health and social care system.[212, 221] This paper presents findings to suggest that as currently constituted, R2R is of limited value for these purposes.

The high levels of variation in R2R related metrics, within and between centres in England, has been attributed to variation in case mix and operational efficiency.[222] However, such extremes of variation are not observed in other metrics that use established data standards. Furthermore, the proportion of patients not meeting R2R criteria correlates poorly with their rate of discharge over the subsequent 24 hours, whereas one might anticipate that such closely related measures of operational efficiency would reflect one another. These findings are most obviously accounted for by the fact that R2R does not constitute a semantic data model. It is therefore susceptible to differing interpretation by individuals and centres. This applies to all the concepts described by R2R, but most obviously those that are necessarily subjective, such as 'acute functional impairment in excess of home/community care provision' and 'diminished level of consciousness where recovery is realistic'.[223, 224]

We therefore developed machine readable data definitions corresponding to each concept, allowing consistent analysis of R2R at scale, using data derived from the EHR in our centre. The SNCT is a global nursing assessment of acuity and dependency that was developed to guide workforce deployment. It is regularly recorded within the EHR at our centre. Because Level 1b describes a group of patients who are highly dependent upon nursing care for daily activities, this was mapped onto the R2R concept 'acute functional impairment in excess of home/community care provision'. However, since the definition of level 1b could include a group of patients suitable for discharge to a less acute setting, two definitions or eR2R were tested, with and without SNCT 1b. Our analysis is therefore likely to represent two extremes of inclusion of patients with acute functional impairment.

Within centre variation in eR2R was low, consistent with it minimising individual interpretation of each data element. eR2R was a poor predictor of discharge within 24 hours.[225] Youden's Index was consistently <0.15 across 3 calendar years, 3 different times of day and two eR2R definitions. For a dichotomous test such as eR2R, a Youden's Index >0.50 is generally considered the empirical benchmark for a test to support clinical decision making.[226] eR2R is therefore unsuited to the provision of clinical decision support tool for discharge. It does not define a sub-population on which to assess discharge performance.[227] The limitations of R2R are not entirely surprising, given the need to interpret concepts that are not semantically defined. Although addressed by eR2R, it nevertheless remains a

simple series of binary responses to questions that have not been validated for the purpose of discharge prediction. For example, NEWS2 was validated as an acuity score to quantify physiological instability on initial presentation to hospital.[228] It was not developed and has not been validated, as a triage tool to assess fitness to leave hospital, at any threshold.

Importantly, more than half of those who remain in hospital without eR2R, subsequently acquired eR2R. This group of patients were older and had multiple long-term health conditions, suggesting that there were clinical grounds for that decision, albeit undefined. This sub-population requires further study.

There are limitations to our analysis. The eR2R was assessed in only one centre, albeit one that serves a diverse, multi-ethnic, urban population, in which more than 1.2 million patient days were assessed. Patients admitted for < 24 hours at the time of analysis were excluded, to allow clinical decisions to be made and executed. The first day post-admission is a highly dynamic situation, with frequent clinical review; a setting in which this embodiment of clinical decision support is arguably less relevant. Another, more intrinsic problem, is that there is no gold standard by which to define all patients suitable for discharge, so that actual discharge was used as a fair test when evaluating the performance of eR2R.[229] This assumes that patients actually discharged are part of a continuous population of all those who could be discharged. It is also the case that each eR2R data element could be defined in different ways, however each definition would relate to that

used, so that the performance of one model would be informed by the other. For example, the 24-hour retrospective time horizon for most evaluations could be altered, but the later model would relate directly to the former.

It is important to validate and evaluate tests within their intended setting. The effects of embedding new care pathways or tools within clinical service delivery, without appropriate evaluation, are increasingly described. There is significant opportunity for unintended consequences to arise from the implementation of poorly considered clinical decision support,[230] particularly when there is competition for clinical resource. This has been recently discussed for NEWS2[231], sepsis alerting and COVID-19 virtual wards.[193] R2R has been endorsed and adopted but without validation or consideration of the unintended consequences of its application. This is not to contend that a significant number of in-patients could not be discharged earlier, simply that there is no evidence that R2R can support clinical decision making. The collective limitations of R2R identified are likely to account for variation in nationally reported metrics which are difficult to explain.

Our study highlights the need for reproducible standardised data definitions to support both implementation and validation of any tool that purports to support clinical decision making. Further research should focus on building, validating and refining tools to inform clinical decisions.

Chapter 7: The safety and efficacy of using age-adjusted D-dimers in hospitalised patients in a diverse urban centre: a real-world data study

This chapter has been published as a pre-print in medRxiv entitled "*The safety and efficacy of using age-adjusted D-dimers in hospitalised patients in a diverse urban centre: a real-world data study*".[232] The paper is awaiting peer-review with *e-Clinical Medicine*.

S. Gallier[1], F. Evison[2], J. Hodson[3], R.Khosla[4], T. Ranasinghe[5], L. Rickard[6], C. Atkin[7], V. Reddy-Kolanu[8], K. Nirantharakumar[9], W. Lester[10], B, Holloway[11], E. Sapey[12]

1. PIONEER Health Data Research Hub in Acute Care, Department of Health Informatics, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK. ORCiD ID: 0000-0003-1026-4125 [redacted]
2. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK. ORCiD ID: 0000-0002-9378-7548 [redacted]
3. A. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK.
   B. Institute of Translational Medicine, Queen Elizabeth Hospital, Birmingham, UK. [redacted]
4. University of Birmingham, Medical School, Edgbaston, Birmingham, B15 2TT, UK. ORCiD ID: 0000-0001-9819-6395. [redacted]
5. Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, B15 2TT, UK. [redacted]
6. Radiology Department, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
7. Institute of Inflammation & Ageing, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. ORCID ID: 0000-0003-0596-8515. [redacted]
8. Acute Medicine, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. [redacted]
9. Institute of Applied Health Research, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. [redacted]
10. University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK. [redacted]
11. University Hospitals Birmingham NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham, B15 2WB, UK. [redacted]
12. A. Director of PIONEER: Health Data Research UK (HDRUK) Health Data Research Hub for Acute Care, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. ORCiD ID: 0000-0003-3454-5482 [redacted]

B. NIHR West Midlands Applied Research Centre, University of Birmingham, B15 2TT, UK
C. NIHR Patient Safety Research Collaboration, University of Birmingham, B15 2TT
D. NIHR Birmingham Biomedical Research Centre, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW.

Authors' contributions

S Gallier contributed to study design, undertook data curation, data analysis and wrote the first full version of the manuscript. C Atkin, B Holloway, W Lester and E Sapey contributed to the study design, collated some data, performed some analysis, and contributed to manuscript writing through review. F. Evison curated some data and supported statistical analysis. R. Khosla undertook initial literature review and assisted in writing the introduction through review. S. Gallier, L. Rickard, T. Ranasinghe, B. Holloway, V. Reddy-Kolanu, W. Lester and E. Sapey undertook the service evaluation and reviewed the clinical notes. J Hodson performed some statistical analyses and support. All authors amended the manuscript and approved the final version.

7.1 Background

Venous thromboembolic events (VTE), presenting as deep vein thrombosis (DVT) and pulmonary embolism (PE), impact millions of people worldwide each year,[233-235] ranking as the third leading cause of acute cardiovascular syndrome.[236, 237] In the UK, the incidence rate is 1-2 per 1,000 people [238, 239] and the crude mortality rate associated with VTE within 90 days following discharge from hospital is 99.4 per 100,000 people.[240] Due to an ageing and multi-morbid population, VTE events

are increasingly common. Over 69,064 hospital episodes of PE were reported in the UK between 2021-2022 which resulted in 36,757 admissions.[241]

With significant mortality and morbidity associated with this disease, it is vital to diagnose VTE as early as possible. However, VTE diagnosis is complicated by the non-specific nature of its presenting symptoms and the high frequency by which these symptoms occur.[242] There are clinical scores which aid the diagnosis of VTE by stratifying people into low or high probability groups. In those with a low probability, a plasma D-dimer test can be used to rule out disease. In those with a raised D-dimer or a high probability of VTE, definitive medical imaging is required. In the UK, the National Institute for Health and Care Excellence (NICE) support the use of the Wells score with a D-dimer test [243, 244] and computed tomography pulmonary angiography (CTPA) or ventilation-perfusion scan (VQ) for a suspected PE or ultrasound scans (USS) for a suspected DVT.[245] This approach has a very low rate of diagnostic failure.[246-248] However, a large increase in CTPAs and ultrasounds has been seen for suspected PE/DVT, placing a significant burden on diagnostic services.[249, 250]

Initial risk prediction models used a standardised threshold for a D-dimer test (ST), but it was increasingly recognised that D-dimers can become elevated with age and in several other systemic conditions. Several studies have indicated an increased specificity in diagnosing DVT or PE when utilising age-adjusted D-dimer threshold (AAT)[251-254] including systematic reviews.[255, 256] The 2020 NICE guideline

[NG158] for the diagnosis of VTE suggested that clinicians consider utilising AAT for people aged over 50 years of age.[257] Despite this, the adoption of AAT D-dimers remains limited across healthcare organisations. Reasons for this include concerns regarding the accuracy of AAT D-dimers in small studies with not all studies showing benefit, clinical uncertainty about the use of AAT D-dimers across diverse populations, and a lack of information on the potential clinical consequence of false negatives using an AAT approach.[258-260]

This retrospective data study aimed to assess and compare the predictive accuracy of ST and AAT D-dimer in patients presenting acutely to hospital with suspected VTE. Separate analyses were also performed for the outcomes of PE and DVT individually and across differing age groups and comorbidities. The secondary aim was to assess the characteristics and presentations of patients who might be misdiagnosed comparing an AAT to a ST for D-dimer. This included an individual note review of all false positives and negatives using an AAT to determine the clinical significance of missing a VTE or providing treatment for a VTE when no such VTE was present. The final aim was to calculate the potential impact on service utilisation including imaging requests (namely CTPA/VQ and Ultrasound tests) were an age-adjusted approach applied.

7.2 Methods

The study was supported by PIONEER, a Health Data Research Hub in Acute Care. Ethical approvals for the study were provided by the East Midlands – Derby REC

(reference: 20/EM/0158). Two in-depth reviews of identifiable patient notes were conducted as part of a service evaluation, both approved by University Hospitals Birmingham NHS Foundation Trust (UHB) Service Evaluation and Clinical Audit Team. In the first, there was a false negative using an AAT D-dimer but a true positive using an ST D-dimer (reference CARMS-21061). The second assessed anyone readmitted with a haemorrhage following a D-dimer in the false positive ST cohort (reference CARMS-21227).

7.2.1 Setting

The study was based on retrospective data collected from the electronic heath record (EHR) system at Queen Elizabeth Hospital Birmingham (QEHB), part of UHB, one of the largest NHS Trusts in England. Patients either presented to the emergency department (ED) or were referred by a general practitioner or other clinical service (e.g. the UK's 111 system) to the acute medical assessment unit directly. If VTE was suspected on triage, risk stratification was performed by the internal medicine or emergency medicine team.

7.2.2 Study cohort

The primary inclusion criteria for the study were patients attending QEHB between 1st Jan 2017 and 31st Dec 2021, with a suspected diagnosis of VTE and where a D-dimer test was performed for that suspected VTE. The following exclusion criteria were then applied, with further details provided in **Supplementary Figure 7.1**:

- Patients who were taking anticoagulants at the time of the D-dimer test, as this impacts D-dimer interpretation.[261] These were defined as patients who

either reported having an active prescription for an anticoagulant at the time of attendance or who were administered a treatment dose of an anticoagulant less than 48 hours prior to the D-dimer test being performed.

- Re-attendances by the same patient within 90 days of the index attendance, as these likely represented the same underlying instance of suspected VTE.
- Patients aged <18 years at the time of attendance.

7.2.3 Data collection

Data were retrospectively extracted from the EHR system at QEHB. The D-dimer level closest to the time of attendance was included, within a maximum interval of ±10 days. D-dimer tests reported levels in D-dimer units (DDU), with a lower limit of detection of 150µg/L. Any values below this threshold were assigned a value of 150µg/L for analysis and are reported as "<150µg/L". Dichotomisation of D-dimer levels used two different approaches: a standard threshold (ST) value of 250µg/L [256, 262], and an age-adjusted threshold (AAT), which used a value of 250µg/L for those aged <50 years, or age (in years) x 5µg/L for those older than 50 years.[263-265]

Baseline characteristics were extracted, including age, sex, ethnicity, and COVID-19 status. Deprivation was quantified using the index of multiple deprivation (IMD), which was categorised based on national quintiles for analysis.[266] The BMI measurement recorded closest to the index attendance, within ±6 months, was also extracted. The primary presenting complaint was identified based on the details recorded on arrival at the ED; this was not routinely available for patients

who directly attended medical or surgical wards, including those referred by their GP, and those on the community DVT pathway. The presence of underlying comorbidities at attendance was identified based on the ICD10 codes recorded at discharge. The first Wells' scores for either PE (Wells-PE) or DVT (Wells-DVT) performed either during the index attendance or a follow-up attendance to the specialist PE/DVT clinic were also extracted, where available, as was the first NEWS2 score recorded during the index attendance.

The primary outcome was the diagnosis of VTE, which was a composite of DVT and PE. The outcome was defined as the presence of an associated ICD10 code either during index attendance, or within ten or five days of discharge for DVT and PE, respectively. ICD10 codes used were: *I80.1, I80.2, I80.3, I80.9, O22.3,* and *O87.1* for DVT, and *I26.X* for PE. Additional outcomes included the total hospital length of stay, mortality during the index attendance, and at three-, six- and twelve-months post-discharge.

Two service evaluations were conducted on those people with a confirmed VTE diagnosis who met the ST but not AAT D-dimer threshold (a D-dimer level of >250µg/L but less than the AAT) – AAT false negatives. For each of these patients, medical notes and imaging review was undertaken by a consultant radiologist and consultant medical physician in an MDT. For each VTE "missed" by AAT, clinicians rated the VTE as low (sub-segmental PE or nonocclusive DVT), or high risk (multiple sub-segmental or segmental PE or occlusive DVT). Two medical consultants also

conducted a service evaluation that reviewed medical notes and discharge summaries of patients who had a raised ST D-dimer which was below the AAT threshold (ST false positives) especially assessing risks associated with anti-coagulation where this was given while awaiting definitive imaging (up to 7 days). Here, any side effects were ranked as being unlikely to be caused by anticoagulation, potentially caused by anticoagulation or highly likely to be caused by anticoagulation, according to the MDT.

7.2.4 Statistical methods

The predictive accuracy of D-dimer with respect to VTE was initially quantified using the area under the receiver operating characteristic curve (AUROC). The classification accuracies of the ST and AAT were then quantified using a range of measures of test performance, which were compared between the two thresholds using Fisher's exact test. This analysis was also repeated within subgroups of age, with trends in sensitivity and specificity visualised using binary logistic regression models with age as a continuous covariate. All analyses were performed using IBM SPSS 24 (IBM Corp. Armonk, NY), with $p<0.05$ deemed to be indicative of statistical significance throughout. Cases with missing data were excluded from the analysis of the affected variable, unless stated otherwise. Continuous variables were not found to follow normal distributions, and so are summarised using medians and interquartile ranges (IQRs) throughout.

Furthermore, the study assessed the number of imaging scans, specifically CTPA and USS, that could have been circumvented utilising the AAT along with the

subsequent potential cost savings. VQ were also identified, for those patients with contraindications to CTPA, and were combined with CTPA scans for analysis including cost modelling. The direct access costs of imaging patients were taken from the latest NHS Reference Costs 2021/22, which were last updated May 2023.[267] The direct access cost for a CTPA is £122.87 and £85.21 for a USS. The number of return visits for care completion in ST false positives were recorded.

7.3 Results

7.3.1 Cohort characteristics

A total of N=27,526 attendances of patients with suspected VTE met the inclusion criteria of the study (see **Supplementary Figure 7.1** for study flowchart). Patients had a median age of 53 years (IQR: 37-69), with 57.7% female and 70.1% of White ethnicity; the most common presenting complaint was chest pain (36.3%, **Table 7.1**). Wells-PE scores were only recorded in the structured EHR system for 14.4% of cases, with the Wells-DVT available for <0.1%; as such, Wells scores were not included in subsequent analysis. PE was diagnosed in N=693 (2.5%) cases and DVT in N=528 (1.9%), of whom N=41 had diagnoses of both PE and DVT. As such, the composite outcome of VTE diagnosis occurred in N=1,180 (4.3%) cases. The in-hospital mortality rate was 2.0%, rising to 8.1% within 12 months post-discharge.

Table 7.1. Cohort characteristics

Factor	Statistic
Age (Years)	53 (37-69)
Sex (% Female) *[N=27,524]*	15887 (57.7%)
Ethnicity *[N=24,420]*	
White	17116 (70.1%)
Asian	4397 (18.0%)
Black	1368 (5.6%)
Mixed/Other	1539 (6.3%)
BMI (kg/m^2) *[N=16,371]*	28.0 (23.8-32.9)
IMD Quintile *[N=27,341]*	
1 (Most Deprived)	13991 (51.2%)
2	5793 (21.2%)
3	4335 (15.9%)
4	2056 (7.5%)
5 (Least Deprived)	1166 (4.3%)
COVID-19 Positive	1331 (4.8%)
First NEWS2 Score *[N=17,091]*	1 (0-3)
Wells-PE Score *[N=3,979]*	5 (3-5)
Wells-DVT Score *[N=121]*	2 (1-3)
Presenting Complaint	
Chest Pain	9981 (36.3%)
Respiratory	4941 (18.0%)
Limb Pain	2081 (7.6%)
Other Pain [a]	932 (3.4%)
Injury	668 (2.4%)
Leg Swelling	795 (2.9%)
Dizziness/Syncope	779 (2.8%)
Neurological	535 (1.9%)
Other Complaint	3959 (14.4%)
Not Recorded [b]	2855 (10.4%)
Previous PE	1747 (6.3%)
Previous DVT	2285 (8.3%)
Hypertension	6593 (24.0%)
Ischaemic Heart Disease	5599 (20.3%)
Diabetes Mellitus	3478 (12.6%)
Asthma	2835 (10.3%)
COPD	2082 (7.6%)
Chronic Kidney Disease	1529 (5.6%)
Cancer	1390 (5.0%)
Cerebrovascular Accident	1059 (3.8%)
Liver Disease	810 (2.9%)
Syncope	654 (2.4%)
Dementia	616 (2.2%)
Interstitial Lung Disease	327 (1.2%)
Length of Hospital Stay (Days)	1 (0-2)
Mortality	
In-Hospital	543 (2.0%)
3 Months Post-Discharge	1224 (4.4%)
6 Months Post-Discharge	1648 (6.0%)
12 Months Post-Discharge	2221 (8.1%)

Legend. *Results are based on N=27,526, unless stated otherwise, and are reported as "median (interquartile range)" or "N (%)", as applicable.* [a] *Pain in locations other than the chest or limbs.* [b] *Patients with no presenting complaint recorded were either referred by their GP or on the community DVT pathway; these were treated as a separate "not recorded" category for analysis.* [c] *Deaths within the stated number of months post-discharge; in-hospital deaths are also included.*

BMI=Body Mass Index; COPD=Chronic Obstructive Pulmonary Disorder; DVT=Deep Vein Thrombosis; IMD=Index of Multiple Deprivation; NEWS2=National Early Warning Score; PE=Pulmonary Embolism.

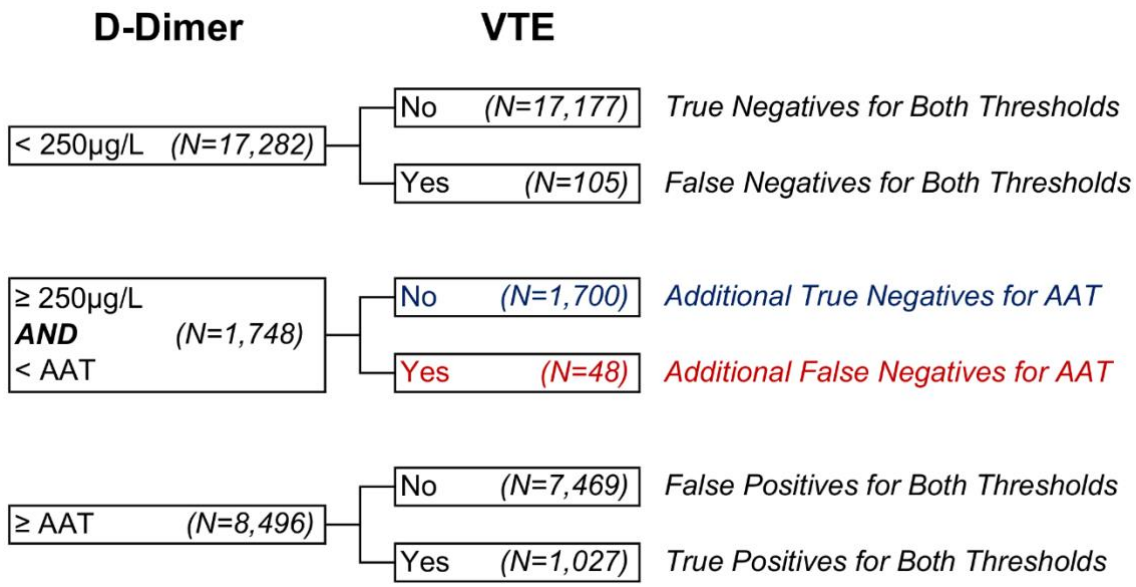
7.3.2 Predictive accuracy of D-dimer levels

The median D-dimer for the cohort was 178µg/L (IQR: <150-383), with 43.4% (N=11,937) having D-dimer values below the lower limit of detection of the assay (<150µg/L). D-dimer was found to be a strong predictor of VTE, with an AUROC of 0.863 (95% CI: 0.835-0.874). When considering the components of the composite outcome separately, performance of D-dimer was superior for PE (AUROC: 0.898, 95% CI: 0.888-0.909) compared to DVT (0.804, 0.785-0.823).

7.3.3 Classification accuracy of D-dimer thresholds

A total of 37.2% (N=10,244) of cases had D-dimer levels above the ST (≥250µg/L) and, hence, were classified as being at high risk of VTE based on this threshold. Of these, N=1,748 had D-dimer levels that were below the AAT; hence, would have been reclassified as low risk had the AAT been used instead of the ST (**Figure 7.1**). These comprised N=1,700 cases who were not diagnosed with VTE; hence, represented additional true negatives for the AAT. However, the remaining N=48 patients were diagnosed with VTE; hence, would have been incorrectly deemed low risk by the AAT, and represented additional false negatives.

Figure 7.1: Flowchart of VTE diagnoses by D-dimer threshold



***Legend**. AAT: Age-adjusted threshold; VTE: Venous thromboembolism.*

To assess the impact of these discrepancies between the two thresholds, the classification accuracies of both thresholds, with respect to VTE, were then compared (**Table 7.2**). This found the ST to have sensitivity of 91.1%, with a negative predictive value (NPV) of 99.4%. However, specificity was modest at 65.2%, with only 10.5% of cases with D-dimer levels above the ST being diagnosed with VTE. The AAT had a significantly lower sensitivity (87.0% vs. 91.1%, p=0.002) and NPV (99.2% vs. 99.4%, p=0.028) than the ST, as a result of the additional N=48 false negatives. However, the AAT also had a significantly higher specificity (71.7% vs. 65.2%, p<0.001).

Table 7.2: Classification accuracy of D-dimer thresholds

D-dimer Threshold	Outcome No	Outcome Yes	Sensitivity	Specificity	Negative Predictive Value	Positive Predictive Value	Accuracy	Odds Ratio (95% CI)
Outcome = VTE			***p=0.002***	***p<0.001***	***p=0.028***	***p=0.001***	***p<0.001***	-
Standard Threshold								
<250µg/L	17177	105	91.1%	65.2%	99.4%	10.5% (1075/10244)	66.3%	19.2
≥250µg/L	9169	1075	(1075/1180)	(17177/26346)	(17177/17282)		(18252/27526)	(15.6-23.5)
Age-Adjusted Threshold								
<Threshold	18877	153	87.0%	71.7%	99.2%	12.1% (1027/8496)	72.3%	17.0
≥Threshold	7469	1027	(1027/1180)	(18877/26346)	(18877/19030)		(19904/27526)	(14.3-20.1)
Outcome = DVT			***p=0.045***	***p<0.001***	*p=0.244*	*p=0.059*	***p<0.001***	-
Standard Threshold								
<250µg/L	17200	82	84.5%	63.7%	99.5%	4.4%	64.1%	9.5
≥250µg/L	9798	446	(446/528)	(17200/26998)	(17200/17282)	(446/10244)	(17646/27526)	(7.5-12.1)
Age-Adjusted Threshold								
<Threshold	18922	108	79.5%	70.1%	99.4%	4.9%	70.3%	9.1
≥Threshold	8076	420	(420/528)	(18922/26998)	(18922/19030)	(420/8496)	(19342/27526)	(7.4-11.3)
Outcome = PE			***p=0.012***	***p<0.001***	***p=0.036***	***p=0.004***	***p<0.001***	-
Standard Threshold								
<250µg/L	17256	26	96.2%	64.3%	99.8%	6.5%	65.1%	46.2
≥250µg/L	9577	667	(667/693)	(17256/26833)	(17256/17282)	(667/10244)	(17923/27526)	(31.2-68.4)
Age-Adjusted Threshold								
<Threshold	18982	48	93.1%	70.7%	99.7%	7.6%	71.3%	32.5
≥Threshold	7851	645	(645/693)	(18982/26833)	(18982/19030)	(645/8496)	(19627/27526)	(24.2-43.6)

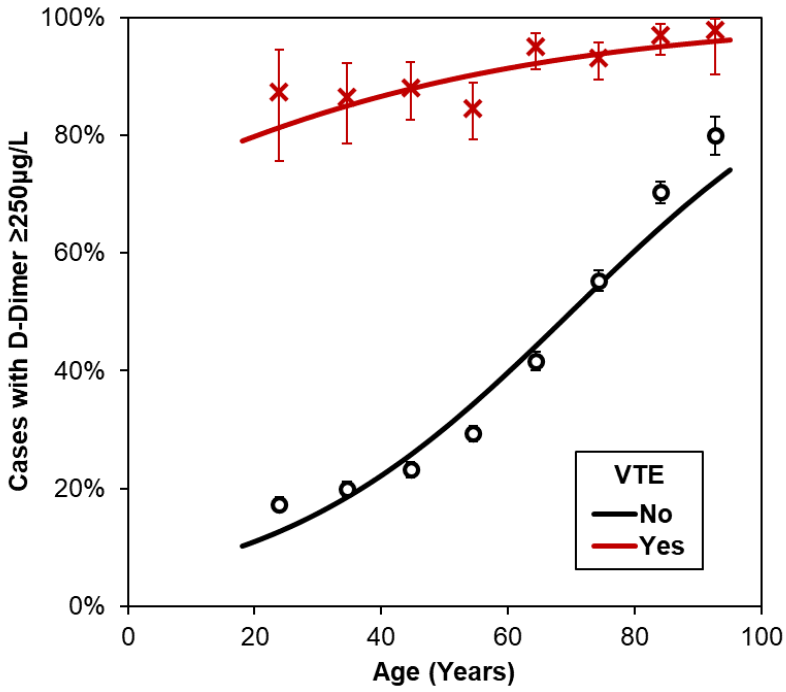
***Legend**. The age-adjusted threshold used a value of 250µg/L for those aged <50 years, or age (in years)*5µg/L for those older than 50 years. p-values are from Fisher's exact tests, comparing the percentages between the standard and age-adjusted thresholds; bold p-values are significant at p<0.05.*

CI=confidence interval; DVT=Deep Vein Thrombosis; PE=Pulmonary Embolism; VTE=Venous thromboembolism.

7.3.4 Impact of patient age on classification accuracy

D-dimer levels were found to increase significantly with age (p<0.001), with this effect being most pronounced in those that were not diagnosed with VTE. Specifically, for patients without a VTE diagnosis, the median D-dimer increased from <150µg/L (IQR: <150-195) in those aged <30 years to 480µg/L (IQR: 282-852) in those aged 90+ years, with a corresponding increase in the proportion with D-dimer levels above the standard threshold from 17.4% to 80.0% (**Figure 7.2**).

Figure 7.2: Association between age and the likelihood of D-dimer ≥250µg/L

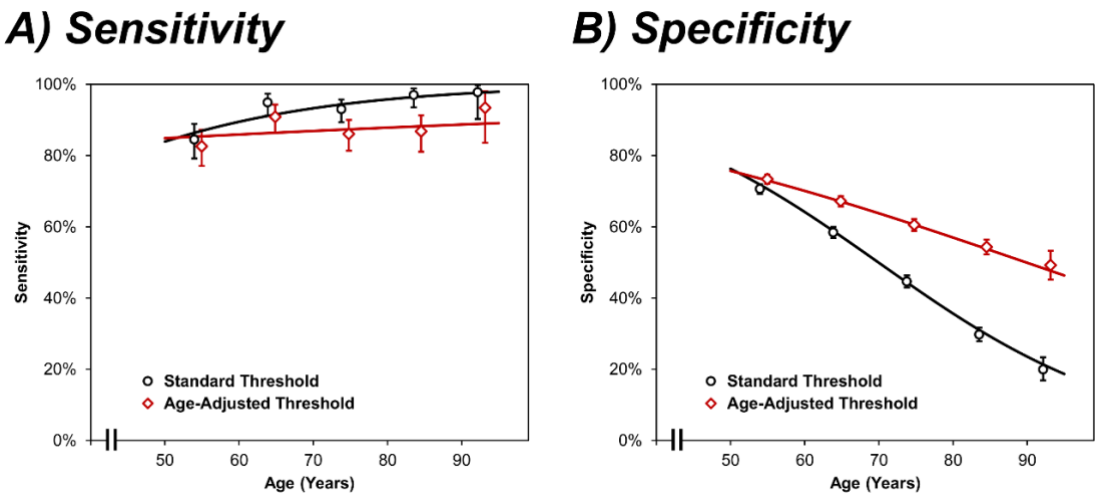


Legend. *Points represent the proportions of cases with D-dimer levels ≥250µg/L within decades of age, with the first point representing <30 years and the final point ≥90 years. Points are plotted at the mean age within each interval, and whiskers represent 95% confidence intervals. Trend lines are from binary logistic regression models, with D-dimer ≥250µg/L as the dependent variable, and age (as a continuous variable) as a covariate; separate models were produced for those that were and were not diagnosed with VTE.*

VTE=Venous Thromboembolism.

In light of this, the effect of age on the classification accuracy of the two thresholds was then assessed. This found a similar trend for both thresholds, with increasing age associated with progressive increases in sensitivity with a corresponding reduction in specificity (**Figure 7.3, Supplementary Table 7.1**). However, this effect was more pronounced for the ST, leading to the difference in classification accuracy between the two thresholds increasing with age. For example, despite both thresholds having identical performance in patients ≤50 years (as the ST and AAT were both 250µg/L in this range), for patients aged 80-89 the AAT had significantly lower sensitivity (86.8% vs. 97.0%, p=0.001) but significantly higher specificity (54.4% vs. 29.7%, p<0.001) than the ST.

Figure 7.3: Sensitivity and specificity of D-dimer thresholds by age



Legend. *Points represent the sensitivity/specificity within decades of age, with the first point representing 50-59 years and the final point ≥90 years. Points are plotted at the mean age within each interval (with jitter), and whiskers represent 95% confidence intervals. Trend lines are from binary logistic regression models, with age (as a continuous variable) as a covariate; separate models were produced for each outcome and threshold. Analyses only included those aged ≥50 years, as the two thresholds are identical below this point.*

7.3.5 Review of the additional false negatives associated with the AAT D-dimer

The AAT yielded an extra N=48 false negatives (0.17% of the overall cohort) compared to the ST, namely cases with VTE diagnoses who had been correctly identified as high risk by the ST but deemed low risk by the AAT; these cases were reviewed as part of a service evaluation. Of these, N=24 had been diagnosed with VTE based on initial imaging which was suggestive of VTE, but inconclusive; follow-up imaging in these patients found no evidence of VTE. As such, it is likely that only the remaining N=24 represented genuine cases of VTE, which is equivalent of an additional 0.9 false negatives per 1,000 attendances for the AAT. Of these patients, N=17 were diagnosed with PEs and N=7 with DVTs; where sufficient imaging was available (N=15), all PEs were small and sub-segmental or inconclusive/sub-optimal imaging, with all DVTs being partial venous occlusions behind the knee. Of note, only N=3 of these cases commenced anticoagulation during the admission, with this potentially being due to a second indication (atrial fibrillation) in N=2. There were N=2 in-hospital deaths; however, neither of these appeared to be related to VTE, instead being attributed to bowel perforation related to malignancy and congestive cardiac failure related to ischaemic heart disease, respectively.

7.3.6 Review of the additional true negatives associated with the AAT D-dimer

The AAT yielded an extra N=1,700 true negatives (6.2% of the overall cohort) compared to the ST, namely cases without VTE who had been identified as high risk by the ST but deemed low risk by the AAT. As such, these patients had the potential to be overtreated, with the associated risk of haemorrhage. Anticoagulation was prescribed in 65.3% (N=1,079) of this subgroup, with 79.5% (N=1,351) being

admitted to a hospital ward, who had a median subsequent hospital stay of 51 (IQR: 8-166) hours. After leaving hospital, 0.8% (N=14) of patients had a subsequent attendance with a haemorrhage within 30 days; rates were similar in those that did and did not receive anticoagulation at the index admission (0.8% vs. 0.8%, p=1.000). A clinical service evaluation of these N=14 readmitted patients found that N=9 had anticoagulation prescribed, but this was only administered during the inpatient stay in N=4. Haemorrhage types included gastrointestinal bleeding, hemarthrosis, and vaginal bleeding; clinical review concluded that these haemorrhagic events were not related to anticoagulation therapy, due to the timing of the event compared to the administration of the medication.

7.3.7 Change in imaging burden associated with the AAT D-dimer

If the decision to refer patients for imaging were made using a D-dimer threshold, then changing from the ST to the AAT could have reduced the number of cases referred for imaging by N=1,748 (i.e. the cases between the two thresholds), equivalent to 64 scans per 1,000 attendances. However, in practice, the D-dimer is not the only factor considered in clinical decision-making. Consequently, only N=658 (of N=1,748; 37.6%) of cases with D-dimer levels between the ST and AAT underwent imaging, comprising a total of N=393 CTPA or VQ scans and N=285 USS scans (N=20 had both scans), equivalent to 14 CTPA/VQ and 10 USS scans per 1,000 attendances. Based on these numbers and the NHS Reference Costs for the fiscal year 2021/22 (CTPA: £122.87, USS: £85.21), changing from the ST to the AAT would equate to a saving of £1,754 on CTPA/VQ and £882 on USS per 1,000 attendances.

7.4 Discussion

Venous thromboembolism is a common cause of acute presentation to the hospital. The lack of sensitivity and specificity of signs and symptoms can make diagnosis challenging. Failure to diagnose VTE can result in dire outcomes, including sudden fatality, lasting cardiopulmonary complications, and a diminished quality of life.[268] In patients with suspected VTE, distinguishing those without the condition is crucial to circumvent unnecessary anticoagulant treatment and its related haemorrhagic complications.[269] Concurrently, excessive testing for PE can incur high costs and increase length of stay, adding to hospital crowding and amplifying service delivery pressures in already strained imaging departments, as well as subjecting patients to risks from radiation and IV contrast. There is evidence to support the use of AAT for D-dimers, and the theoretical benefits of this approach have been discussed, but the adoption of AAT remains patchy across health services.

This study, conducted on the largest, most diverse cohort to date, explored the efficacy of the age-adjusted threshold (AAT) compared to the standard threshold (ST) in D-dimer testing for diagnosing VTE. The findings offer important insights with potential implications for clinical practice, particularly in managing healthcare resources and improving diagnostic accuracy. The AAT showed a lower sensitivity (87.0%) than the ST (91.1%), indicating a slight increase in false negatives. The failure rate of 0.8% for AAT correlates to reported failure rates for USS that range between 0.57% and 2.0% (CIs ranging from 0.2% to 5.1%).[270, 271] Compared to the

reported venogram failure rate between 1.3% and 43.7%, it is reassuringly favourable.[272, 273] However, importantly, when these false negative cases were explored in depth, the risk of missing a VTE was deemed low and any adverse event was not thought related to the VTE.

The AAT's higher specificity (71.7% vs. 65.2%) suggests it is more effective in reducing false positives. Approximately 65.3% of the ST false positive cohort received unnecessary anticoagulation but the clinical review concluded that the haemorrhagic events seen in a subset of these patients were not related to their anticoagulation therapy. However, these patients did go on to receive imaging and had a longer length of stay than the true negatives.

The data demonstrates the diminishing effectiveness of both D-dimer thresholds with advancing age, but more so with the ST. The analysis also showed that the AAT maintains greater accuracy and specificity across various patient subgroups, including those with comorbidities. However, due to small subgroup sample sizes, these findings should be interpreted cautiously.

A significant finding of the study is the potential reduction in unnecessary imaging procedures by adopting the AAT. The analysis suggests a substantial decrease in the number of scans required, resulting in considerable cost savings, a critical consideration for healthcare systems like the NHS.

The results advocate for adopting AAT in clinical settings, especially in populations where age and comorbidities may impact the accuracy of ST, including in a diverse urban setting. Clinicians should weigh the benefits of reduced false positives and resource savings against the slight decrease in sensitivity.

7.4.1 Strengths and limitations

The major strength of the study was the large sample size, which allowed for analyses of D-dimer within patient subgroups. However, the retrospective study design also led to several limitations, which need to be considered when interpreting the results. Primarily, it was assumed that the ordering of a D-dimer test indicated that a clinician suspected that a patient had VTE. However, the fact that the rate of VTE diagnosis in the present study was considerably lower than similar studies in the literature would suggest that there was a degree of over-testing, where D-dimer tests were ordered in patients at low risk of VTE.[244, 274, 275] Consequently, the results of the analysis are only generalisable to situations which apply similar criteria for ordering D-dimer testing and may not be applicable to situations where D-dimer tests are ordered more sparingly. Secondly, the retrospective data collection resulted in some missing data. This was a particular issue for the Wells' Scores, where the Wells-PE was recorded for only 14.4% of cases, with the Wells-DVT available for <0.1%. Further review found that, whilst these scores were routinely calculated for patients, they were generally recorded in the handwritten patient notes rather than the EHR, and so could not be readily extracted for analysis. As such, it was not possible to perform any meaningful analysis of the Wells-DVT score, and analyses of the Wells-PE must be interpreted

with caution, due to the risk of selection bias. Similarly, the presenting complaint was not recorded for patients who attended via either a GP referral or the community DVT pathway; hence, these patients were either excluded or grouped into a “not recorded” category for analysis. This will have introduced selection bias into analyses of the presenting complaint, which is demonstrated by the fact that cases where this was not recorded had the highest rate of VTE diagnosis. Finally, the D-dimer assay used during the study period had a lower limit of 150μg/L, with over 40% of patients being in this range. All of these patients were assigned the same value for analysis, which may have impacted the calculated predictive accuracy of the D-dimer test when analysed as a continuous variable (e.g. when calculating AUROCs).

7.5 Conclusion

In conclusion, this study provides evidence that age-adjusted D-dimer thresholds offer a more accurate and resource-efficient approach for diagnosing VTE, particularly in older patients and those with comorbidities. Adopting this approach could lead to better patient outcomes and significant cost savings, although careful consideration of its limitations and further validation is necessary. This discussion aims to stimulate further research and debate on the optimal use of D-dimer testing in clinical practice, considering the complex interplay of accuracy, patient demographics, and healthcare resource management.

Chapter 8: Testing federated analytics across secure data environments using differing statistical approaches on cross-disciplinary data

This chapter has been published as a pre-print in medRxiv entitled "*Testing federated analytics across secure data environments using differing statistical approaches on cross-disciplinary data*".[276] The paper is undergoing formatting to submit to a journal for peer review.

1. A. PIONEER Health Data Research Hub in Acute Care, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK. ORCiD ID: 0000-0003-1026-4125 [redacted]
   B. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
   C. HDR-UK Midlands Physical Site, University Hospitals Birmingham, Birmingham, UK
2. A. PIONEER Health Data Research Hub in Acute Care, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
   B. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
3. A. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
   B. Institute of Translational Medicine, Queen Elizabeth Hospital, Birmingham, UK
4. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
5. Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham, NG8 1BB
6. Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham, NG8 1BB
7. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
8. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
9. Research Development & Innovation Department, University Hospitals Birmingham NHS Foundation Trust, Birmingham, B15 2WB, UK.
10. Faculty of Medicine & Health Sciences, University of Nottingham, Nottingham, NG8 1BB
11. A. Director of PIONEER: Health Data Research UK (HDRUK) Health Data Research Hub for Acute Care, Birmingham Acute Care Research Group, Institute of Inflammation and Ageing, University of Birmingham, B15 2TT, UK
    B. Acute Medicine, University Hospitals Birmingham NHS Foundation Trust, Edgbaston, Birmingham, B15 2GW, UK. ORCiD ID: 0000-0003-3454-5482 [redacted]

SG contributed to study design, undertook data curation, data analysis and wrote the first full version of the manuscript. ES designed the study, collated some data,

performed some analysis and contributed to manuscript writing through review. JH, DMcN and AT curated some data and supported statistical analysis. All authors amended the manuscript through review and approved the final version.

8.1 Introduction

Embedding new, data driven technologies into health and care systems can improve population health and bring efficiencies to health and social care delivery. Correspondingly, digital health innovation is a stated priority for international organisations and governments, such as the World Health Organisation[277] and the UK Government.[278]

Tackling complex health and societal challenges using data-driven approaches requires access to data from different sectors and geographical sources. However, data access can be challenging. Aside from the technical challenges of integrating large, disparate data, there are ethical and governance restrictions associated with pooling highly sensitive, individual-level data. Recent papers and reviews have recognised the barriers to data egress and have suggested different solutions for analysis, including the concept of federated analytics.[279-282] Federated analytics is a data paradigm that enables different Data Controllers, and those they authorise, to collaboratively perform analytics on their respective local data, without exchanging the raw data itself.[283, 284] In essence, Data Controllers enable the deployment of code across their data with only aggregated results extracted from their local environments in lieu of the data itself.

There are advantages and disadvantages to a federated approach to data analysis. Limited direct exposure to data and a lack of data egress can address some concerns of privacy, security and governance, although model updates and partial aggregates can inadvertently, under certain circumstances, lead to the sharing of personal information.[285, 286] Without direct exposure to the data, analysts are more reliant on the Data Controller or agreed processor to perform data cleansing, and opportunities to explore the data are limited.[287] Also, there are concerns that federated analytics may reduce the accuracy of results in comparison to performing analysis on pooled data.[283]

This study tested the ability to federate analytics utilising differing statistical approaches, namely general linear models (GLMs) and machine learning (ML) models. The resulting outputs were then compared to those produced using non-federated data.

8.2 Methods

This research was conducted with Health Research Authority and Research Ethical Approvals (East Midlands – Derby Research ethics committee, reference 20/EM/0158).

8.2.1 Sample data

This study used a real-world dataset, from which a synthetic dataset was generated for the purpose of testing federated versus pooled data analysis. The real-world data was from a cohort of 381 patients with a physician-confirmed

diagnosis of asthma who were admitted to secondary care at a single centre in 2019. The response variable was readmission within 30 days, which occurred in 12·9% of cases. Clinical data was linked to meteorological and air quality data from The Centre for Environmental Data Analysis (CEDA), for the day of admission using the subjects' home address for geolocation; see **Table 8.1** for details of the variables included in the real-world dataset. From this two synthetic datasets were generated using a Conditional Transformation Generative Adversarial Network (CT-GAN) deep learning method[288] from the Synthetic Data Vault (SDV) library, an open-source Python library.[289] The first synthetic dataset was a “training set” of N=10,000 cases, and the second was a “test set” of N=1,000 cases.

Table 8.1: Characteristics of synthetic data used in modelling

Variable	Levels
Outcome	
Readmission within 30 Days	No, Yes
Patient Demographics	
Age at Index Admission	*Continuous*
Sex	Female, Male
Ethnicity	White, South Asian, East Asian, Black, Mixed, Other
IMD Decile	1, 2, 3, 4, 5, 6, 7, 8, 9, 10
Height	*Continuous*
Weight	*Continuous*
Patient Physiology	
Asthma Type	SNOMED195967001, J450, J458, J459, J46X
Eosinophil Count	*Continuous*
Respiratory Rate	*Continuous*
O2 Saturation	*Continuous*
Peak Flow	*Continuous*
Medications	
Oral Prednisolone	No, Yes
Inhaled Steroids	Beclometasone, Budesonide, Ciclesonide, Duoresp, Fluticasone, Flutiform, Fostair, None, Oxis, Relvar Ellipta, Sereflo, Seretide, Sirdupla, Symbicort, Trelegy
Date of Index Admission	
Month	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
Weekday	Working Day, Weekend, Public Holiday
Hour of Day	0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23
Atmospheric Conditions at Index Admission	
PM10 Concentration	*Continuous*
PM2.5 Concentration	*Continuous*
Nitrous Oxide Concentration	*Continuous*
Nitrogen Dioxide Concentration	*Continuous*
Sulphur Dioxide Concentration	*Continuous*
Temperature	*Continuous*
Relative Humidity	*Continuous*
Dew Point	*Continuous*

***Legend**. Variable characteristics of the synthetic data used in the modelling provided in category groups.*

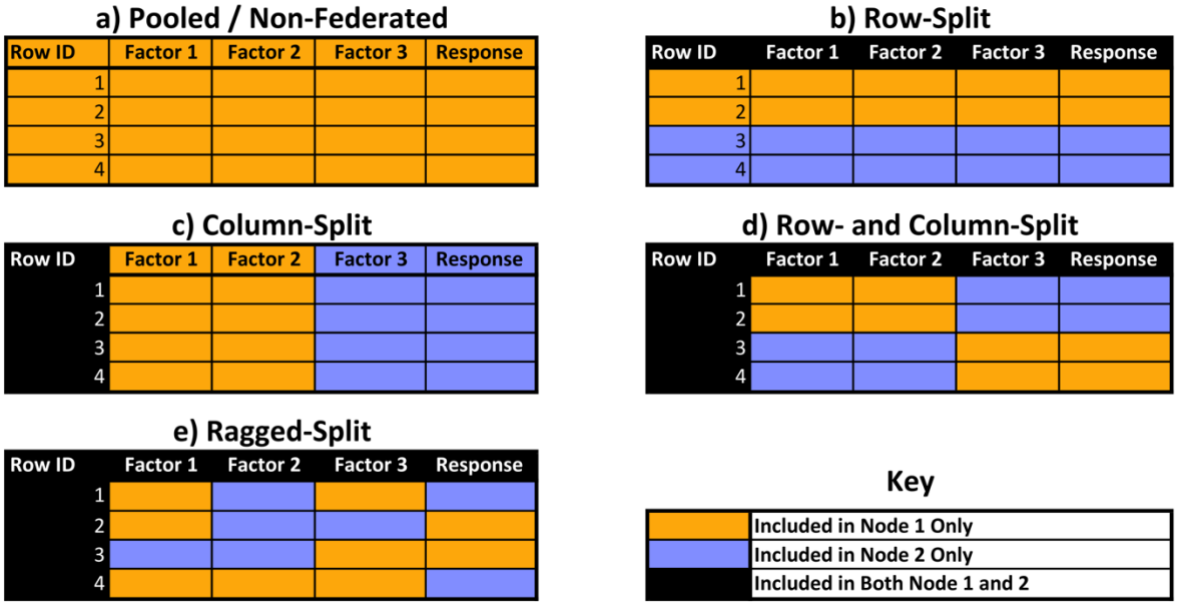
IMD=Index of Multiple Deprivation; O2=Oxygen; PM10=Particular matter 10 particle count; PM2.5=Particular Matter 2.5 particle count.

To simulate a scenario where federated analytics would be applicable, datasets were then divided across “nodes”, each of which was a Microsoft Azure Trusted Research Environment (TRE), and represented the data held in a different database by a different Data Controller (e.g., in different hospitals). In addition, the full dataset was also held, to allow non-federated (“pooled”) analysis to be performed, as the gold standard for comparison.

8.2.2 Federated learning for general linear models

The algorithms underlying the calculation of the standard deviation, analysis of variance (ANOVA), and Fisher-Neyman factorisation were evaluated, to understand their potential for federation (see **Supplementary Analysis 8.1** for further details). A simple one-way ANOVA was selected to test the federation of a GLM, with the resulting model being compared to one produced using a non-federated approach. This used the test set of N=1,000 cases, with the 10-micron particulate matter (PM10) counts as the dependent variable, and readmission within 30 days as a (binary) independent variable. For the models on federated data, the dataset was divided between two simulated nodes using four different approaches to simulate different scenarios; see **Figure 8.1.** Specifically, the "row-split" randomly divided the cases in a 1:1 ratio between the two nodes, to simulate the situation where each node held data for a different set of cases, but the same set of variables. The "column-split" divided the data such that the dependent and independent variables were on different nodes, to simulate the situation where each TRE held data for all cases, but for a different set of variables. These two approaches were also combined into a "row- and column-split" and "ragged-split", where each TRE held data for different sets of cases, and different sets of variables for these.

Figure 8.1: Approaches to splitting data across federated models



Legend. *Each panel represents a different approach to dividing the rows (cases) and columns (variables) of a table across two nodes, with the cell colours indicating the node on which data for a specific cell would be held. Figure a) represents pooled/non-federated data, where the whole table is held on a single node; b) represents a row-split, where cases are divided between the two nodes, both of which include all variables; c) represents a column-split, where variables are divided between the two nodes, both of which include all cases; d) represents a combination of a row- and column-split, where subsets of variables and cases are held on different nodes; and e) represents a ragged-split, where individual variables*case combinations can be held on either node.*

For the federated models, in addition to the TRE nodes, there was also a controlling hub, which sent requests for data to the individual TRE nodes and compiled the resulting data to perform the ANOVA analysis. The controlling hub never directly accessed the underlying datasets, with TRE nodes instead only sharing aggregated data, including sums, and row counts, which could be used to compute global means and degrees of freedom accurately (see **Figure 8.2**).

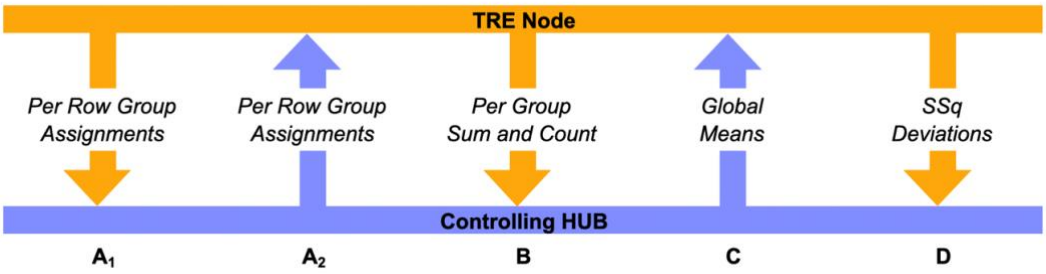
In scenarios where the data were partitioned among TRE nodes in a column-wise manner, either solely or in combination with row-wise partitions, unique identifiers were established for each row. The TRE nodes then shared the factors assigned to

each unique row throughout the network (**Figure 8.2**, steps A_1 and A_2) to produce the statistical outputs.

Once the unique row identifiers and factor assignments were established, the following steps were shared across all partitioning modes:

1. Calculation of Sum and Row Counts: Each TRE node returns the sum and row counts for each combination of factors to the controlling hub. This step allows for the computation of group-wise and global means of the response variable, as well as various degrees of freedom across the federated data set (**Figure 8.2**, step B).
2. Distribution of Global Mean: The global mean is sent back to each TRE node (**Figure 8.2**, step C).
3. Computation of Sum of Squared Deviations: Each TRE node calculates the sum of squared deviations from the global mean and returns it to the controlling hub (**Figure 8.2**, step D).
4. Calculation of ANOVA Statistics: The final ANOVA statistics, along with confidence intervals for the differences between means, are computed using the sum of squared deviations and Tukey's HSD respectively.

Figure 8.2: Data communications in a federated ANOVA environment



Legend. *Hub-to-node communications are indicated by blue arrows, and node-to-hub communications by orange arrows. A_1 and A_2 are necessary for column-split, a combined row- and column-split, and ragged data partitioning, where each node has incomplete sight of the covariates for each row, and so it is necessary for the hub to retrieve the known covariates from each node, combine them and distribute the complete set back to each node, thus relying on covariates not being sensitive in nature. In all partitioning modes, for every group of covariates, the nodes can return the sum of the response and row count (B), as well as being able to compute and return the sum squared deviation (D) from a given global mean computed by the hub using the per-group sum and row counts (C).*

API= Application Programming Interface; SSq Deviations=Sum of Squared Deviations; TRE=Trusted Research Environment.

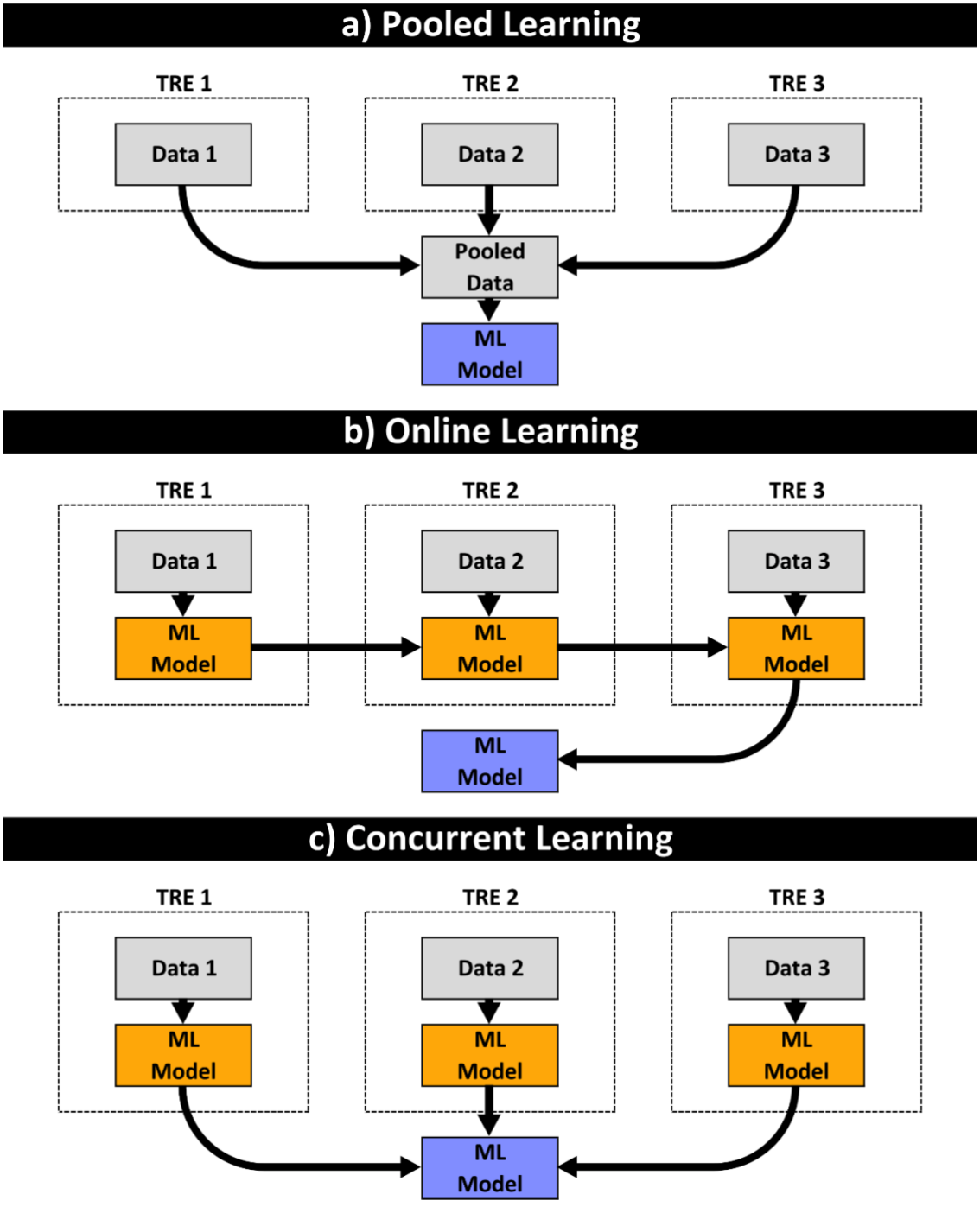
8.2.3 Federated learning for machine learning models

The performance of ML models using existing software stacks, trained using a federated approach was assessed. For this analysis, only the row-split scenario was considered, with the cases from the training set (N=10,000) being randomly divided between three TRE nodes in a 5:3:2 ratio. We tested two different modes of federation, which are visualised in **Figure 8.3**. The first was "online" learning, where a single ML model is initialised and passed sequentially between all federated environments. The second approach was "concurrent" learning, where separate models are trained in each federated environment and returned to the controlling hub, where they are combined or averaged. The response variable was 30-day readmission, with all 24 factors in **Table 8.1** considered as predictors. ML models comprised Gradient Boosted decision trees from CatBoost 1.2 (Yandex, Moscow, Russia), a high-performance open-source library.[290, 291] An Application Programming Interface (API) endpoint was utilised to execute a training cycle using

the concurrent mode of federation. All models were generated using the same random seed, in order to negate the impact of this when comparing across models. However, to test the potential impact that changing the random seed could have, the pooled (i.e., non-federated) model was also repeated a further three times using different random seeds, which were compared to the original pooled model.

The resulting models were then applied to the test set (N=1,000), to compare consistency and performance. Each model was used to produce both a predicted probability of 30-day readmission, and a predicted binary classification for this outcome for each case. The predicted probabilities were compared between models using Spearman's rho, and the binary classification using the percentage agreement, in order to test for consistency of the models. In addition, the predictive accuracy of each model was quantified using the area under the receiver operating characteristic curve (AUROC) for the predicted probability, and the accuracy, sensitivity, specificity and positive/negative predictive value statistics for the binary classifications. The AUROCs were then compared between the models using the algorithm suggested by Delong et al., with $p<0.05$ deemed to be indicative of a statistically significant difference in performance.[292]

Figure *8*.3: Schematic of the learning methods utilised for federated machine learning.



Legend. *Figure a) illustrates pooled (i.e., non-federated) learning, where data are moved from each TRE node into a central pooled environment for analysis by the ML algorithm. For the federated approaches, the federated learning system first passes an ML model into each TRE node. In online learning (Figure b), this ML model is trained iteratively across each TRE node, with each node performing local model updates using its own data, before sending only the updated model parameters to the next node, with the final node sending the final model parameters to a central server. In concurrent learning (Figure c), the ML model training is performed in parallel across all nodes, before updating the global model simultaneously.*

ML=Machine Learning; TRE=Trusted Research Environment.

8.3 Findings

8.3.1 Federation of general linear models

ANOVA models were produced for the pooled data, as well as on data federated across two TREs, using the four approaches detailed in **Figure 8.1**. All five of these models returned identical results, which are reported in **Table 8.2**.

Table 8.2: Comparison of ANOVA models across pooled and federated methods

Federation Method	Coefficient (95% CI)	p-Value
Pooled	-1.56 (-2.907, -0.212)	0.023
Row-Split	-1.56 (-2.907, -0.212)	0.023
Column-Split	-1.56 (-2.907, -0.212)	0.023
Row- and Column-Split	-1.56 (-2.907, -0.212)	0.023
Ragged Split	-1.56 (-2.907, -0.212)	0.023

***Legend**. Results are from ANOVA modelling on the synthetic dataset, with PM10 concentration as the dependent variable, and readmission within 30 days as a (binary) independent variable. The coefficient represents the difference between the 30-day readmission yes versus no groups, and is reported alongside the 95% confidence interval (95% CI) computed using Tukey's HSD. Separate models were produced using non-federated data ("pooled"), as well as using the four approaches to federation described in Figure 8.1.*

CI=Confidence Interval; HSD=Honesty significance difference; PM10=Particular matter 10 particle count.

8.3.2 Federation of machine learning models

ML models were then trained on the training dataset, both using a pooled approach, and with data federated across three TREs using a row-split approach; the federated models were produced using both concurrent and online learning approaches (as per **Figure 8.3**). Applying the resulting models to the test set for validation found that the classifications made by pairs of models to be in agreement in between 84·7-90·4% of cases, with Spearman's rho for the predicted probabilities ranging from 0·844-0·938 (Table 3). The pooled (i.e., non-federated) model was also repeated a further three times, with each using a different random seed, in order to assess how this would impact the resulting models. The

agreement between the classifications produced by these models and the primary pooled model ranged from 90·9-91·5%, with Spearman's rho for the predicted probabilities ranging from 0·914-0·931. As such, the consistency of classifications made between ML models trained on differently federated data was only marginally lower than that stemming from training repeated ML models on identical, non-federated datasets.

Table 8.3: Comparison of classifications made by machine learning models

Pooled versus Online *(Agreement: 84.7%; rho: 0.844*)*			
		Online	
		Classification: No	***Classification: Yes***
Pooled	***Classification: No***	573	99
	Classification: Yes	54	274
Pooled versus Concurrent *(Agreement: 90.4%; rho: 0.904*)*			
		Concurrent	
		Classification: No	***Classification: Yes***
Pooled	***Classification: No***	652	20
	Classification: Yes	76	252
Online versus Concurrent *(Agreement: 87.7%; rho: 0.938*)*			
		Concurrent	
		Classification: No	***Classification: Yes***
Online	***Classification: No***	616	11
	Classification: Yes	112	261

Legend. *Results are from machine learning models trained on a non-federated ("pooled") or federated ("concurrent" or "online") synthetic dataset, for the prediction of 30-day readmission. The resulting models were then applied to the test set (N=1,000), and the binary classifications made by each pair of models were compared. *The Spearman's rho correlation coefficient between the predicted probabilities produced by the two models.*

Despite the differences between the binary classifications made by the federated and non-federated approaches, the pooled, online and concurrent models had similar predictive accuracies when applied to the test set (**Table 8.4**). The overall accuracy statistic ranged from 64·4%-71·7% and the AUROC for the predicted probabilities ranged from 0·663-0·669. Specifically, the AUROC for the pooled

model was 0·667 (95% CI: 0·621-0·713), which did not differ significantly from the 0·663 (95% CI: 0·616-0·710) for the online model (p=0·739) or the 0·669 (95% CI: 0·623-0·716) for the concurrent model (p=0·824).

Table 8.4. Comparison of predictive accuracy of machine learning models

Model	Accuracy	Sensitivity	Specificity	PPV	NPV	AUROC (95% CI)*
Pooled	67·5% (675/1000)	51·0% (78/153)	70·5% (597/847)	23·8% (78/328)	88·8% (597/672)	0·667 (0.621-0.713)
Online	64·4% (644/1000)	55·6% (85/153)	66·0% (559/847)	22·8% (85/373)	89·2% (559/627)	0·663 (0·616-0·710)
Concurrent	71·7% (717/1000)	46·4% (71/153)	76·3% (646/847)	26·1% (71/272)	88·7% (646/728)	0·669 (0·623-0·716)

***Legend**. Results are from machine learning models trained on a non-federated ("pooled") or federated ("concurrent" or "online") synthetic dataset, for the prediction of 30-day readmission. The resulting models were then applied to the test set (N=1,000), and the accuracy of the predictions made by each model was assessed. *The area under the receiver operating characteristic curve (AUROC) was calculated using the predicted probabilities from each model.*

P(N)PV: Positive (Negative) Predictive Value.

8.4 Interpretation

Federated analytics and learning is increasingly prevalent and may be default methodology for analysing sensitive health data.[293-295] However, the security benefits this offers[296] can only be realised if the resulting analysis accurately reflects the pooled data analysis.

This study demonstrates the feasibility of employing various statistical approaches within a federated analytics framework across diverse data domains. Selected traditional statistical methods, namely ANOVA, produced identical outputs irrespective of the way the data were partitioned between TRE nodes, which were in turn identical to the non-federated analysis of the pooled dataset. Therefore, for

studies requiring analysis using GLM models, federated analytics can be used without impacting the results of the analysis.[297, 298]

The federated analytics for ML models found differences between the models resulting from federated and non-federated approaches, and between the different learning methods used in the federated approaches. The classifications made by the three approaches were generally consistent, with the level of agreement between models being only marginally lower than for repeated models trained on identical non-federated datasets. In addition, the predictive accuracies of the ML models produced using pooled, online, and concurrent models were similar, ranging from 64·4% to 71·7%.

However, it is important to recognise that differences exist in the ML models generated using a federated versus pooled approach. The clinical relevance of the differences in ML models generated using a federated versus pooled dataset, and the resulting impact on the performance of a tool at the individual level will be context dependent. This may be of relevance to regulators, especially for tools used as a medical device, and should be considered in regulatory pathways. Although several aggregation strategies for federated learning knowledge have been proposed, the field is still in its early stages of development, and more work is needed to determine the impact on the models derived. As well as the potential differences in ML models generated using a federated approach, there are other challenges with federated analytics which need to be explored.

As well as the potential differences in ML models generated using a federated approach, there are other challenges with federated analytics which need to be explored. Primarily, it is vital to ensure that data are consistent and accurately matched across nodes. This results in a heightened reliance on metadata, which must accurately reflect the definitions and coding of variables. In addition, the responsibility of data cleansing and harmonisation resides with data controllers, creating potential inconsistencies in data quality across nodes. The lack of standardised frameworks and common data models can also exacerbate difficulties in conducting analytics across varied datasets. The levels of data consistency, cleansing or harmonisation are difficult to identify where a federated approach is used, since no one individual has access to the whole dataset, potentially propagating misinterpretations and flawed analyses where these are inadequate. Secondly, whilst the federated approach can be effective in addressing privacy concerns, sophisticated strategies are required to balance privacy preservation with effective analysis. The governance associated with federated analytics is still in development.[299, 300]

In conclusion, we demonstrate the potential of federated approaches in maintaining predictive accuracy while preserving data privacy and security. For traditional statistical techniques (here, a one-way ANOVA), the models generated using federated approaches were identical to those generated using a non-federated approach, irrespective of how the data were split across nodes. For ML analyses, there was some variability in the models produced using the federated

and non-federated approaches, and across the different federated approaches. Although there was no statistically significant difference in predictive accuracy observed between the models, the impact on clinical performance may be context specific and warrants further exploration.

Chapter 9: General Discussion

9.1 Thesis overview

Healthcare is an information-driven process. However, with the current digital revolution, how information is handled is changing dramatically.[301] EHRs offer several potential benefits for clinicians and patients, such as direct access to information to assist in clinical decision-making.[302] They also facilitate clearer communication between healthcare providers and enable patients to take a more active role in their own healthcare.[303]

Although EHRs have been around for over 50 years, concerted effort to increase their use began in the 1980s. The initial uptake of these systems was slow due to the significant expense in implementation.[304] This, compounded with the challenges of extracting and using this data for research, means that their effects on healthcare quality are largely uncertain. More studies need to be conducted, and only time will tell the direct and indirect effects on healthcare quality and service. In summary, the digital revolution's effects on healthcare can be broken down into three parts: how information is managed, how information can be used to improve care, and the culture surrounding care.

This thesis aimed to describe the utility of EHRs within the context of healthcare quality and safety improvement. **Chapter 2** defines the key principles and processes required to establish, operate and provide ethical and secure access to unconsented health data. This is the foundation to demonstrating and deriving benefit from real-world health data through research, by enabling access to data

without specific consent from patients. **Chapter 3** and **Chapter 7** examine the potential for EHRs to assess and enhance the implementation of clinical guidelines. These chapters examine the use of EHR as a tool for improving patient care and quality. **Chapter 3** takes a learning system approach that is focused on medicines management, specifically the prescribing of LMWH as a prophylactic therapy. The study explored if EHRs can support increased guideline compliance and reduce the prescribing errors as the evidence to date was inconclusive. **Chapter 7** utilises real-world data to assess the impact on safety of using an age-adjusted D-dimer threshold in a diverse urban centre.

Chapter 4 assesses if EHRs lead to improved efficiencies, as the literature again is conflicting with some studies suggesting that it can impact negatively on pathways and outcomes. The study examined the impact on turnaround time for blood results following implementation of an electronic ordering system. The efficacy of EHRs in testing the effectiveness of healthcare processes proposed by policymakers was explored in **Chapter 5** and **Chapter 6**. These chapters reviewed the COVID Virtual Ward model and NHS England's 'reason to reside' criteria and evaluated the need for rigorous validation before adoption to avoid potential unintended consequences. Finally, **Chapter 8** reflects the current requirement to be able to federate analytics between secure data environments. The chapter compares results from analyses run on the data directly and via federation using both traditional statistics and machine learning.

Overall, this body of work presents significant findings in the following areas:

- **Positive Impact on Healthcare Quality**: EHRs contribute to healthcare quality by streamlining processes, improving accuracy, and supporting evidence-based decision-making.
- **Enhanced Patient Outcomes**: The D-dimer study demonstrated that EHR data can improve patient outcomes by reducing unnecessary treatments and procedures.
- **Efficiency Improvements**: The implementation of EHR systems with CPOE, can lead to significant and sustained improvements in operational efficiencies, particularly in laboratory and clinical processes.
- **Support for Policy Decisions**: The policy and regulatory landscape is evolving and the use of RWD for regulatory decisions increasing. However, the success relies on ensuring appropriate quality data is utilised to ensure robust decisions.
- **Innovative Data Techniques:** As the use of machine learning increases, the opportunity to drive innovation will be significant. Federated analytics are going to be pivotal in support access to disparate databases, whilst ensuring privacy is maintained.

9.2 Chapter overview

This final chapter will summarise the main findings of this thesis, including strengths and limitations. Detailed discussions can be found in the respective chapters of this thesis. This chapter will focus on the key findings in relation to healthcare and propose research that can follow on from my work.

9.3 Summary of findings

The literature examined for **Chapter 2** indicates the disparity between the burden of acute care to research output from this specialty. It was this critical need to bring innovation through new therapeutics, clinical decision support tools, patient pathways and devices that lead to the creation of PIONEER. Literature and the workshops held suggested the public is 'broadly' supportive of sharing data for research.[305-307] However, concerns were raised around ensuring public and patient involvement in decisions and that the data were appropriately de-identified. The success of these data hubs is founded on robust, transparent governance processes. Equally as important that the north star of patient benefit is apparent in each data request supported.

There was some evidence in the literature to suggest the effectiveness of EHRs around prescribing and medication management. However, most studies were on smaller, less diverse populations and for shorter time periods. What was less clear in the literature was if EHR systems could impact on guideline compliance. In **Chapter 3**, the study focussed on whether these systems could improve prescribing compliance of LMWH to reduce the risk of VTEs. This study was able to demonstrate the effectiveness and impact of real-time prescribing prompts on guideline compliance. Prior studies suggested employing a specialist VTE nurse to provide real-time feedback as an effective approach to improve compliance.[308, 309] The results from this study were promising in terms of compliance achieved,

although EHRs are not cost neutral they are available at any time day or night, and performance was maintained over time.

In **Chapter 7**, the use of EHRs for guideline compliance was further explored, specifically examining the safety and efficacy of an age-adjusted threshold compared to the standard threshold in D-dimer testing. The study utilised EHR data to support the planned adoption of an alternative threshold in clinical pathways. As the largest study of its kind, it provided substantial evidence that the age-adjusted threshold improves patient outcomes by reducing the risk of over-medication and unnecessary scans. Additionally, this approach enhances patient flow efficiency by decreasing the need for return appointments, thereby also generating financial savings.

Chapter 4 focused on a lesser-known aspect of EHRs: their potential to improve efficiencies. This study examined the impact of computerised ordering (CPOE) systems on turnaround times from blood sample collection to the reporting of results to clinicians. Utilising PIONEER's extensive data set, which included over 1.8 million blood samples collected over six years, the study had significant statistical power to analyse the impact of CPOE implementation. By examining trends two years before and after implementation, the study assessed sustained impacts. The findings demonstrated that despite an increase in blood samples by 31%, there was clear evidence of improved efficiencies in the pathway, particularly in laboratory flow.

As the NHS, Government, and Regulatory agencies increasingly look to use RWD to support guideline development and regulatory decisions, it is crucial to evaluate the utility of such data. **Chapters 5** and **6** explored whether EHRs could support two different policy decisions: COVID Virtual Wards and the 'Reason to Reside' (R2R) criteria. The findings from these studies provided strong evidence in favour of using RWD to support future pathways and initiatives. Currently, decisions are primarily based on smaller randomised controlled studies. However, the analysis of implementing the COVID Virtual Ward in a large acute hospital showed that, while improving patient safety and avoiding hospitalisation were important goals, these plans should be modelled and tested in RWD settings. The study found no additional benefits from this service, and it would have significantly increased staff resources and costs without additional benefits. Similarly, the R2R study revealed the need for more in-depth analysis and modelling, as the current tool does not support decision-making and could lead to unintended consequences.

Federation is emerging as a promising approach for breaking down the silos and barriers faced by researchers accessing data across multiple organisations. **Chapter 8** examined the reliability and accuracy of federated analytics across SDEs. This emerging topic is crucial for enabling seamless data sharing while maintaining accuracy and security. Achieving federation has been challenging for the NHS, and efforts are ongoing to establish the necessary infrastructure and data formats. However, there is limited evidence in the literature regarding the challenges and accuracy of running federated analyses on healthcare data. The

results of this study were promising for traditional statistics, as the models produced identical results when comparing federated results to the gold standard pooled data. For ML, the results were not statistically different, though some variability was observed, indicating that further work is needed to ensure accuracy when using a federated approach.

9.4 Future Directions

The core aim of the Department of Health and Social Care (DHSC) and NHS England (NHSE) in equipping the healthcare system for the future is to enable people to have access to the right data at the right time. In November 2023, NHSE announced that 90% (N=189) of trusts now have EHRs, a month ahead of the target initially set[310]. This significant investment in EHRs set the foundational building blocks required for the next steps towards digital transformation. To meet the core level for this foundation, the NHS Long Term Plan has committed to all trusts having an EHR by March 2025.[24, 311]

The NHS England Digital Maturity Assessment was created for providers and integrated care systems across England to "…understand their level of digital maturity by identifying key strengths and gaps in the provision of digital services".[312] The assessment was designed around the What Good Looks Like (WGLL) framework [313] that has 7 measures of success, these being:

1. Well led
2. Ensure smart foundations
3. Safe practice

4. Support people
5. Empower citizens
6. Improve care
7. Healthy populations

These measures provide a framework to identify areas for improvement to enable organisations to plan their digital transformation. Implementing an EHR is only part of the journey to digital maturity. The measures ensure that each organisation has a clear digital and data strategy, along with secure and modern environments. Security is maintained by several robust criteria including cyber security and clinical safety. Measures 4 and 5 centre around a digitally literate workforce and that citizens are at the centre of the service design. Measures 6 ensures that these digital services improve health and well-being by ensuring the right care at the right place. The final measure 7 focusses on health populations and reducing health inequalities. It is only when all these measures are addressed that an organisation can be considered digitally mature. It is pertinent to state here that despite the progress with EHR implementation figures released in June 2022 suggested that only 20% of NHS organisations are digitally mature.[310]

Digital health technology is crucial for evolving national health and care systems that actively utilise data to enhance decision-making in policy, public health, research, and individual care. The COVID-19 pandemic created an urgent requirement to accelerate digitisation and data sharing throughout Europe.[314] As digital maturity still differs significantly between providers, the field is engaged in

both assessing and levelling up the adoption of technology. Organisations are required to undertake digital maturity assessments to identify gaps in their service provision that enable them to identify opportunities for development and plan the future delivery of health services.[312]

The rapid adoption of these technologies within healthcare has contributed to the generation of large and complex datasets.[315] In order to maximise the benefits of this complex siloed data, health data hubs and SDEs have emerged (as introduced in **Chapter 1**), to provide secure ethical access. The success of these environments will rest on their ability to simplify this complex and rapidly evolving landscape. Furthermore, these data providers will need to ensure they maintain public trust whilst being able to service requests in a timely manner.

The growing evidence, including that presented in this thesis, suggests that digital technologies can change how healthcare is delivered through improved quality, safety and efficiency. However, the field needs to balance these positive effects with the risks of increasing health inequalities that could lead to exclusion and disadvantage for the public and staff. Digital exclusion occurs where an individual lacks skills, access or capabilities to engage with devices or services. The field is currently focussed on ensuring digital inclusion. It will be pivotal that this does not remain a static response but is dynamic to react and evolve to the change in technologies as they emerge. The approaches taken will need to include working

with communities most affected and ensuring solutions are developed to improve inclusion and the services offered.

Looking forward, the UK is focused on refining its health information technology by balancing centralised and localised approaches. System usability is being enhanced and a significant focus placed on interoperability, along with expanding capabilities in data management and analysis. These efforts also encompass addressing concerns over privacy and security and promoting digital inclusion. Future directions involve expanding the integration of electronic health records, bolstering health data science and leveraging real-world data.

As demonstrated through the research in this thesis, healthcare systems are complex environments. However, one key innovation with the potential to transform the NHS and healthcare in general is artificial intelligence (AI)[316, 317]. Integrating AI into healthcare offers significant opportunities to enhance healthcare quality, including improving disease diagnosis, optimising medication management, supporting guideline compliance, enhancing health management, and enabling patients to manage chronic diseases.[318-320]

Effective AI implementation must address data privacy concerns and ensure that it does not exacerbate health inequalities.[321] These advancements require robust regulatory frameworks and guidelines to manage the ethical challenges posed by new technologies, ensuring their safe and equitable application in healthcare settings.[322]

9.5 Strengths and limitations of real-world health

The strengths and limitations of each of the studies have been discussed in detail in **Chapters 2** to **8**. However, there are some core strengths and weaknesses of real-world data recognised by researchers in the literature which are discussed in more detail below.

9.5.1 Strength of using real-world EHR data

Real-world health data (RWD) offers numerous strengths in research, particularly in its ability to provide insights from a large and diverse population. As stated in the introduction, RCTs were considered the gold standard for evidence-based medicine when trying to determine the safety and efficacy of medical products. In recent times the generalisability of these trials has been challenged as more evidence has emerged that indicates underrepresented populations may have differing presentations and responses to the product.[323-325]

RWD addresses this risk as it includes a diverse sample population that is more representative and reflective of the real world. This broad representation enhances the generalisability of research findings, especially when compared to the controlled settings of a clinical trial. As data are gathered from everyday healthcare settings the analyses provide the actual effectiveness and safety of pathways and treatments in the general population, compared to a controlled clinical trial population.

One of the most significant benefits of RWD is the potential for access to significantly large sample sizes. RWD can be sourced from numerous extensive sources, such as EHRs. The CPOE that examined the impact of electronic order communications on laboratory turnaround times (**Chapter 4**) accessed over 2 million samples over a six-year period. This vast volume of data allows for robust statistical analyses and power for calculations. Patterns and associations can be revealed that might not be apparent in smaller studies, therefore enhancing the precision and reliability of research findings. Furthermore, utilising existing data can often be more cost effective than conducting clinical trials and collecting data for a study. Therefore, more exploratory studies can be undertaken as they are affordable.

RWD often contains longitudinal data over considerable time periods, offering insights into long-term outcomes such as disease progression or the impact of an intervention. For example, the VTE prescribing concordance study (**Chapter 3**) had access to data spanning nearly a decade. This extended timeframe allows researchers to assess whether interventions have sustained impact over time.

9.5.2 Limitations of the data source

Whilst RWD offers significant benefits for research, there are various challenges that can impact the validity and reliability of study findings. A primary concern is the quality and completeness of the data, which can vary significantly across differing sources. RWD is collected for clinical or administrative purposes rather

than research. As a result, not all the relevant information may be captured leading to missing data which may cause inaccuracies and affect the research outcomes.

Furthermore, RWD is susceptible to various bias and measurement errors that stem from multiple sources.[326] Selection and information bias are particularly prevalent, arising from the non-randomised nature of data collection. Certain populations might be over- or underrepresented in the data due to patterns of health seeking behaviours. Furthermore, the methods of data measurements and recording can lead to inaccuracies. Non-random errors can be created through data entry mistakes and/or the misclassification of variables. Researchers need to be aware of these errors and potential biases as they can skew findings and affect accuracy.[327]

Moreover, ethical and regulatory considerations create additional challenges. The use of RWD must comply with strict privacy laws and ethical guidelines regarding the handling of patient information. These laws can restrict access to detailed data and complicate the sharing of information across different providers.

Lastly, the integration of data from multiple sources adds complexity due to variability in data collection methods, formats, and standards. The heterogenous data can require extensive pre-processing before any analysis to ensure the data are standardised.

9.6 Future Research

This thesis has been able to shed light on the potential use of EHR within healthcare, specifically providing evidence of improved quality and efficiency. **Chapter 1** introduced the concept that EHR data had the potential to revolutionise future medicine.[1] The implications and recommendations for practice, policy and research were discussed in **Chapters 2** to **8**. These findings inform the next steps and the potential future research required to maximise the benefit of EHR data. These potential options for research are summarised below.

Firstly, further studies are needed to explore the efficiencies derived from EHR systems, as current evidence is still limited in this area. Research should aim to quantify the benefits of EHRs in various clinical and operational contexts to provide a comprehensive understanding of their impact on healthcare delivery.

Additionally, the collaboration with policymakers and regulators is essential. Their expertise will be crucial in understanding how EHR data can be used to enhance the robustness of healthcare policies and guidelines. Frameworks will need to be developed that ensure data integrity, privacy, and security while maximising the utility of EHR data in the decision-making processes.

Further research is required to explore the role of AI in healthcare, particularly how federated analytics can support advancements in this field. With over 80% of health data now in unstructured formats, it is crucial to develop technologies that

can effectively utilise these data types.[328] Key considerations in this evolving field are particularly focussed on the potential of AI to augment clinical practice.[319] The initial barrier to accessing larger databases is being resolved through research hubs. Therefore, the focus can be turned to ensuring models do not create biased outcomes, especially those created by machines viewed as 'black-boxes'. Furthermore, work will need to focus on how these models can be validated and implemented in clinical practice.

Finally, it will be crucial to address the ethical and equity challenges associated with the use of AI within EHR data. Research should focus on developing strategies to ensure that these technologies do not contribute to health disparities and that their benefits are equitably distributed across all patient populations. Guidelines and best practices for the ethical use of AI in healthcare will need to be created.

9.7 Future Direction

As a result of the projects included in this thesis, my work with PIONEER as a Technical Director, and other projects and grants outside the thesis, I have significantly developed my skills as an independent researcher. My experiences have fostered a strong interest in expanding real-world data studies and bringing innovation to acute care.

9.8 Conclusion

Electronic Health Records (EHRs) have brought about a paradigm shift in healthcare delivery, exerting a profound influence on patient safety, clinical quality, operational efficiency, and financial stewardship. A crucial element contributing to the success of EHRs is the establishment of organisations such as PIONEER, which underscores the importance of upholding ethical practices in handling healthcare data. The involvement of patients and the public in the decision-making process concerning data access is not merely a procedural requirement. It is imperative to ensure that the voices of data providers are duly acknowledged, thereby fostering transparency and cultivating trust in the system.

The next undertaking involves the provision of further in-depth acute care research on comprehensive longitudinal real-world data. This will empower clinicians and policymakers to make well-grounded decisions pertaining to future healthcare provisions.

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Appendices

Appendices for Chapter 2

Supplementary File 2.1: Published manuscript for Chapter 2

Open access Protocol

BMJ Health & Care Informatics

Infrastructure and operating processes of PIONEER, the HDR-UK Data Hub in Acute Care and the workings of the Data Trust Committee: a protocol paper

Suzy Gallier,[1] Gary Price,[2] Hina Pandya,[2] Gillian McCarmack,[2] Chris James,[2] Bob Ruane,[2] Laura Forty,[2] Benjamin L Crosby,[2] Catherine Atkin,[2] Ralph Evans,[3] Kevin W Dunn,[4] Eliot Marston,[5] Clark Crawford,[6] Martin Levermore,[7,8] Shekha Modhwadia,[3] John Attwood,[9] Stephen Perks,[10] Rima Doal,[1] Georgios Gkoutos,[11] Richard Dormer,[12] Andy Rosser,[13] Hilary Fanning,[14] Elizabeth Sapey [2,15]

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For numbered affiliations see end of article.

Correspondence to
Dr Elizabeth Sapey;
e.sapey@bham.ac.uk

ABSTRACT

Introduction Health Data Research UK designated seven UK-based Hubs to facilitate health data use for research. PIONEER is the Hub in Acute Care. PIONEER delivered workshops where patients/public citizens agreed key principles to guide access to unconsented, anonymised, routinely collected health data. These were used to inform the protocol.

Methods This paper describes the PIONEER infrastructure and data access processes. PIONEER is a research database and analytical environment that links routinely collected health data across community, ambulance and hospital healthcare providers. PIONEER aims ultimately to improve patient health and care, by making health data discoverable and accessible for research by National Health Service, academic and commercial organisations. The PIONEER protocol incorporates principles identified in the public/patient workshops. This includes all data access requests being reviewed by the Data Trust Committee, a group of public citizens who advise on whether requests should be supported prior to licensed access.

Ethics and dissemination East Midlands–Derby REC (20/EM/0158): Confidentiality Advisory Group (20/CAG/0084). www.PIONEERdatahub.co.uk

INTRODUCTION

The National Health Service (NHS) is the publicly funded health provider for the UK. Specific NHS organisations hold identifiable patients' medical information,[1] increasingly within electronic health records (EHRs). EHRs facilitate health data sharing for personal medical care (the primary purpose of the health data) and also for health service planning, research and innovation, collectively termed 'secondary uses'.

Health Data Research UK (HDR-UK), the national institute for health data science, coordinated the designation of Health Data Hubs in alignment with the UK's Industrial Strategy to improve the quality, discoverability and accessibility of health data for research.

PIONEER is a Health Data Research Hub that focuses on providing licensed access to acute care health data. It was developed to curate routinely collected health data from unplanned healthcare contacts across community, ambulance and hospital providers and then facilitate the transparent and ethical use of deidentified data for research and innovation purposes. PIONEER has a principle aim of improving patient care and well-being through research. PIONEER is not a clinical system and does not provide healthcare to individuals. For clarity, PIONEER is not a Health IT System for use in the health and care environment, it sits within the Health and Social Care Research Framework, not driving clinical care for the data subjects within the research database.

'Acute care' is any unplanned health episode. Each year the NHS provides approximately 110 million urgent same-day patient contacts[2] with the numbers rising year on year. There are known health inequalities associated with acute care, as people from lower socioeconomic groups are more likely to present to emergency departments.[3] Acute care provides a unique and useful microcosm of wider health service challenges, for example, one in five patients with cancer is diagnosed as an emergency, with significant implications for long-term outcomes.[4]

Despite the scale and cost of acute care, this specialty has not benefited from significant innovation.[5] There is a critical need for new patient pathways, diagnostic processes,

therapeutics and devices in acute care. Licensed access to acute care health data could offer unique insights and design potential solutions to some of the challenges this health sector faces.

Previous research suggests there is public support for data sharing but with key concerns.[6] The PIONEER Hub conducted a series of public and patient events and developed a framework for health data secondary use, in collaboration with patients and public stakeholders.[7] The agreed framework included health data access if the supported research could benefit patients and citizens, a commitment to transparency with data sharing overseen by the NHS and patient/public involvement in data access decisions. Studies have described greater confidence in data sharing when the NHS is involved,[8 9] that public involvement is important[10] and that the principles of data minimisation should be applied.[8] The PIONEER protocol was developed to ensure this framework was embedded within all operating processes.

METHODS AND PIONEER OPERATING PROCESSES

The principle of public good

PIONEER is a partnership between patient and public members, the NHS, universities, data scientists and selected industry partners. For the full protocol, please see the online supplemental file.

The aim of PIONEER is to link routinely collected health data from acute care providers and use this in an anonymised form to innovate healthcare through research.

PIONEER supports the following objectives:

1. To develop a research database and analytics platform of linked, routinely collected health data from different healthcare providers.
2. To work with patients, the public and other stakeholders to ensure that data access through PIONEER is in the public interest.
3. To make datasets discoverable and appropriately accessible to research organisations, NHS bodies and commercial organisations, where the supported research is likely to lead to patient benefit.
4. To support research, development and innovation within a robust governance system.

The potential uses of the PIONEER dataset include but are not limited to research supporting improvements to service delivery, reducing diagnostic delay, reducing chronic disease burden, and development of new treatments and technologies such as point of care testing, self-management software and live data streaming to provide interventions closer to home and avoid unwanted or unnecessary hospital admissions.

Proximity to the NHS

University Hospitals Birmingham NHS Foundation Trust (UHB) is the data controller for PIONEER. UHB is one of the largest NHS Trusts in England, with 2750 beds, more than 22 000 staff, an in-house built and clinically lead EHR (Prescribing Information and Communication System) and a shared primary and secondary care record (Your Care Connected).

Patient inclusion criteria

Any patient with an acute health issue who has sought medical advice/care from a PIONEER data partner. Any and all acute episodes can be included with no restriction on disease, condition or age. Patient data within PIONEER is collected as part of routine care. Longitudinal data will be eligible if it relates to, leads to or stems from an acute care contact. Patients will not need to specifically consent to their health data being used within PIONEER, but patients will not be included if they have chosen to opt out of the use or disclosure of their data for research and planning via the NHS National Data Opt-Out[11] or if they have opted out of PIONEER specifically (see ethical considerations).

Included data

PIONEER includes data about patient demographics (age, gender, ethnicity), past and current medical diagnoses, medications, allergies and healthcare contacts. There is serial data on vital signs, investigations including laboratory, pathology, physiology and imaging, all acute medical prescriptions and administrations and health process data (clinical review specialty, ward type). This is supplemented with health data prior to and after the acute care contact, linked across healthcare providers, to enable assessment of preceding health and subsequent outcome. The PIONEER dataset adds to publicly available datasets, as highlighted in the examples provided in table 1.

Research database design and security

Data will be stored on a secure, UHB-controlled Microsoft Azure cloud platform in accordance with the 14 UK Cyber Cloud Principles,[12] which include data protection in transit; asset protection and resilience; separation between users; a robust governance framework; operational security; secure user management; identity and authentication; and audit. The cloud provision will follow the International Organization for Standardization (ISO) 27 001 standards, an international specification for information security management.[13] This ISO outlines a broad range of quality control processes, many of which apply to data collection, processing and management with a strong emphasis on information security. An example of how this will be met for PIONEER is that data transferred between organisations will be mathematically checked to ensure it has not been tampered with.

The database platform will comply with the Department of Health Information Governance policies and standards for secure processing of patient healthcare data, as set out in the Information Governance Toolkit of the Health and Social Care Information Centre.[14] The database platform will undergo cyber-security checks by an independent and external company. The platform's design enables the

Table 1 A summary of related data sources

Name	Country	Subject areas	Update period	Description
HES	UK	All healthcare	Daily (A&E is quarterly)	High-level, does not include physiological measurements outside of classifications in main diagnoses
MIMIC	USA	Intensive care	Static	Deidentified data covering period '01–'12, in high detail
WHO Global Health Observatory	Global	All healthcare	Variable	High-level count data, on a global scale, does not go to the level of individual patients
Global Health Data Exchange	Global	All healthcare	Variable	Catalogue of existing datasets, generating novel data is outside of its scope
NIHR Health Informatics Collaborative	UK	Thematic		Open only to member of the HIC for collaboration, does not provide a TRE
PIONEER	UK	Acute care including preceding and subsequent health contacts	On demand	Datasets tailored to specific use cases, updated on demand and available via a secure TRE. Individual patient level data that includes medications, physiological measurements, images over 20 years. Individually linked data from primary care, ambulance and secondary care.

This should not be considered fully comprehensive, but highlights the differences between currently available datasets and PIONEER.
HES=Hospital Episode Statistics.[24] MIMIC Critical Care Dataset,[25] Global Health Observatory,[26] Global Health Data Exchange[27]
NIHR=National Institute for Health Research Health Informatics Collaborative.[28]
TRE, trusted research environment.

rapid build of bespoke trusted research environments (TREs) which provide approved and licensed researchers with access to specific curated, deidentified datasets and a suite of analytical tools (description available from corresponding author). The use of a TRE circumvents data travel from the data controller to the data user. PIONEER is committed to promoting the protection of privacy and data security in line with the Organisation for Economic Co-operation and Development (OECD) Recommendation of the Council on Health Data Governance[15] .

Data processing

Data is extracted, transformed and securely transmitted to PIONEER/UHB's managed cloud environment. The data held internally within the PIONEER Research Database is pseudonymised (with personal identifiers replaced with other values (pseudonyms), from which the identities of individuals cannot be intrinsically inferred). Pseudonymisation does not change the status of the data as personal data. Only anonymised data is released to our approved partners (where identifiable data features are removed). The PIONEER Research Database does not contain direct and recognisable identifiers such as name, full address, images of a face or NHS number.

Risk will be managed proportionately when providing access to data that might, alone or through combination, lead to a risk of identification of an individual. A specific example is a postcode. PIONEER holds postcode data to support studies into equity and social deprivation. To reduce risk, a postcode will not be provided directly to researchers. Instead, PIONEER will provide a less specific geographical unit such as the Lower layer Super Output Area (LSOA)[16] or the associated data of interest such as the Index of Multiple Deprivation score.[17]

Diagnoses including rare diseases are included within PIONEER. A rare diagnosis may enable identification if combined with enough additional indirect identifiers. Access decisions will be evaluated on a case-by-case basis and appropriate restrictions will be placed on accompanying data that might significantly increase the risk of identification. Of note, PIONEER processes were developed after discussion with patients with rare conditions, and they explicitly supported the inclusion of rare diseases in PIONEER (even very rare diseases which risk identification due to rarity) to improve acute care services for these conditions.

Data quality

Each healthcare provider who uses electronic systems will conduct quality checks on their data to ensure that it is suitable to provide clinical care (the primary purpose of data collection). Data quality assurance (QA) checks will also take place within PIONEER and to ensure the quality of data contained within datasets and PIONEER works towards meeting particular standards, including to the metadata catalogue (ISO 11179),[18] data quality (ISO 8000)[19] and QA (ISO 25012).[20]

Metadata catalogue (ISO 11179)

A metadata catalogue is used to help the potential user of a database to understand what it contains. The referenced standard addresses the semantics of data, how data

is represented and the registration of the data descriptions. ISO 11179 specifically specifies the kind and quality of metadata necessary to describe data as well as the management and administration of that metadata in a metadata registry. The purpose of this standard is to promote the standard description of data and a common understanding of data across and between organisations. PIONEER works to meet this standard through organising data using data element concepts, data elements, conceptual domains and value domains. The 11 179 standard also provides a way to depict relationships among concepts. We use this feature to represent relationships among data. PIONEER links to the HDR-UK Innovation Gateway, which allows researchers to explore datasets, tools, papers and related resources used in health research across the UK through a metadata catalogue, which includes many of the features described above (see https://www.healthdatagateway.org).

Data quality (ISO 8000)

Data quality is a broad term that encompasses a range of evaluation and data management techniques. Generally, to be of high-quality data must be considered to be accurate, complete, fit for the required purpose (meeting the needs of the end user) and assessable via a good quality management framework such as those described in ISO 8000. An example of how this will be met for PIONEER is that each table will be inspected to identify fields that are intended to link with other data, and these links will be tested.

Quality assurance (ISO 25012)

'Quality assurance' is the overarching term for a range of steps that are designed to ensure that a process meets a quality goal; this is distinct from 'quality control' that relates to testing the outputs of a QA process. The data quality management framework defines the activities to be undertaken to ensure that data is collected accurately and completely, meeting predefined quality targets and governance constraints. PIONEER data officers will be trained in current information governance good practice and work to a predefined standard operating procedure to meet this standard.

PIONEER improves data quality through checks applied during the processing stage, examples are to identify common data errors such as values that exceed the prescribed limit of characters, to ensure the values are in line and format with those in the NHS Data Dictionary and to ensure all mandatory data fields are complete, including completeness and count checks on the number of NULL values.

If any issues are identified, there is an iterative support loop in place to assist with feeding back and working through if it is a system or user error. The data is then re-extracted and the process of checking resumes until it is ready to stage.

Data deidentification

Pseudonymisation is needed for linkage purposes. As PIONEER processes healthcare data, industry standard best practices have been adopted, which ensures compliance with the Information Commissioner's Office and UK GDPR. These techniques are field level encryption (where the value is replaced with an encrypted version with a key) and hashing. See figure 1 for a diagram of this process. Hashing is a technique that uses standard functions based on mathematical algorithms to create new values. The selected value is represented by a 32-character hexadecimal string (combined letters and numbers), to enhance this security a random 'salt' is added. The data are then transferred to the PIONEER database via secure file transfer. Once received by PIONEER the data are reidentified to enable linkage (where applicable) and for QA and quality control checks, before being re-pseudonymised and moved to a secure safe-haven on Microsoft

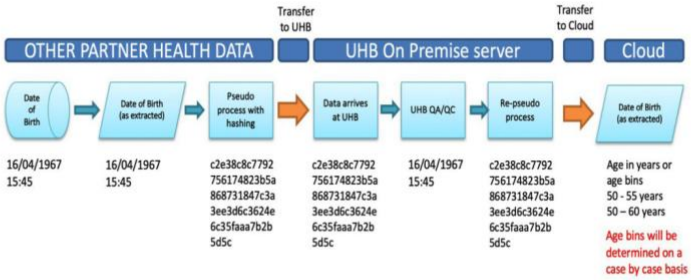

Figure 1 The process of pseudonymising health data in PIONEER. This describes the process to move data using a salt code. Data partners contain identifiable health data, as shown by the date and time of birth. This is extracted from the record in an identifiable form, and then made pseudonymised using a salt code. The date and time of birth cannot be calculated from this hash. The data is then transferred by secure and encrypted pathways to University Hospitals Birmingham NHS Foundation Trust (UHB). At UHB, a proportion of records will have the data made reidentifiable, for QA/QC purposes, but it then remains in the hashed format. If that data is requested, the hash will be transformed into an age in years or into appropriate age bins, as determined on a case by case basis, and as approved by the Data Trust Committee (DTC).

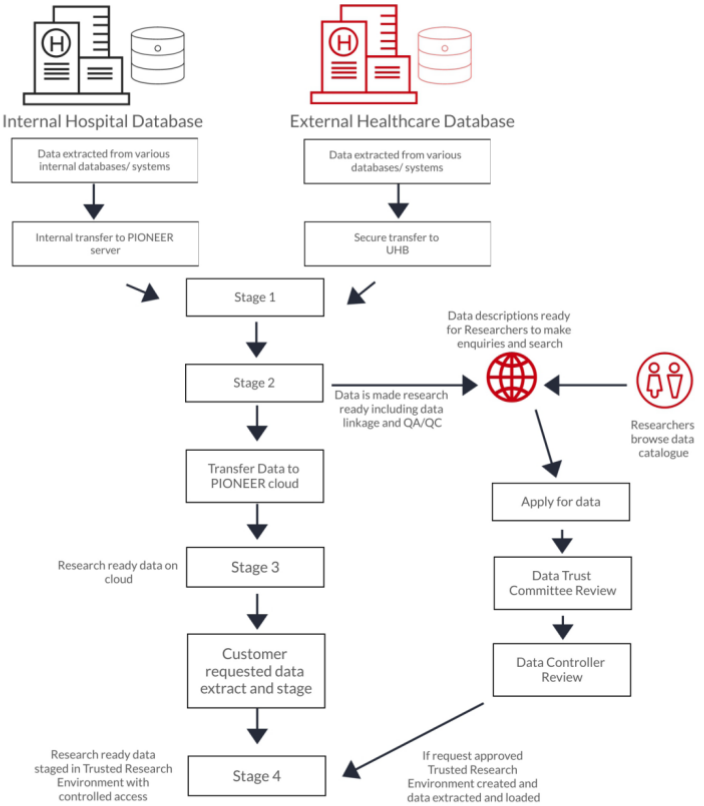

Figure 2 The data staging and access process. Data can enter PIONEER from internal (UHB) and external data providers. At stage 1, data has been cleansed, normalised and sent to UHB in a pseudonymised form. At stage 2, the pseudonymised data is checked, cleansed and undergoes QA/QC by the PIONEER team. From this data, a metadata catalogue is formed, providing high-level data descriptions, which describe the kind of data PIONEER holds. The metadata catalogue is available for researchers to browse. At stage 3, the pseudonymised data is moved to the secure cloud, only accessible by PIONEER team members for further QA/QC processes. If a data request is received, it is reviewed by the Data Trust Committee (DTC) and PIONEER team. The PIONEER team perform a due diligence check and assess the request in terms of risk (see table 1). If the DTC do not support data access, no data access occurs. If the DTC support data access, a data licensing agreement is formed and the exact cut of data required is anonymised, extracted and staged in a bespoke trusted research environment (TRE). At stage 4, this staged and anonymised data can then be accessed by the researchers using specific log on processes and only approved data can leave the TRE (which would be aggregate data and not individual data lines).

Azure for final processing. Prior to staging for research purposes, data is anonymised and K-anonymity modelling[21] is performed, to objectively assess the potential for reidentification. The acceptable value will be assessed case by case with data controller and public oversight and agreement.

Figure 2 is a description of the data preparation process. Data made accessible via PIONEER will be necessary and proportionate to the purposes required, ensuring data minimisation. Data minimisation is assessed on a case by case basis. Data fields shared are only those deemed relevant to the specific research question and limited to what is necessary for the purposes for which they are processed as part of that research question. PIONEER can offer clinical expert consultancy to support this process. Approaches taken include to coarsening some potentially identifiable data (such as age into age groups) or to move a date to the start of a week and adjust all date and time-stamped data accordingly. A risk-based approach to deidentification was adopted to assess the required level of protection, while ensuring the utility and scalability levels required were considered. The data controller

maintains the overarching decision to approve the technique selected.

Deidentification of image files involves multiple steps for the three areas requiring attention—image filename; image metadata and identifiers burned onto the image. The image filename is checked to ensure it does not contain any patient identifiers, which are linkable outside the curating organisation, for example, the patient's NHS number would be replaced with a new unique key value associated with the patient's clinical data. The image metadata is examined, depending on the type of image (tags for the DICOM standard or EXIF fields for JPG images) to ensure they retain essential clinical information, such as modality, but do not contain any patient identifiers. Where found, identifiers are either removed or replaced with a new unique key value associated with the patient's clinical data. Lastly, the image is checked to ensure that it does not contain any burned-in patient identifiers. This is done using a combination of manual visual scanning and an evolving AI algorithm, which is being trained to take over this task. Burned-in patient identifiable data is manually removed by obfuscation, while ensuring that any burned-in clinical data is retained.

Data access

All requests for licensed data access will be reviewed against the principles of the 'Five Safes'[22] by the Data Trust Committee, the PIONEER management team and the PIONEER data controller. The 'Five Safes' framework is increasingly adopted by health data providers and includes an assessment of the safety of the project, safety of the researchers requesting access to the data, safety of the data (the risk of disclosure or reidentification) and safety of the data setting. PIONEER has contractual safeguards, with data access licensed to expressly preclude any attempts at reidentification and limit the use of the data to the purposes described within the contract, within a specific time frame. The final 'Safe' refers to safe outputs, ensuring the statistical results of data analysis are non-disclosive. PIONEER reserves the right to refuse an application or limit the data fields available, based on concerns around possible identification.

Data request pathways

This process was developed in collaboration with patient and public contributors.

Data requests will be considered from organisations, companies, researchers, members of the public or any agency or body, referred to as data Requestors.

All requests for licensed access to data will be considered against core principles for data access:

1. Benefit to patients, to the NHS, or society.
2. No due diligence concerns
3. Data requests are ethical, appropriate and are not excessive in the data requested nor include data which has more than remote possibility of being reidentified by other data held by the requestor or in the public domain—that is, data requests which pass the risk evaluation.

Data requestors complete a Data Request Form (DRF). The DRF mandates specific training before health data access. This includes reading the Data Security and Protection Toolkit[23] and the National Data Guardian's Review of Data Security, Consent and Opt-Outs[1] as well as taking an e-learning course for data security training. PIONEER will undertake due diligence checking for all data requestors. Requests are then assigned a Data Request Risk Rating: green for low risk, amber for moderate and red for a failed risk assessment. The rating will be based on the data requested, potential for risk and potential for patient gain. See table 2 for an overview of this process.

The DRF, due diligence and risk register will be reviewed by the PIONEER senior team, data controller and Data Trust Committee. The specific cut of data required for the project is deidentified and moved to the PIONEER TRE. The data requestor receives specific permissions to access that data within the terms of the Data License Agreement.

The Data Trust Committee

The Data Trust Committee (DTC) is an advisory function for PIONEER and acts as the public conscience of PIONEER, advising on data release decisions. A decision to support licensed data access by the DTC will lead to data access as long as contractual safeguards are in place. A decision not to support licensed data access by the DTC will be binding for PIONEER and no data will be shared.

The DTC will be made up of individuals recruited by application. All members of the DTC must declare all relevant conflicts of interest. The DTC will be assisted, when needed, by experts in relevant healthcare specialities, data research, information governance and UK data law. These experts will have an advisory capacity only and will not be voting members of the DTC. All data requests will be regarded as confidential. The DTC will discuss each data request form, due diligence and risk assessment and form a consensus decision whether to support the data request. The DTC will seek to form a unanimous decision regarding data access through discussion and reflection. Where this is not possible, non-unanimous decisions to support data access will require 80% of the DTC to support data access. A quorum of at least half of the DTC (rounded up) is required for the DTC to convene and the DTC will generate lay summaries of their activity for public review.

Building a framework for proportionate, retrospective data release reviews

In time, it is envisaged that the DTC will form proportionate review criteria, categorising some reviews as low risk based on self-developed and tested procedures, which might allow retrospective reviews of some data requests. However, this will only occur when the DTC have been operating for sufficient time to form a view about what a low risk application is, and after specific ethical approval.

Table 2 An overview of the Data Request Form and data access considerations

Heading	Requirements
The Data Request Form	
A summary of the data request	
The project: Technical summary	Project title, aims, scientific rationale and background in technical language.
The project: Lay summary	Project title, aims, scientific rationale and background in lay language.
Patient and public involvement	To describe the patient and public involvement and engagement (PPIE) work completed so far and to offer the opportunity for PIONEER supported PPIE.
Expected value of the project to the NHS and general public	To describe how the project is likely to lead to patient and public benefit.
Data requirements and analysis plan	This includes an exact description of the data fields required, whether aggregate or individual data lines are needed, and the justification for this. PIONEER offers the ability to perform analysis on behalf of the researchers. If the researchers wish to perform their own analysis, a description of techniques and tooling required is requested.
Security	Data access is only permitted with a data licensing agreement, but if necessary, anonymised data can be sent to an external trusted research environment (TRE). The security arrangements for this TRE will be listed and reviewed by the PIONEER team, including whether specific ISO standards are met.
Expertise	Listed to ensure the researchers have the relevant training and expertise to conduct the analysis.
Dissemination plan	PIONEER supports open access of data outputs to ensure insights benefit as many people as possible. The 'Five Safes' includes an assessment of whether data outputs could lead to patient reidentification, so the DRF includes a description of how this will be avoided.
Due Diligence	
An assessment of the data requestor, which is completed for all data access requests	
Human rights violations and significant harm	All data requestors undergo a due diligence assessment to determine evidence of serious human rights violations, arms manufacturing or trade and tobacco industry involvement.
Controversies and data breaches	All data requestors undergo a due diligence assessment to determine evidence of data breaches, falsified scientific reports or involvement in significant controversies including financial irregularities and health and safety fines.
Risk Assessment	
A summary of the potential benefit vs risk of the project, the researcher, the data and the data environment	
Benefit	Designated as clear benefit to NHS patients or society, potential benefit or no potential benefit.
Data	Designated as data which is aggregated or highly unlikely to or may lead to patient identification or data which has a realistic potential patient identification.
Security	Designated as provides evidence of data security which meet all requirements or meet most requirements with additional support or does not meet data security requirements.
Potential reputational risk to PIONEER	Designated as low, moderate or high based on due diligence check.
Previous dealings	To determine the outcome of previous data access activities.
Overall assessment of risk	Low, moderate or high with a recommendation to support or not support data access.

Ethical considerations and opting out

PIONEER operates within Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') to process confidential patient information without consent. The rationale for using health data without consent was that, to be effective, PIONEER will include data from millions of patients and be fully representative of the patient population as a whole. PIONEER will include data from people who have died and data from people who may not have the capacity to consent, so that the acute health journeys of more vulnerable people also have the potential to benefit from innovation.

As this is an important consideration, the use of data without explicit consent was specifically discussed with more than 300 members of the public prior to the development of PIONEER,[7] to specifically test if the majority of the public would support data use in this way.

Transparency

PIONEER is committed to open and transparent communications, which will support and acknowledge patient

and public input and help maximise access for high-quality collaborative research, including an Open Science approach and open access publication. PIONEER will provide data in the public domain regarding its operation and purpose.

CONCLUSION

This protocol paper outlines the working operations of PIONEER, the Health Data Research Hub in acute care. The ethically approved protocol has been devised to ensure patient and public voices are central in data access decisions and that PIONEER processes reflect the wishes and concerns of patient and public stakeholders. For more information about PIONEER projects and outputs, see www.PIONEERdatahub.co.uk.

Author affiliations
[1]PIONEER Health Data Research Hub, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[2]PIONEER Data Hub, University of Birmingham College of Medical and Dental Sciences, Birmingham, UK
[3]PIONEER Data Hub, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[4]HDR-UK Midlands Physical Site, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[5]Research Support Services, University of Birmingham College of Medical and Dental Sciences, Birmingham, UK
[6]Research and Development Governance, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[7]Medical Devices Technology International Limited (MDTi), Wolverhampton, UK
[8]Faculty of Business, Law and Social Sciences, Birmingham City University, Birmingham, UK
[9]Health Informatics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[10]PIONEER Health Informatics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[11]Institute of Cancer and Genomic Sciences, University of Birmingham College of Medical and Dental Sciences, Birmingham, UK
[12]Insignia Medical Systems Limited, Basingstoke, UK
[13]West Midlands Ambulance Service NHS Foundation Trust, Brierley Hill, UK
[14]Research and Development, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[15]Acute Medicine, Birmingham Acute Care Research, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

Twitter Hina Pandya @hinapublish and Catherine Atkin @catatkin

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Patient consent for publication Not required.

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ORCID iD
Elizabeth Sapey http://orcid.org/0000-0003-3454-5482

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Appendices for Chapter 3

Supplementary File 3.1: Published manuscript for Chapter 3

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Electronic prescribing systems as tools to improve patient care: a learning health systems approach to increase guideline concordant prescribing for venous thromboembolism prevention

S. Gallier[1], A. Topham[1], P. Nightingale[2], M. Garrick[3], I. Woolhouse[4], M. A. Berry[5], T. Pankhurst[6], E. Sapey[7*] and S. Ball[8]

Abstract

Background: Venous thromboembolism (VTE) causes significant mortality and morbidity in hospitalised patients. Risk factors for VTE are well known and there are validated risk assessment tools to support the use of prophylactic therapies. In England, reporting the percentage of patients with a completed VTE risk assessment is mandated, but this does not include whether that risk assessment resulted in appropriate prescribing. Full guideline compliance, defined as an assessment which led to an appropriate action—here prescribing prophylactic low molecular weight heparin where indicated, is rarely reported. Education, audit and feedback enhance guideline compliance but electronic prescribing systems (EPS) can mandate guideline-compliant actions. We hypothesised that a systems-based EPS intervention (prescribing rules which mandate approval or rejection of a proposed prescription of prophylactic low molecular weight heparin based on the mandated VTE assessment) would increase full VTE guideline compliance more than interventions which focused on targeting individual prescribers.

Methods: All admitted patients within University Hospitals Birmingham NHS Foundation Trust were included for analysis between 2011 and 2020. The proportion of patients who received a fully compliant risk assessment and action was assessed over time. Interventions included teaching sessions and face-to-face feedback based on measured performance (an approach targeting individual prescribers) and mandatory risk assessment and prescribing rules into an EPS (a systems approach).

Results: Data from all 235,005 admissions and all 5503 prescribers were included in the analysis. Risk assessments were completed in > 90–95% of all patients at all times, but full guideline compliance was lower (70% at the start of this study). Face-to-face feedback improved full VTE guideline compliance from 70 to 77% ($p \leq 0.001$). Changes to the EPS to mandate assessment with prescribing rules increased full VTE compliance to 95% ($p \leq 0.001$). Further

*Correspondence: E.sapey@bham.ac.uk
[7] PIONEER Health Data Research Hub in Acute Care, University of Birmingham, Edgbaston, Birmingham B15 2TH, UK
Full list of author information is available at the end of the article

amendments to the EPS system to reduce erroneous VTE assessments slightly reduced full compliance to 92% ($p < 0.001$), but this was then maintained including during changes to the low molecular weight heparin used for VTE prophylaxis.

Discussion: An EPS-systems approach was more effective in improving sustained guideline-compliant VTE prevention over time. Non-compliance remained at 8–5% despite this mandated system. Further research is needed to assess the potential reasons for this.

Keywords: Compliance, Deep vein thrombosis, Guidelines, Prescribing errors, Risk assessment

Introduction

Hospital Acquired Thromboembolism is defined as a venous thromboembolic event (VTE) (a deep vein thrombosis and/or pulmonary embolus) which was not present on admission but diagnosed within hospital or within 90 days of hospital discharge [1]. Hospital acquired thrombosis accounts for a significant amount of potentially avoidable morbidity and mortality [2] with an incidence rate of 9.7 per 1000 hospital admissions, with 71% diagnosed post-discharge [3].

The risk factors for VTE during admission are well known [4], there is an effective prophylactic therapy [2] and there are well-validated guidelines to assist assessment of the risk of VTE and where prophylaxis therapy should be prescribed[5]. However, rates of concordance with guidelines vary across international providers, from 16 to 85% [6, 7].

In England, a Commissioning for Quality and Innovation (CQUIN) framework set a threshold rate for acute hospital providers to undertake risk assessments for at least 90% of inpatients each month in 2010–2011 [8], which increased to 95% by 2013 [9]. This reporting is nationally mandated with each acute care hospital providing the number of adults admitted each month who have had a VTE risk assessment and the number of adults admitted in total, with specific groups of patients excluded from this analysis [10]. A recent National Health Service report suggests that the majority of acute hospitals in England are meeting the target of 95% of patients having a VTE risk assessment [11]. However, there is a difference in completing a risk assessment and acting upon it (either prescribing low molecular weight heparin (LMWH) when it is indicated or not when it is not). Currently, there are no figures to describe or targets to ensure full VTE guideline compliance (assessment and action on assessment).

Prescribing errors include inappropriate or erroneous inclusion or omission of drugs and an inappropriate assessment of the potential harm from giving or omitting a treatment [12]. Not acting on a VTE risk assessment is a prescribing error. The potential reasons for prescribing errors are complex but studies suggest that most mistakes were made because of slips in attention, or because prescribers did not apply relevant rules [13]. A number of reports have highlighted strategies to improve prescribing practices [14] including education, prescription aids (both paper and computerised) [15], mandated prescribing [16] and prescriber feedback and audit [17]. Given the relative short-term placements of junior medical staff within a specific hospital, targeting individual prescribing may be less effective for a single centre than implementing systems change to enhance safety [18].

It is important to note that some guideline-discordant prescribing behaviour may be appropriate depending on the clinical circumstance. For example, prophylactic low molecular weight heparin might not be appropriate in the last few days of life or those who are chronically bed ridden. Not all discordant prescribing should be viewed as an error.

Electronic prescribing systems (EPS) have been shown to improve inpatient medication management, especially by reducing medicine-reconciliation, dose, and avoidable delay-of-treatment errors [18, 19]. It is less clear whether EPS can reduce venous thromboembolic (VTE) prescribing errors associated with guideline non-compliance [20] and whether this is sustained or can be improved with further support in the prescribing process.

We hypothesised that systemic prescribing interventions would be more effective in improving full VTE guideline compliance, compared to face-to-face educational interventions, and that these improvements would be sustained.

Prescribing interventions were:

- Feedback of individual performance of doctors with identification and interviewing outliers (known as the Junior Doctor Clinical Dashboard)
- An EHR systems approach of adding mandatory VTE steps to the EHR during the admission processes.
- A systems approach change to the EHR VTE assessment form after clinician feedback to reduce options to "work around" mandated prescribing proposals.

Methods

Ethical approval

This research used anonymised health data and the protocol and all research activities were conducted with appropriate Health Research Authority and Research Ethical Committee (East Midlands—Derby Research ethics committee, reference 20/EM/0158) and HRA Confidentiality Advisory Group approvals (20/CAG/0084).

Setting

The hospital trust included in this study (University Hospitals Birningham NHS Foundation Trust (UHB)) is one of the largest NHS Trusts in England. The analysis made use of an in-house built, clinically-led EHR. This is a rules-based prescription-support system that includes all clinical documentation for admission, physiological and laboratory measurements, provides real-time drug prescribing checks and recommendations by triangulating physiological and laboratory results, comorbidities and prescribing data, as well as supporting institutional and individual audit of prescribing practices.

UHB question reported a VTE risk assessment completed in 98.5% of admitted patients for 2019–2020 [11] and has met all national targets since 2010. However, hospital staff wanted to ensure that these risk assessments were being acted upon, with full guideline compliance (a risk assessment and appropriate prescription and administration of LMWH when indicated, or no prescription of LMWH when not indicated).

Prior to the implementation of the VTE prophylaxis interventions described in the current paper, all staff received a hospital induction to ensure familiarity with procedures and policies. This included a specific induction talk with a focus on VTE assessments and the importance of prescribing LMWH. Additionally, there were rolling lectures held by Consultant Haematologists to reinforce learning. Online videos were available on prescribing LMWH along with other key clinical focus areas.

Patients

All emergency and elective adult admissions to the NHS Foundation Trust from January 2011 to October 2020 were included. Post first intervention, all data collection and analyses were prospective.

Prescribing practices outcome

The primary outcome for this study was full VTE guideline concordance within 24 h, defined as a risk assessment completed and the recommended treatment prescribed, expressed as a proportion for each week. Guideline non-compliance was defined as no VTE assessment performed, or where the VTE risk score suggested prophylaxis was needed and yet it was not prescribed or VTE prophylaxis was not indicated, yet it was prescribed.

Interventions

Interventions were developed in discussion with hospital management, pharmacists, hospital doctors of all grades and specialties and bio-informaticians. Interventions were designed after discussion with clinical specialists in that field and were compliant with national guidelines for patient care.

Intervention 1—Education by individual feedback: the junior doctor clinical dashboard

The Junior Doctor Clinical Dashboard was developed utilising z-scores. For VTE prophylaxis this was based on their correct assessment and prescription of VTE prophylaxis on the PICS against current guidelines [5]. Z-scores were calculated following standard z-score methodology and explained in full in the online supplement (see Additional file 1).

Each doctor was grouped according to their grade to ensure fair comparisons. Any doctor with a z-score less than −3 or greater than+3 was considered an outlier. The doctors were selected from the extreme of both lowest and highest, moving towards the threshold of 3 standard deviations and were required to attend a face-to-face interview with a senior clinician and a senior member of Hospital Management, where any learning points, positive and negative, were shared. A written summary of the session was provided to the doctor and their educational supervisor. Following these interviews performance was reviewed after one month for the low performing end. If there was no significant improvement, the doctor was recalled to further interview and the process repeated. The Junior Doctor Clinical Dashboard was implemented in January 2013.

Intervention 2—Electronic prescribing: a mandatory action for VTE assessment and prescribing

The PICS EHR was updated so that following completion of a VTE assessment module, an automatic prescription proposal was generated for either mechanical prophylaxis, pharmacological prophylaxis or both. The admitting doctor could authorise the VTE prophylaxis prescribing proposal or delete it but no further prescriptions could be added or modified to that patient record until a decision had been made on the VTE prophylaxis. Data on each step was captured in a

structured form. This intervention was implemented in January 2014.

Intervention 3—Amending the mandated proforma following clinician feedback

The previous version of the EHS allowed for the admitting clinician to choose 'no reduced mobility' early in the VTE prophylaxis proforma and thus quickly circumvent the automatic proposal for prescribing. After a risk review and feedback groups, it was apparent that in general, these decisions did not reflect actual VTE risk. A systems approach change to the VTE assessment form was made in consultation with prescribers, where the position of 'no reduced mobility' was moved from a check box at the top of the assessment to a much lower down part of the dropdown list of contra-indications, meaning the majority of the VTE assessment was completed prior to reaching this risk criteria. This change was made in October 2015.

Further changes to prescribing practices

During the period of this analysis the Trust changed the drug of Low Molecular Weight Heparin prescribed due to low stock levels from the drug company nationally, from enoxaparin to tinzaparin. Once the stock levels were restored the Trust switched back to enoxaparin. Whilst this was not an intervention, it required the doctors to be trained on the new medication so the effect of these changes was measured as it occurred during this analysis.

For VTE, two-years of data were assessed prior to the implementation of the first intervention to gain baseline until October 2020 (a period of 9 years of prescribing practices).

Statistical analysis

Weekly values were used to avoid any day-of-the-week effect. The proportions were plotted against the weeks in chronological order. A probit transformation was applied to the proportions prior to analysis to achieve best fit of the assumptions required to then use a segmented linear regression model to determine whether there were significant step changes and/or significant changes in gradient at the times corresponding to the three interventions. Goodness of fit of the model was assessed by graphical assessment of the residuals, and the degree of any autocorrelation of residuals was quantified by the Durbin-Watson statistic. The model was then evaluated, to estimate the proportions at the start and end of each segment, with rates of change calculated by treating the change in proportions within each segment as linear. All analyses were performed using IBM SPSS Statistics Version 22.0 (Armonk, NY: IBM Corp.)

Results

Data from 235,005 admissions were included in total, which represented all admitted adult patients during the study period. The number of patient admissions admitted in each timeframe, and the basic demographics of the

Table 1 Demographics for patient admissions

	Pre- intervention: 2 year run in period for data collection (Jan 2011–Nov 2012)	After intervention 1: introduction of Junior Doctor Clinical Dashboard (Nov 2012–Feb 2014)	After intervention 2: introduction of mandatory VTE assessment and prescribing (Feb 2014–Nov 2015)	After intervention 3: change in order of 'no reduced mobility' (Nov 2015–Nov 2020)
n	31,071	26,260	39,931	137,743
Female, n (%)	14,740 (47.4%)	12,675 (48.3%)	19,135 (47.9%)	67,340 (49.0%)
Age (years)	74 (59–86)	73 (57–85)	72 (57–84)	68 (53–80)

Values are counts (and percentages), except for age where they are medians and quartiles

Table 2 The distribution of prescriber seniority in the four main time intervals

Time interval	Consultant	Specialty grade	Core medical trainee	Foundation doctor	Staff grade
Pre-intervention: 2 year run in period for data collection (Jan 2011–Nov 2012)	19	32	17	29	4
After intervention 1: introduction of Junior Doctor Clinical Dashboard (Nov 2012–Feb 2014)	18	33	15	27	7
After intervention 2: introduction of mandatory VTE assessment and prescribing (Feb 2014–Nov 2015)	17	34	14	27	8
After intervention 3: change in order of 'no reduced mobility' (Nov 2015–Nov 2020)	16	33	11	32	8

Distribution of user type in the four main time intervals (values are percentage frequencies). There were no differences in prescriber seniority over the study period

patients are given in Table 1. There were no significant differences in patient characteristics during the study period.

The number of prescribers during the period was 5503. Although the prescribers changed during this time (reflecting doctor's rotations across regions during their postgraduate training) the seniority of doctor grades represented in the Trust did not alter over the study period, (assessed using Chi Squared, see Table 2).

Full guideline VTE compliance (risk assessment and correct action) within 24 h of recommendation was 70.2% (230 out of 327 in an average week) in the period prior to any intervention (Jan 2011–Dec 2012). It increased significantly to 77.2% (312 out of 404) in the period after

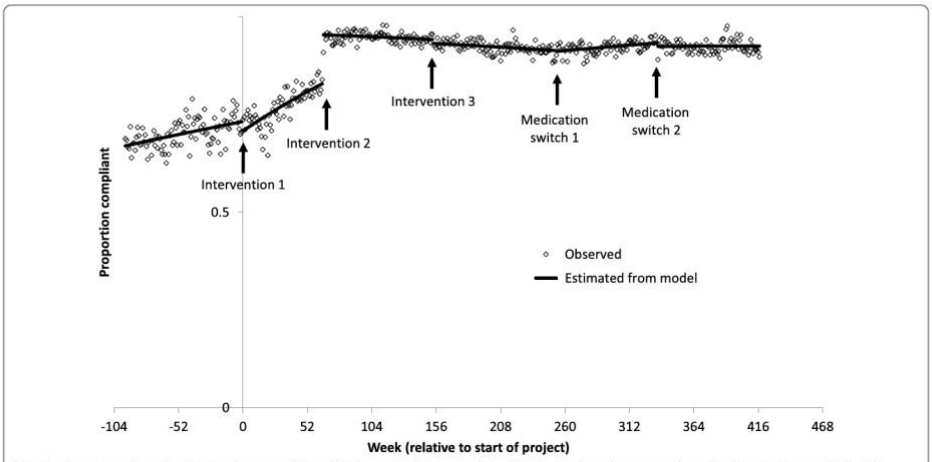

Fig. 1 The proportion of patients who were fully guideline compliant over time. Graph showing the proportion of patients who were fully VTE guideline compliant, meaning they had both a risk assessment and then were either appropriately prescribed VTE prophylaxis or not, depending on that risk assessment. The regression lines are fitted over the time periods before intervention 1 (education/doctor's dashboard), after intervention 2 (introduction of mandated VTE assessment action), after intervention 3 (change to PICS "no reduced mobility") and Medication switch 1 (from enoxaparin to tinzaparinand then return to enoxaparin (Medication switch 2) until study end

Table 3 Observed full VTE guideline compliance over the study period

Time interval	Length of interval (weeks)	Total number of admissions	Total number with full VTE guideline compliance within 24 h	Compliance (%)
Pre-intervention: Run in period for data collection (Jan 2011–Nov 2012)	95	31,071	21,809	70.2
After intervention 1: Introduction of Junior Doctor Clinical Dashboard (Nov 2012–Feb 2014)	65	26,260	20,264	77.2
After intervention 2: Introduction of mandatory VTE assessment and prescribing (Feb 2014–Nov 2015)	89	39,931	37,801	94.7
After intervention 3: Change in order of 'no reduced mobility' (Oct 2015–Sept 2017)	100	49,931	46,028	92.2
After medication change from enoxaparin to tinzaparin (Oct 2017–Mar 2019)	81	45,092	41,583	92.2
After medication change back to enoxaparin to study end (Mar 2019–Nov 2020)	83	42,234	38,955	92.2

Full VTE compliance is where a VTE risk assessment was completed and the correct action was taken. To be fully compliant, both VTE risk assessment and the correct action is needed. For example, non-compliance would be where a risk assessment was not completed, or a VTE assessment suggested LMWH was required and it was not prescribed or a VTE assessment suggested LMWH was not required (or contraindicated) and it was prescribed

the initiation of the Junior Doctor Clinical Dashboard ($p < 0.001$).

There was another significant increase in VTE compliance to 94.7% (425 out of 449) in the period following the change in the EPS with mandatory VTE assessment ($p < 0.001$). There was a small but significant decrease to 92.2% (479 out of 520) following the amendment to relocate "no reduced mobility" from the initial VTE checklist to a subsequent drop-down box ($p < 0.001$). Weekly compliance is shown in Fig. 1.

Table 3 summarised the VTE guideline compliance during six time periods. (1) Prior to any new intervention; (2) after the junior doctor dashboard interventions until the EHR mandate; (3) after the EHR mandate to the amendment of "no reduced mobility"; (4) after the amendment of the "no reduced mobility" option to the change from one LMWH to another brand; (5) to the use of this brand until a switch back to the original therapy; (6) from the reintroduction of the original therapy to study end.

The estimates from the segmented linear regression model show that at time 0 (intervention 1: Junior doctor dashboard) compliance decreased from 73.2 to 70.7% but the rate of increase in compliance then changed from 3.4% per 52 weeks to 9.8% per 52 weeks. As a result, compliance increased to 82.9% by the time of the second intervention (the change in the EPS). After this intervention, there was a step increase to 95.4%. Subsequently, compliance remained relatively stable, although the third intervention (the change in order of "no reduced mobility") produced a small step decrease from 94.2 to 93.2%. All the changes are described in Table 4.

Discussion

This study is the first to assess the cumulative impact of a series of interventions to improve full guideline compliant prescribing for VTE prophylaxis over a prolonged (nine-year) period, in a large NHS Trust which already offered a suite of educational tools such as lectures and videos and with high, and target compliant VTE assessment rates. This study highlights several important points.

First, that risk assessments do not automatically convert into an appropriate action following the assessment. Even after the introduction of the EPS system to mandate VTE risk assessment and appropriate prescribing, there was still a difference between completed risk assessments and prophylaxis prescribing. Altering reporting criteria to assess full guideline compliance may be a more effective means to improve patient safety.

Second, the interventions with demonstrable impact (the doctors dashboard clinic and rules based prescribing algorithms) require an EPS which supports dynamic evidence generation and application, enabling rapid learning and improvement based on data flowing from routine patient care. Both of these interventions were based upon the principles of a learning healthcare system, defined by the United States Institute of Medicine (now the National Academy of Medicine) as systems where "science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience" [21].

The most impactful intervention was a systems approach, with an EPS tool which mandated VTE assessment and prescribing as part of the admission process. These improvements were maintained at a higher level than seen following the individual feedback intervention, for the entire follow up period.

Table 4 Estimated compliance from the segmented linear regression model and equivalent rates of change immediately before and after each intervention and medication switch

Intervention	Estimated compliance			Equivalent rate of change in compliance per 52 weeks		
	Before	After	*p* value	Before	After	*p* value
1. Intervention 1. Introduction of a Junior doctor dashboard	73.2	70.7	0.035	3.4	9.8	< 0.001
2. Intervention 2. Introduction of mandatory VTE assessment and prescribing	82.9	95.4	< 0.001	9.8	− 0.7	< 0.001
3. Intervention 3. Change in order of 'no reduced mobility'	94.2	93.2	0.010 (0.464)	− 0.7	− 1.0	N/A (0.085)
Medication switches						
1. Enoxaparin to Tinzaparin	91.4	91.2	< 0.001	− 1.0	1.4	< 0.001
2. Tinzaparin back to Enoxaparin	93.3	92.5	0.023	1.4	0.0	0.011

Figures in parentheses for intervention 3 are p values if a slope change for intervention 3 is included in the model. As this was not significant, it was excluded and as a result the step change for intervention 3 became significant (the p value changing from 0.464 to 0.010). The final model includes five step changes and four slope changes

Our learning healthcare system included re-evaluating the PICS EPS to see where further improvements could be made. Feedback from prescribers and an assessment using the principles of human factors [22] suggested that the placement of "no reduced mobility" at the top of the risk assessment algorithm potentially suggested that this was true for many patients and an audit of care records suggested that this was being erroneously applied in some instances. In light of this, the EPS was altered to place this option at the end of the list of contraindications, to ensure the prescriber considered co-morbidities and reason for admission prior to considering this option. This change did not have the impact expected on VTE compliance, and in fact contributed to a small, but significant, step decrease in full compliance. The reason for this is unclear and requires further study.

In this real-world study, there was a change in national LMWH availability, requiring a change in drug and prescribing rules (from enoxaparin to tinzaparin and then back to enoxaparin). These were introduced with traditional education but also necessitated a change in the EPS with a new series of prompts and rules. Despite the changes in prescribing practice, there was no significant change to full VTE guideline compliance, highlighting the resilience of the EPS systems-based approach.

This study did not assess why the systems approach was more effective than other interventions, but there are a number of potential reasons. As the Doctors Clinical Dashboard only identifies statistical outliers, only repeated failures to comply with guidelines will be identified. It is likely that many prescribing errors are made singularly and on an ad hoc basis, and these would not necessarily trigger a review. Educational and training events are one -off, and repetition in training has been shown to enhance performance [23, 24]. Healthcare is increasingly complex in terms of organisation and delivery [25] and our ageing population often are multimorbid and poly-medicated, making healthcare decisions more complex [26]. The complexity of healthcare and of patients might increase the potential for prescribing errors. A systems-based approach with prescribing support tools, that provides the same support for all prescribers on all occasions, is therefore more likely to impact on practice.

The current paper highlights the difference between VTE assessment compliance and full VTE guideline compliance (an assessment and appropriate prescribing action). While both are important, only the latter will reduce risk from hospital acquired thrombosis, but this information is not nationally collected or reported.

This study highlights the benefit of a paperless system, where real-time prescribing prompts can be given which account for clinical information, as opposed to static prompts, and where analysis includes all records overs a prolonged period. Some quality improvement papers in this field are based on standard audit procedures, where only a proportion of records are reviewed over a short period, leading to a significant risk of bias and making it unclear whether improvements were maintained [27, 28].

Of note, the systems in place were unable to raise full VTE guideline compliance to 100%, and full VTE guideline compliance plateaued at approximately 92% (with risk assessment completion remaining > 95% throughout). The reason for the small but important discordance in VTE risk assessment completion and subsequent correct action are unclear, but a further suite of electronically delivered tools are in development to determine if this can be improved.

This study has many strengths. It includes all patients within the hospital, and thus captures a high number of prescriber events in an unbiased manner. It also describes practices for a sustained period of time (nine years in total) which provides considerable reassurance that the changes in prescriber behaviour were sustained even as the workforce changed.

The paperless EHS deployed at the NHS Trust provides real-time, instantaneous feedback to all prescribers, highlighting the need for a VTE risk assessment, preventing further prescribing until this is completed and the suggested prescription is either approved or deleted. There are then further, automatically generated prompts every 24 h to review the risk assessment. There are a number of reported interventions which provide retrospective feedback on VTE risk assessment and prescribing practices. These include a mandatory field within the electronic discharge system that record whether a VTE risk assessment on admission took place, the study of hospital coding on discharge or through audit [29]. These provide the opportunity for learning but do not improve compliance or reduce risk for the patient included in the event. Other studies have suggested a VTE nurse specialist can provide real time feedback, reviewing notes in areas of low compliance and high risk [30]. This requires a significant workforce investment to operationalise a twenty-four hours a day, seven days a week service. An EPS solution is available to all, at all times.

This study also has limitations. All prescribing episodes were considered the same, while some guideline-discordant prescribing behaviour may be appropriate depending on the clinical circumstance. The study did not assess whether the improvement in prescribing practices benefited some patient groups or some specialities more than others. Nor did it assess whether the change in prescribing practices

was associated with an improvement in patient outcomes (such as a reduction in VTE events) or reduced healthcare costs. Other studies have focused on in-patient HAT events and shown a reduction in the proportion of HAT attributable to inadequate thromboprophylaxis following an intervention with increased guideline compliance [14] suggesting there would be significant clinical benefit from these interventions. The study did not report the reasons for non-compliance, be it omission (a failure to prescribe low molecular weight heparin when the risk score suggested it was indicated) or commission (where low molecular weight was prescribed when the risk score suggested it was not needed). The clinical system in place required the prescription of low molecular weight heparin to be completed by a consultant-level doctor if the prescription was contraindicated by the risk score, while a suggested prescription of low molecular weight heparin could be deleted by medical staff if thought not indicated, even when supported by the risk score. This would make omission more likely, but further studies would be needed to assess the reason for non-compliance.

In summary, the use of mandatory assessment rules for VTE prophylaxis within an electronic prescribing system and continuous monitoring and feedback was successful in delivering and sustaining improved concordance between guidelines and prescribing practices in a large secondary and tertiary care hospital. Further work is required to determine whether these methods can be translated to other hospitals and whether these tools can be successfully used to improve performance in other areas. However, the significant and sustained impact demonstrated suggests this learning health systems approach, applied using routine clinical data to inform and refine practice, may demonstrate patient benefit across all areas of prescribing.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12911-022-01865-y.

Additional file 1. Statistical methods for z-score calculations.

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Author contributions
SG, SB, TP, MB, IW, ES designed the study, collated data, performed some analysis, wrote the manuscript. AT curated data and performed statistical analysis. PN curated data and performed statistical analysis and helped write the manuscript. MG supported data collection. All authors amended the manuscript and approved the final version. All authors read and approved the final manuscript.

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Availability of data and materials
The anonymised data and a data dictionary defining each field is available through application to the corresponding author.

Declarations

Ethics approval and consent to participate
The authors confirm that all methods were carried out in accordance with relevant guidelines and regulations. This research used anonymised, routinely collected health data from the electronic health records of University Hospitals Birmingham NHS Foundation Trust. All research activities, including the use of unconsented health data, were conducted with appropriate UK Health Research Authority and Research Ethical Committee (East Midlands—Derby Research ethics committee, reference 20/EM/0158) and HRA Confidentiality Advisory Group approvals (20/CAG/0084).

Consent for publication
N/A.

Competing interests
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Author details
[1]PIONEER Health Data Research Hub in Acute Care, Department of Health Informatics, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK. [2]NIHR Clinical Research Facility, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK. [3]Department of Health Informatics, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK. [4]Respiratory Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK. [5]Acute Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK. [6]Digital Healthcare and Department of Renal Medicine, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK. [7]PIONEER Health Data Research Hub in Acute Care, University of Birmingham, Edgbaston, Birmingham B15 2TH, UK. [8]HDR-UK Midlands Site and Better Care Programme, Queen Elizabeth Hospitals NHS Foundation Trust, Mindlesohn Way, Edgbaston, Birmingham B15 2WB, UK.

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Publisher's Note

Supplementary File 3.2: Online Supplement

Electronic prescribing systems as tools to improve patient care: a learning health systems approach to increase guideline concordant prescribing for venous thromboembolism prevention.

Online supplement

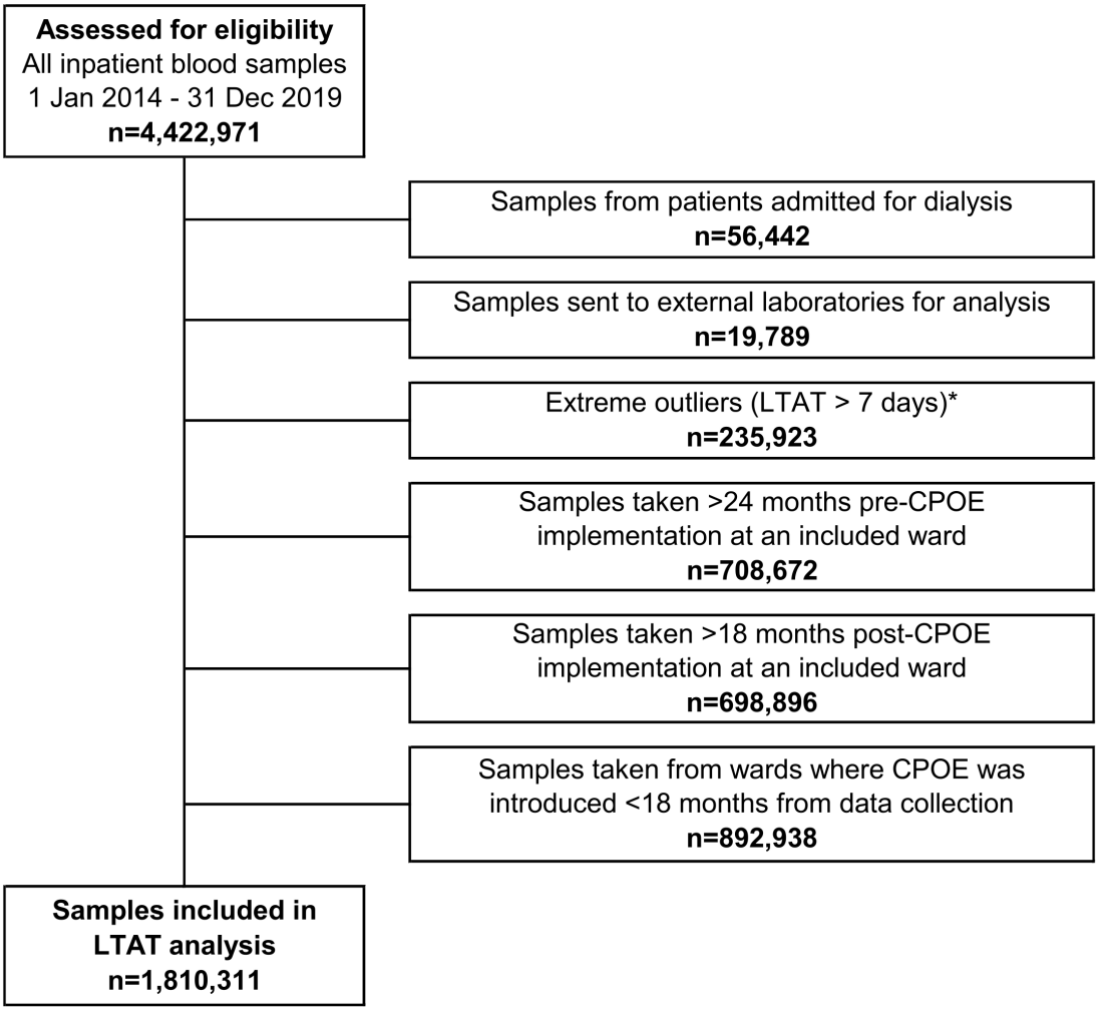
S. Gallier, A. Topham, P. Nightingale, M. Garrick, I. Woolhouse, M.A. Berry, T. Pankhurst, E. Sapey, S. Ball

Statistical methods for z score calculations.

If doctor "*I*" correctly treats "r_i" cases from "n_i" cases the expected proportion p of correct responses across all doctors is $p = \frac{sum(r_i)}{sum(n_i)}$ and has standard deviation $\sqrt{\frac{p(1-p)}{sum(n_i)}}$. The observed proportion of correctly treated patients by doctor *i* is $p_i = \frac{r_i}{n_i}$ and has standard deviation $\sqrt{\frac{p(1-p)}{n_i}}$. The standard deviation uses the expected proportion p of correct responses across all doctors and number n_i cases treated by doctor *i*. The z score is $z = \frac{(p_i - p)}{\sqrt{\left(p(1-p)*\left(\frac{1}{n_i}+\frac{1}{sum(n_i)}\right)\right)}}$. When sum($n_i$) is much larger than any n_i the z-score may be simplified to $z = \frac{p_i - p}{\sqrt{\frac{p(1-p)}{n_i}}}$. If z-scores are independent, the sum of *k* z-scores has mean 0 and standard deviation $\sqrt{k}$.

Appendices for Chapter 4

Supplementary Figure 4.1: Modified Consort flow diagram explaining how the eligible samples for analyses were selected.



Legend. **Samples were defined as extreme outliers if the results were not returned within 7 days (10,080 minutes); the majority of such cases represented either instances where tests were ordered but no sample was taken, or highly specialised tests that required considerable time to be analysed, both of which were outside the scope of this study.*

CPOE=Computerised Provider Order Entry; LTAT=Laboratory Turnaround Time.

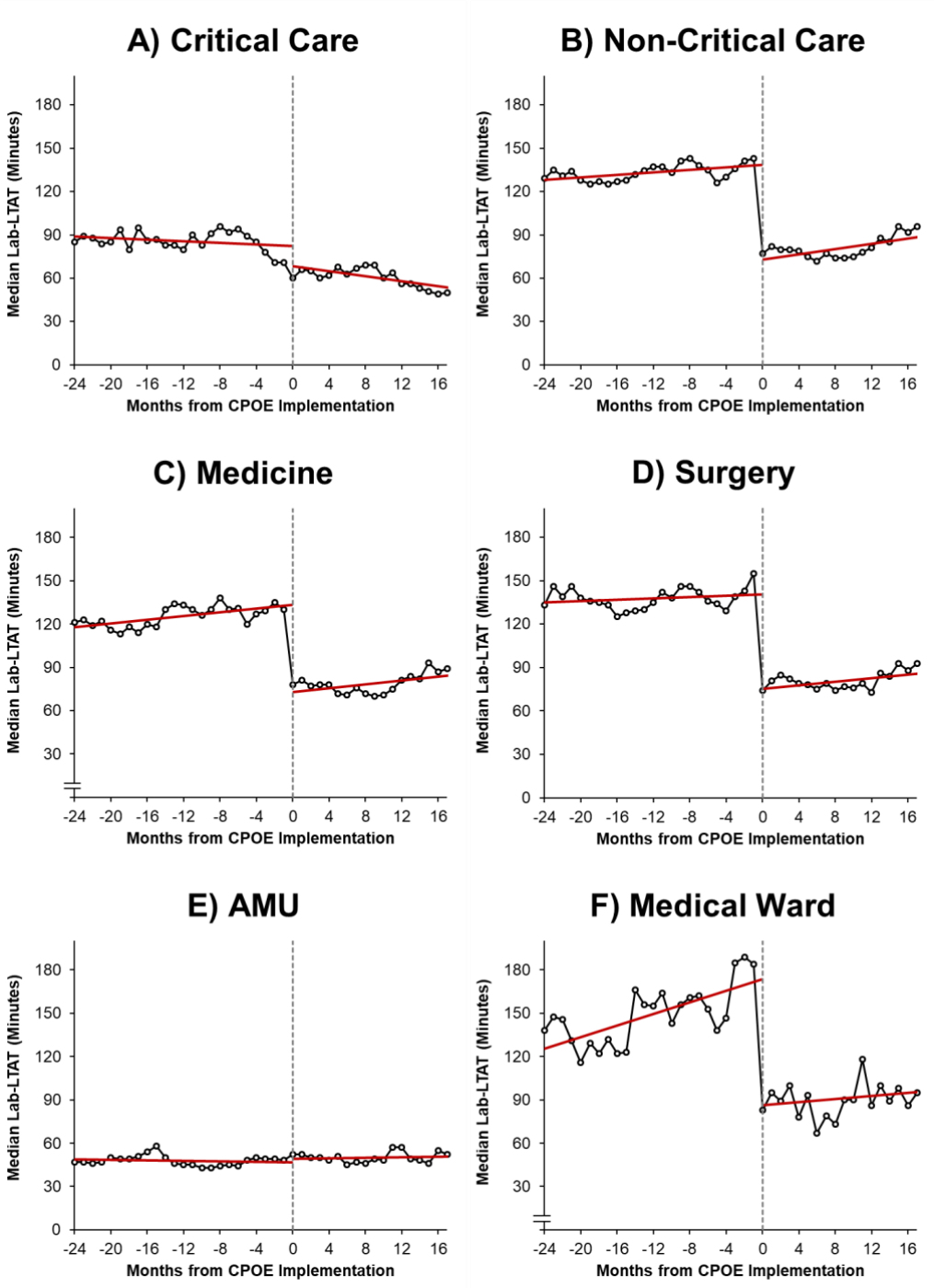
Supplementary Table 4.1: Segmented regression models of the median Lab-LTAT for inpatient blood samples by specialty/area

	Coefficient (Minutes; 95% CI)	p-Value	Coefficient (Minutes; 95% CI)	p-Value
	Group 1			
	Critical Care		***Non-Critical Care***	
Intercept	89.2 (84.2, 94.2)	**<0.001**	127.7 (123.2, 132.2)	**<0.001**
Gradient Pre-CPOE	-0.3 (-0.6, 0.1)	0.121	0.4 (0.1, 0.7)	**0.008**
Step-Change Post-CPOE	-13.9 (-21.5, -6.4)	**<0.001**	-65.6 (-72.3, -58.9)	**<0.001**
Change in Gradient Post-CPOE	-0.6 (-1.2, 0.1)	0.072	0.5 (-0.1, 1.1)	0.102
	Group 2			
	Medicine		***Surgery***	
Intercept	117.2 (112.4, 122.0)	**<0.001**	134.8 (129.2, 140.3)	**<0.001**
Gradient Pre-CPOE	0.6 (0.3, 1.0)	**<0.001**	0.2 (-0.2, 0.6)	0.236
Step-Change Post-CPOE	-60.5 (-67.6, -53.3)	**<0.001**	-65.2 (-73.5, -57.0)	**<0.001**
Change in Gradient Post-CPOE	0.0 (-0.6, 0.6)	0.937	0.4 (-0.3, 1.1)	0.279
	Group 3			
	AMU		***Medical Ward***	
Intercept	48.9 (45.8, 51.9)	**<0.001**	123.4 (111.8, 135.1)	**<0.001**
Gradient Pre-CPOE	-0.1 (-0.3, 0.1)	0.420	2.0 (1.2, 2.8)	**<0.001**
Step-Change Post-CPOE	2.4 (-2.1, 7.0)	0.285	-87.3 (-104.8, -69.8)	**<0.001**
Change in Gradient Post-CPOE	0.2 (-0.2, 0.6)	0.367	-1.5 (-3.0, 0.0)	0.054

Legend. *Results are from segmented linear regression models of the monthly median Lab-LTAT over the 24 months pre- and 18 months post-CPOE implementation, as described in the Materials and Methods section. Separate models were produced for each of the specialty groups/areas. Analyses of Group 1 and 2 include only those N=27 wards with at least 18 months of post-CPOE follow-up, to maintain a consistent cohort; analysis of Group 3 is based on individual wards. Coefficients are reported in minutes, and gradients are reported per calendar month. Bold p-values are significant at p<0.05.*

CPOE=Computerised Order Entry System; LTAT=Laboratory Turnaround time; QA/QC=Quality Assurance/Quality Control

Supplementary Figure 4.2: Segmented regression models of the median Lab-LTAT for inpatient blood samples by specialty/area



Legend. *Points represent the median Lab-LTAT within each calendar month, with Month 0 (and the broken line) designating the month in which CPOE was implemented. Figure A-D include only those wards with at least 18 months of post-CPOE follow-up, in order to maintain a consistent cohort; Figure E-F represent data for individual words. Trend lines are from a segmented regression model on the stated specialty/area, as described in* ***Supplementary Table 4.1****.*

AMU=Acute Medical Unit; CPOE=Computerised Order Entry System; LTAT=Laboratory Turnaround time.

Appendices for Chapter 5

Supplementary File 5.1: Published manuscript for Chapter 5

Original Article

Applying a COVID Virtual Ward model, assessing patient outcomes and staff workload

S Gallier, C Atkin, V Reddy-Kolanu, D Parekh, X Zou, F Evison, S Ball & E Sapey

Abstract

A COVID virtual ward (CVW) is recommended by NHS England, but 'usual care' outcomes have not been reported.
A retrospective study of all adults with COVID-19 attending Queen Elizabeth Hospital Birmingham between 01/06/2020-31/01/2021, assessed against CVW criteria and followed for 28 days.
Of 2301 COVID-19 patients, 571(25%) would have met CVW criteria. Of these, 325(57%) were discharged after review and 246(43%) admitted. Of admitted patients who met CVW criteria, 81% required hospital-supported therapies; 11% died. Of the 325 discharged, 13% re-presented, 9% with COVID-related symptoms, 2% required intensive care admission, and one died (0.3%).
In this comparison, discharging patients without a CVW did not lead to more re-presentations, re-admissions, ITU escalations or deaths compared to published outcomes for hospitals with a CVW.

Keywords

Virtual ward, discharge, readmissions, mortality, intensive care

Suzy Gallier
PIONEER Technical Director, Lead for Research Analytics Department of Health Informatics
Health Informatics, University Hospitals Birmingham NHS Foundation Trust

Catherine Atkin
NIHR Lecturer in Acute Medicine
Institute of Inflammation and Ageing, University of Birmingham

Vinay Reddy-Kolanu
Consultant in Acute Medicine
University Hospitals Birmingham NHS Foundation Trust

Dhruv Parekh
Senior Lecturer in Acute Care, Birmingham Acute Care Research Group
Institute of Inflammation and Ageing, University of Birmingham

Xiaoxu Zou
Research Analytics, Health Informatics
University Hospitals Birmingham NHS Foundation Trust

Felicity Evison
Senior Research Analysis
Health Informatics, University Hospitals Birmingham NHS Foundation Trust

Simon Ball
Cheif Medical Officer, Director of Better Care Programme
University Hospitals Birmingham NHS Foundation Trust

Elizabeth Sapey
University of Birmingham
Email: e.sapey@bham.ac.uk

Introduction

The global pandemic caused by SARS-CoV-2 continues to provide health challenges worldwide. During infection 'waves', affected areas experience a high number of hospital presentations and admissions,[1] requiring significant reconfiguration of staff and health services to meet the demands for care.

On 13th January 2021, National Health Service England (NHSE) published a document which provided a standard operating procedure for a 'COVID Virtual Ward' (CVW), with an aim of enabling the safe discharge of patients with COVID-19 from the hospital setting to the community early upon presentation to hospital, with daily contact and safety netting. NHSE recommended that all areas should pursue the roll out of a COVID virtual ward model to reduce pressures on acute hospital services, and that the CVW should be delivered by the acute hospital.[2]

The recommended CVW model was as follows[2]: Subject to completion of a satisfactory exercise test, patients with oxygen saturations of 95-100% and low NEWS2 (< 3) and improving clinical trajectories could be discharged to a COVID virtual ward where clinically appropriate. Patients with saturations of 93-94% with improving clinical trajectories (symptoms, signs, blood results, chest x-rays), could also be considered for the COVID virtual ward where clinically appropriate. Patients with oxygen saturations of 92% or lower or experiencing moderate/severe shortness of breath would generally be unsuitable for early supported discharge, unless the patient was stable, and this represented their usual baseline oxygen saturation.

In the CVW model, patients are discharged home with an oximeter and asked to take three readings each day and to call a staffed hospital number immediately if they note a reading of less than 92%, or they should attend their nearest emergency department within an hour or call 999. The patient would be proactively contacted by phone every day (seven days a week, as they would be for a hospital-based ward round). At 14 days (or before if deemed clinically appropriate) patients would either be discharged from the CVW or receive a further clinical assessment if symptomatic. A friend or family member, or an NHS Volunteer Responder, would then return the oximeter for decontamination and reuse.

To deliver this model, the CVW telephone line requires staffing for at least 12 hours a day (8am–8pm) seven days a week with locally arranged provision of out of hours cover. These staff should be supervised by an experienced, clinically registered professional who is also responsible for making the proactive daily calls, i.e., virtual ward round. The CVW should have a named medical consultant or senior trainee (ST3+ doctor), usually an acute or respiratory physician.

This model, or similar, have been applied in several care settings. In June 2020, an article reported that of 200 patients managed on a CVW in a UK secondary care hospital, 13% of all cases re-presented to hospital, and 10% of all cases were readmitted.[3] In November 2020, a retrospective study of 273 COVID-19 was published assessing a similar system, but with 5 days of virtual follow up rather than the 14 days described by NHSE, and an

option for discharge without enrolment to the CVW for those at lowest risk.[4] The authors describe an 11% readmission rate and one death. A multi-site mixed methods study assessing clinical sites which had implemented a similar service suggested the cost of implementing such a service was approximately £400 to £553 per patient.[5]

These studies support the safety of the CVW system. However, there are implied assumptions; first that all patients would otherwise be admitted to hospital and second, that the provision of the CVW impacts positively on re-presentations (either reducing unnecessary readmissions or identifying where re-assessment is needed). Also, there are no descriptions of the patients who did not meet the CVW criteria, to understand the volume of patients who still required in-patient care. Implementation of such a system as the CVW has an opportunity cost, as staff must be redeployed from other clinical areas and the reliance on acute or respiratory physicians to deliver the CVW may re-direct care from high intensity clinical environments during pandemic waves. Traditionally these care pathways would be assessed in randomised control trials with health economic reviews. In the absence of such trials, understanding both the "natural history" of those discharged who meet the CVW criteria and the care burden which remains in the hospital is important to place the staffing needs of the CVW in context.

Birmingham is one of the most ethnically diverse cities in the UK with a high burden of COVID-19 cases and COVID-19 associated mortality in all the UK COVID-19 waves.[6,7]

The study was conducted to understand the potential impact of a CVW by studying retrospective, routinely collected health data. The study hypothesis was that introducing a CVW system was would a significant burden to staff workload, without improving hard outcomes such as death and readmission.

The study objectives were:

- To retrospectively assess the proportion of patients who would have met criteria for a potential virtual ward
- To evaluate outcomes in patients with COVID-19 who were discharged within 24 hours of admission without the support of a CVW
- To assess the proportion of admitted patients meeting potential CVW criteria who required hospital level intervention, and their outcomes
- To estimate the additional time required to deliver a CVW service for patients who would have met criteria for management through CVW

Retrospectively, patients were labelled as either meeting or not meeting the criteria for inclusion in a putative CVW, based on reported NHSE criteria. Their outcomes and clinical pathways were assessed, assessing those who would have met the criteria for a CVW, were one in operation, and the potential time and staffing levels needed to deliver such a system, in a hospital trust with a high burden of COVID-19 presentations.

Methods

This data study was supported by PIONEER, a Health Data Research Hub in Acute Care. All study activities complied with the ethical approvals provided by the East Midlands – Derby REC (reference: 20/EM/0158).

University Hospitals Birmingham NHS Foundation Trust (UHB), UK is one of the largest Trusts nationally, covering 4 NHS hospital sites, treating over 2.2 million patients per year and housing the largest single intensive care unit (ICU) in Europe. UHB saw the highest number of COVID admissions in the UK (>10,000 confirmed cases by March 2021) and the highest number of patients ventilated, with an expanded ICU capacity of >200 beds.

Study population

Health data from all adults with a confirmed positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) swab result between 1st June 2020 and 31st January 2021 who attended UHB at the time of or up to two weeks following a positive SARS-CoV-2 swab test were included. COVID cases were confirmed following a nasopharyngeal and oropharyngeal swab in all cases,[8] processed in accordance with NHS guidance within UHB NHS laboratories (9).

UHB has built and runs its own electronic health record (EHR) and developed a structured electronic clerking proforma where all patients with suspected COVID-19 could be identified on admission. For all patients, the results of the first positive swab were included but patient records were checked for subsequent positive swab results if associated with a subsequent admission. Mortality and patient admission status (discharged and alive, continued admission and alive) were assessed 28 days after the first positive swab result.

Data collection and variable definitions

Patient demographics and clinical data were collected from the UHB EHR. Clinician confirmed co-morbidities were available from the EHR, the summary primary care record (Your Care Connected) and diagnostic codes derived from previous hospital episodes, including NHS Digital

SNOMED CT coding,[10] mapped to historically entered ICD-10 codes.[11]

English Indices of Deprivation scores were calculated using postcodes.[12] Ethnicity was self-reported by the patient or their family members on admission, grouped as per national guidelines.[13]

All adult patients with a positive COVID-19 swab admitted during the time period were included with no exceptions. Patients with or suspected with COVID-19 have a structured assessment at UHB as part of usual care. This includes serial physiology and NEWS2 recordings, a rapid walk test (which consists of patients taking 40 steps around their assessment area (of any step length) with oxygen saturations measured both before and after the 40 steps) and a Chest radiograph. Usual care in UHB does not include a CVW, but instead patients are either admitted for assessment and treatment in designated COVID wards or discharged with safety netting advice to contact health services if needed. Patients are not invited for post-COVID follow-up unless they are referred by their GP or referred by their hospital physician for complications of COVID. Patients are not routinely provided with pulse oximeters.

The current study was observational only. Results of the 40 steps walk test, physiological assessments, chest radiograph reports and acuity scores were used to retrospectively determine whether a patient could have been suitable for a COVID virtual ward. Clinical trajectories were considered using the same parameters over the first 24 hours of admission. For the purposes of this study, patients with either oxygen saturations of 95–100% and low NEWS2 (<3) or with saturations of 93–94% with improving clinical trajectories over the first 24 hours of admission were considered suitable for a potential COVID virtual ward, if they did not desaturate after completing a 40 step walk test below levels described above. Trajectories had to include oxygen saturations improving to >94% on room air without deterioration in NEWS2 scores to meet the CVW criteria, except where oxygen saturations of 92% or lower were compatible with baseline levels as demonstrated through previous monitoring. Decisions as to whether a patient would have met the criteria for a CVW were made against objective parameters by one clinically qualified person and ratified by another (both acute medicine trained), with blinding to all patient outcomes.

In all admitted cases, clinical note reviews were undertaken to assess whether any assessments or treatments were delivered which would preclude discharge and could not be given at home – these included intravenous therapies, supplemental oxygen or other respiratory support, initiation of treatment dose anti-coagulation subcutaneously or requirement for increased social care.

Outcomes

Primary outcome was re-presentation to QEHB (via the Emergency Department or Acute Medical Unit) for any cause, or death within 28 days of discharge, as per national reporting.[14] For those patients discharged from hospital, primary care records were reviewed and any patients who had died in the community within the censor period were noted. Those with an on-going admission were censored 28 days after a positive swab result.

Statistics

Statistical analysis was performed using STATA (SE) version 15 (StataCorp LLC, Texas, USA). Baseline characteristics for the total population are presented as mean (standard deviation) or median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables. Continuous variables were compared between datasets using Mann-Whitney U tests. Categorical variables were compared using Fisher's exact and Chi-Square tests. Results were considered significant if the p-value was <0.05. There was no adjustment for multiple comparisons, but exact p values are given.

Results

In total, 2301 swab confirmed cases of COVID-19 were assessed in the 245day time period. Of note, 23,803 patients who were COVID negative were assessed in the same period, of which 2827 (11.9%) were discharged and 20740 (87.1%) admitted. Figure 1 shows overall patient numbers across categories.

Patient demographics

Overall demographics of all patients presenting with COVID-19 during the time period criteria are given in table 1, divided by whether they would have met the criteria for a CVW. Table 2 compares the demographics of patients who retrospectively met potential CVW criteria, comparing those discharged within 24 hours of presentation and those admitted for ≥24 hours. In general, patients admitted for ≥24 hours were more likely to be older, with 14.5% of patients aged >65 years in the discharged group, compared to 44.8% in the admitted group. Those admitted were more likely to have significant comorbidities, including dementia, stroke, active malignancies, and heart disease.

Outcomes for those discharged from hospital after initial review

Outcomes at 28 days for the 325 swab positive patients who would have met the COVID virtual ward criteria and were discharged within 24 hours were assessed. 281 patients (86.4%) were not readmitted and were still alive at 28 days post initial

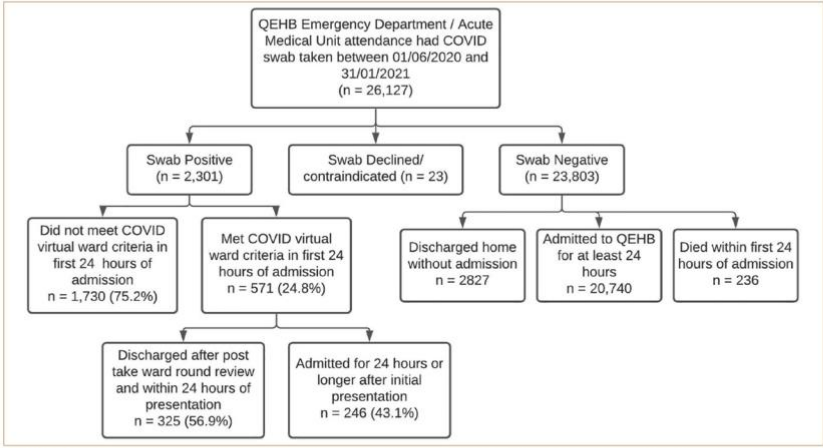


Figure 1. Modified consort diagram of patients presenting to the Emergency Department or Acute Medical Unit at Queen Elizabeth Hospital Birmingham

Legend. Presentations were all presentations for the time period stated. Only those with a confirmed positive PCR SARS-CoV-2 Swab were included in pathway mapping. Those with no swab results (23 individuals where swabs were declined or contraindicated due to facial injury) were not included in the pathway analysis. Patients were labelled as those retrospectively meeting potential COVID Virtual Ward criteria or those who did not meet these criteria, and their "usual care" outcomes followed for 28 days. QEHB: Queen Elizabeth Hospital Birmingham

presentation. 44 patients (13.5%) re-presented within 28 days, 30 due to COVID-related symptoms (68.2% of re-presentations or 9.2% of those meeting CVW criteria) and 14 with a diverse list of conditions (Table 3). The median length of time at home prior to re-presentation was 2.5 days (IQR 1.5 – 5 days).

Nine (20.5%) of the 44 patients were discharged within 24 hours of this second presentation. Of the COVID-associated re-presentations, the overall median length of stay in hospital was 4 days (IQR 1 – 7.5 days). Of the 44 re-presenting patients, 5 (11.4%) were transferred to ITU. One (2.3%) patient died within 28 days.

Outcomes for those who were admitted to hospital after initial review

Treatment pathways and outcomes for the 246 swab positive patients who met the potential COVID virtual ward and were admitted to hospital for ≥24 hours were assessed. 191 patients (77.6%) received an intravenous infusion including fluids or antibiotics, and 94 patients (38.2%) required oxygen therapy after the first 24 hours of admission. 14 patients (5.7%) received therapeutic dose anticoagulation. 47 (19.1%) patients did not require intravenous treatment, supplemental oxygen, or a community care assessment in hospital.

For these 246 patients, the median length of hospital stay was 4 days (IQR 2 – 9 days). 9 patients (3.7%) were transferred to intensive care. 26 patients (10.6%) died within 28 days of presentation. Of those 26 who died, 18 died during the inpatient stay.

Of those who survived to discharge, 215 (87.4%) patients were discharged to their own home (204 patients) or to their usual care home (11patients). 12 (4.8%) were discharged to a community hospital.

For the 47 patients who did not require intravenous therapies, oxygen or community care review, the median length of stay was 34 hours (IQR 28 – 40 hours). None of these patients were readmitted during the follow-up period. They were younger (median age 47 years (35-59), p=0.002) but with co-morbidities. A notes review revealed that these patients were not reviewed by an Acute Medicine or Respiratory consultant within the first 24 hours of their admission.

Comparing reported outcomes

Outcomes for patients discharged from hospital within the current study were compared to previous studies assessing CVW services (Table 4). No difference was demonstrated in the proportion of patients re-presenting to hospital, or the proportion who re-presented who required ITU care or who died.

Time required for service provision

If modelling virtual care requirements of the 325 patients sent home within 24 hours, assuming 14 days

Table 1. Demographics of all swab positive patients, comparing patients who would or would not have met potential COVID virtual ward criteria
Legend: Data is number (percentage) unless otherwise stated. Ethnicity was self-reported (see Methods). English Indices of deprivation (IMD) were calculated using postcode. Diabetes includes type 1 and type 2 diabetes. COPD= Chronic Obstructive Pulmonary Disease. Patients could (and often did) have more than one co-morbid condition*

		Would have met the COVID virtual ward criteria	Would not have met COVID virtual ward criteria	p-value
	Overall Count	571 (24.8%)	1730 (75.2%)	
Sex	Female	309 (54.1%)	803 (46.4%)	p = 0.001
	Male	262 (45.9%)	926 (53.5%)	
Age	Median (IQR)	51 (37-68)	62 (50-78)	
	50 and under	285 (49.9%)	445 (25.7%)	p<0.001
	51-65	129 (22.6%)	525 (30.3%)	
	66-75	52 (9.1%)	267 (15.4%)	
	76-85	54 (9.5%)	280 (16.2%)	
	Over 85	51 (8.9%)	213 (12.3%)	
Ethnicity	White	238 (41.7%)	823 (47.6%)	p = 0.124
	Black	30 (5.3%)	79 (4.6%)	
	South Asian	141 (24.7%)	425 (24.6%)	
	Mixed	14 (2.5%)	34 (2%)	
	Chinese	3 (0.5%)	9 (0.5%)	
	Any Other Ethnic Group	18 (3.2%)	61 (3.5%)	
	Unknown or declined to self-report	127 (22.2%)	299 (17.3%)	
IMD Quintile	1 (Most Deprived)	308 (53.9%)	943 (54.5%)	p = 0.765
	2	127 (22.2%)	351 (20.3%)	
	3	79 (13.8%)	266 (15.4%)	
	4	40 (7%)	108 (6.2%)	
	5 (Least Deprived)	16 (2.8%)	60 (3.5%)	
	Unknown	1 (0.2%)	2 (0.1%)	
Co-morbidities*	Chronic Kidney Disease	69 (12.1%)	259 (15%)	p = 0.087
	Dementia	38 (6.7%)	170 (9.8%)	p = 0.022
	Interstitial Lung Disease	5 (0.9%)	29 (1.7%)	p = 0.169
	Stroke or cerebrovascular	65 (11.4%)	243 (14%)	p = 0.105
	Ischaemic heart disease	108 (18.9%)	364 (21%)	p = 0.275
	Asthma	101 (17.7%)	343 (19.8%)	p = 0.262
	Hypertension	205 (35.9%)	903 (52.2%)	p < 0.001
	Diabetes	132 (23.1%)	586 (33.9%)	p < 0.001
	Any active malignancy	91 (15.9%)	334 (19.3%)	p = 0.072
	COPD	28 (4.9%)	224 (12.9%)	p < 0.001
	Atrial fibrillation	63 (11%)	236 (13.6%)	p = 0.108
BMI	Underweight	13 (2.3%)	40 (2.3%)	p = 0.003
	Normal weight	93 (16.3%)	338 (19.5%)	
	Overweight	91 (15.9%)	463 (26.8%)	
	Obese	78 (13.7%)	508 (29.4%)	
	Morbid obesity Unknown	21 (3.7%) 275 (48.2%)	136 (7.9%) 245 (14.2%)	

of follow-up (as per NHSE guidance) and a steady admission rate during the assessed time period, 4550 telephone calls would be required in the 245 days of the study period plus 14 days to allow for follow-up (259 days), an average of 18 calls per day. If each telephone contact required 25 minutes (5 minutes preparation/5 minutes note making and 15 minutes conversation with the patient), the daily workload

Table 2. Comparison of demographics between swab positive patients who would have met the potential COVID virtual ward criteria who were either discharged within 24 hours of attendance or admitted to hospital for > 24 hours
Legend: Data is number (percentage) unless otherwise stated. Ethnicity was self-reported (see Methods). English Indices of deprivation (IMD) were calculated using postcode. Diabetes includes type 1 and type 2 diabetes. COPD= Chronic Obstructive Pulmonary Disease. Patients could (and often did) have more than one co-morbid condition

		Discharged within 24 hours	Admitted for > 24 hours	p-value
	Overall Count	325 (56.9%)	246 (43.1%)	
Sex	Female	185 (56.9%)	124 (50.4%)	p = 0.122
	Male	140 (43.1%)	122 (49.6%)	
Age	Median (IQR)	45 (34-57)	63 (44-80)	
	50 and under	202 (62.2%)	83 (33.7%)	p < 0.001
	51-65	76 (23.4%)	53 (21.5%)	
	66-75	25 (7.7%)	27 (11%)	
	76-85	12 (3.7%)	42 (17.1%)	
	Over 85	10 (3.1%)	41 (16.7%)	
Ethnicity	White	114 (35.1%)	124 (50.4%)	p = 0.010
	Black	16 (4.9%)	14 (5.7%)	
	South Asian	90 (27.7%)	51 (20.7%)	
	Mixed	10 (3.1%)	4 (1.6%)	
	Chinese	1 (0.3%)	2 (0.8%)	
	Any Other Ethnic Group	13 (4%)	5 (2%)	
	Unknown	81 (24.9%)	46 (18.7%)	
IMD Quintile	1 (Most Deprived)	175 (53.8%)	133 (54.1%)	p = 0.012
	2	76 (23.4%)	51 (20.7%)	
	3	48 (14.8%)	31 (12.6%)	
	4	23 (7.1%)	17 (6.9%)	
	5 (Least Deprived)	2 (0.6%)	14 (5.7%)	
	Unknown	1 (0.3%)	0 (0%)	
Co-morbidities*	Chronic Kidney Disease	14 (4.3%)	55 (22.4%)	p < 0.001
	Dementia	6 (1.8%)	32 (13%)	p < 0.001
	Interstitial Lung Disease	2 (0.6%)	3 (1.2%)	p = 0.443
	Stroke or cerebrovascular	9 (2.8%)	56 (22.8%)	p < 0.001
	Ischaemic heart disease	32 (9.8%)	76 (30.9%)	p < 0.001
	Asthma	50 (15.4%)	51 (20.7%)	p = 0.097
	Hypertension	66 (20.3%)	139 (56.5%)	p < 0.001
	Diabetes	41 (12.6%)	91 (37%)	p < 0.001
	Any active malignancy	20 (6.2%)	71 (28.9%)	p < 0.001
	COPD	13 (4%)	15 (6.1%)	p = 0.250
	Atrial fibrillation	15 (4.6%)	48 (19.5%)	p < 0.001
BMI	Underweight	2 (0.6%)	11 (4.5%)	p = 0.436
	Normal weight	19 (5.8%)	74 (30.1%)	
	Overweight	22 (6.8%)	69 (28%)	
	Obese	21 (6.5%)	57 (23.2%)	
	Morbid obesity	8 (2.5%)	13 (5.3%)	
	Unknown	253 (77.8%)	22 (8.9%)	

would be 450 minutes/7.5 hours each day (without break), or 52.5 hours per week, for every week of the study period. While it is unlikely that all patients who met the CVW criteria within the first 24 hours of presentation would have been deemed medically fit for discharge to the virtual ward, the same modelling for the 571 cohort who met the CVW criteria would require 7994 telephone calls over the study period plus

Table 3. Reasons for COVID-positive patients re-presenting to hospital within 28 days after initial discharge.
Legend: Data was collected via routine clinical coding, but individual notes were checked to confirm medical reason for re-presentation by a consultant physician

Readmission diagnosis	Number	Percentage of readmissions
COVID- associated re-presentation	30	68.20%
Poisoning	3	6.82%
Musculoskeletal / limb pain	3	6.82%
Fractured bone	2	4.55%
Congestive heart failure	1	2.30%
Epilepsy, unspecified	1	2.30%
Headache	1	2.30%
Pilonidal cyst with abscess	1	2.30%
Pulmonary embolism	1	2.30%
Syncope and collapse	1	2.30%
Total	44	

follow-up period of 14 days, which equates to 31 calls per day, taking 775 minutes or 13 hours per day. This excludes the provision of a manned telephone service that patients could call if concerned. This would require at least 2 or 3 staff members each day, as well as senior medical oversight and out of hours cover.

Discussion

This retrospective analysis of health data for patients admitted to hospital with a positive COVID-19 swab result found that 24.8% of patients would have met criteria for management via a Covid Virtual Ward. Of these patients, 56.9% were discharged from hospital without the provision of a CVW and received usual care. In this cohort, only 13% re-presented to hospital and 10% were readmitted. The outcomes from the current study are similar to reported outcomes from CVWs, but in the current study, these outcomes were achieved without the additional and considerable time and staffing commitment required to deliver a CVW service during the peak of a wave.

Of the 246 patients who would have met criteria for management via a CVW and were admitted to hospital, 80.9% required other management necessitating hospital admission such as intravenous treatment, and these patients were older and had significant co-morbidities, which are known to significantly contribute to the need for admission in patients affected by COVID-19.[15] Those who were admitted to hospital for >24 hours were more likely to have chronic kidney disease, ischaemic heart disease, diabetes and active malignancy and COVID-19 outcomes are poorer in patients with these conditions.[18,19]

The NHSE CVW was developed to facilitate the care of COVID-19 patients who had presented to hospital, but who could be cared for at home. Thrice daily oxygenation saturations and daily contact by trained hospital staff were provided for appropriate safety netting. The hope for the service was that it would free hospital beds, enable staff to focus on the most unwell patients with COVID-19, while providing a safe clinical service for patients.

To date, the CVW has not been evaluated in a gold standard, robust randomised clinical trial. Instead, CVWs have been reported in a series of observational studies and summarised in a recent systematic review.[16] These studies present some evidence of the safety of the CVW service but have not described the burden of COVID where criteria were not met, nor described the natural history of

Table 4. Comparing outcomes in patients managed without CVW at Queen Elizabeth Hospital Birmingham to outcomes from published evaluations of CVW services
Legend. UHB numbers are those who retrospectively met the criteria for potential management through CVW and were discharged without CVW service, compared to those who were discharged to a CVW in Thornton and Nunan studies. Re-presentation is defined as reattendance at the Emergency Department or acute medical unit. Figures are compared using Fisher's Exact tests. * = comparing reported Nunan at el(4) and UHB re-presentation rates.**= comparing reported Thornton(3) and UHB reported re-presentation rates.

	Total number	Re-presented to hospital n (%)	Did not re-present n (%)	p-value	Admitted to ITU n (%)	p value	Died n (%)	p value
UHB	325	44 (13.5%)	281(86.5%)		5 (1.5%)		1 (0.3%)	
Nunan et al[4]	273	31 (11.4%)	242 (88.6%)	p=0.458*	2 (0.7%)	p=0.693	1 (0.4%)	p=0.999
Thornton[3]	200	26 (13.0%)	174 (87.0%)	p=0.895**	Not reported			

discharged patients without this service, to enable a comparison of opportunity costs as well as gains.

This study presents retrospectively analysed, routinely collected health data for all patients admitted to QEHB with a positive COVID-19 swab result. Patients were assessed as to whether they would have met the criteria for the CVW parameters as presented by NHSE[2] either on initial presentation or during the first 24 hours, using time-stamped data available in the clinical record.

Of note, 75.2% (1730) of patients presenting to hospital during this period did not meet the CVW criteria, suggesting that during a wave of COVID-19, the CVW would only be suitable for a quarter of patients. In the 24.8% (571) who did meet the CVW criteria, 325 (56.9%) patients were discharged despite the lack of a CVW facility and with no planned follow-up, and of those discharged, 13% re-presented and 10% were admitted. Patient outcomes for those discharged within 24 hours in this study were compared to those discharged with CVW support in published evaluations of CVW services, to determine whether any difference in outcome was seen in this cohort discharged without CVW support. No difference in outcome was demonstrated, suggesting that in this cohort, and the lack of a CVW made no difference to hard outcomes, such as death, re-admission, or admission to ITU(4). In this study, the single patient death following re-presentation and re-admission was due malignancy. It was reported as a COVID-19 related death, in line with national reporting criteria for deaths occurring within 28 days of a positive swab result.[17] Of note, 20.5% of patient reviewed in ED and AMU who did not have COVID were readmitted for assessment in the same period of time (8041/39269 patients).

This study does not include a health economic analysis of service provision, nor have specific costs been suggested, as staffing models for CVW have varied across centres. However, we report the substantial staffing required to operate a CVW during COVID-19 waves, and this would be required for 7-day work patterns, as the CVW requires telephone calls to be made daily, irrespective of weekday or weekends. It is unclear whether there is the capacity to redeploy these skilled staff members from caring for the 75% of patients who did not meet CVW criteria to the 25% who did, especially if this does not confer improvements in hard outcomes such as mortality, ITU provision or re-presentation and admission. Previous studies have reported patient satisfaction with the CVW, reducing the potential anxiety of being discharged.[4] The current study does not assess this important factor.

Of note, a number of studies have reported remote monitoring for COVID-19 patients either initially in the community for positive patients as part of a triage system with lower presentations to hospital,[5] such as 4%,[18] which probably reflects the screening of milder cases, less likely to present to hospital in the current study. However, where focusing on a secondary care delivered CVW, a re-presentation rate of approximately 13% has been reported.[19]

This study has limitations. First, this study only labelled patients as being suitable for CVW or not, and then followed their usual care outcomes, it did not actually deploy a CVW model, and therefore results should be interpreted with this in mind. Second, by comparing outcomes across studies, there is an assumption that patient populations including demography, burden of disease and impact of COVID-19, are similar across published studies. Most studies to date have not presented in depth demography and therefore these direct comparisons should be reviewed with caution. Third, in the current paper, the objective criteria for the CVW were applied using the granular electronic health record at QEHB without the benefit of seeing the patient or considering the time of the initial presentation, and all these factors are important when making the decision to admit or discharge. Fourth, it is possible that more of the patients who met the CVW criteria might have been discharged were the CVW in place. Fifth, when assessing staffing needs it has been assumed that all patients will require follow up for 14 days, as described in the NHSE SOP. It is highly likely that some would require much less follow up prior to discharge. Sixth, this is not a formal health economic review, which would form part of the evaluation of any new service. Although we have included an estimate of the additional time that would be required to staff a CVW service based on the number of patients meeting CVW criteria in this analysis, there is no clear guidance for the staffing levels that would be needed to deliver a CVW service 7 days a week safely and effectively, and this may well vary from centre to centre, dependent on other factors including local population demographics. To fully assess the cost of a CVW service would require a full health economic analysis, which is beyond the scope of the current analysis.

The study has significant strengths. Decisions as to whether the patient met the CVW criteria were made independently by two senior clinical researchers, without knowledge of outcomes, thus reducing bias. All patients were included in the study, reducing the population bias which can hinder consented studies. As data includes all medications and electronic noting, reasons for continued admission could be assessed.

In summary, this study reports similar percentage re-presentations, admissions, escalations to ITU and deaths in patients who were discharged without a CVW compared to studies where a CVW was implemented. The study also highlights that only 25% of COVID-19 admissions were suitable for the CVW based on objective criteria, and the potential intensity of work created by implementing a CVW. The study begins to explore the potential opportunity costs of the CVW system, but does not consider patient factors, such as the reassurance potentially given by discharge to a CVW setting.

Any new care pathways or initiatives have opportunity gains and costs, and in usual times, processes are often assessed using rigorous randomised control trials which often include quantitative, qualitative and health economic analyses. While the CVW was established to enhance patient safety and reduce unneeded hospitalisation, it is important to assess whether the service achieves this compares to usual care. More research is needed before this service is fully implemented.

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Conflicts of Interest

C.A, V.R-K, F.E, XZ have nothing to declare. D.P reports grant funding from NIHR. S.G and S.B report grant funding from HDR-UK. E.S reports grant funding from HDR-UK, Wellcome Trust, MRC, BLF, NIHR, EPSRC and Alpha 1 Foundation.

Author contributions

C.A, V.R-K, D.P assisted with clinical data insights, F.E, X.Z and S.G analysed the data. S.G, S.B and E.S designed the study and wrote the manuscript. All authors approved the final manuscript.

Data Access

Data from this study is available from PIONEER, the Health Data Hub in Acute care, in accordance with Hub processes. Contact PIONEER@uhb.nhs.uk for more details.

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Appendices for Chapter 6

Supplementary File 6.1: Published manuscript for Chapter 6

Open access Original research

BMJ Open

Variability and performance of NHS England's 'reason to reside' criteria in predicting hospital discharge in acute hospitals in England: a retrospective, observational cohort study

Elizabeth Sapey ,[1,2] Suzy Gallier,[1,3] Felicity Evison ,[3] David McNulty,[3] Katherine Reeves,[3] Simon Ball [4,5]

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For numbered affiliations see end of article.

Correspondence to
Dr Elizabeth Sapey;
e.sapey@bham.ac.uk

ABSTRACT

Objectives NHS England (NHSE) advocates 'reason to reside' (R2R) criteria to support discharge planning. The proportion of patients without R2R and their rate of discharge are reported daily by acute hospitals in England. R2R has no interoperable standardised data model (SDM), and its performance has not been validated. We aimed to understand the degree of intercentre and intracentre variation in R2R-related metrics reported to NHSE, define an SDM implemented within a single centre Electronic Health Record to generate an electronic R2R (eR2R) and evaluate its performance in predicting subsequent discharge.

Design Retrospective observational cohort study using routinely collected health data.

Setting 122 NHS Trusts in England for national reporting and an acute hospital in England for local reporting.

Participants 6 602 706 patient-days were analysed using 3-month national data and 1 039 592 patient-days, using 3-year single centre data.

Main outcome measures Variability in R2R-related metrics reported to NHSE. Performance of eR2R in predicting discharge within 24 hours.

Results There were high levels of intracentre and intercentre variability in R2R-related metrics ($p<0.0001$) but not in eR2R. Informedness of eR2R for discharge within 24 hours was low (J-statistic 0.09–0.12 across three consecutive years). In those remaining in hospital without eR2R, 61.2% met eR2R criteria on subsequent days (76% within 24 hours), most commonly due to increased NEWS2 (21.9%) or intravenous therapy administration (32.8%).

Conclusions Reported R2R metrics are highly variable between and within acute Trusts in England. Although case-mix or community care provision may account for some variability, the absence of a SDM prevents standardised reporting. Following the development of a SDM in one acute Trust, the variability reduced. However, the performance of eR2R was poor, prone to change even when negative and unable to meaningfully contribute to discharge planning.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The intracentre and intercentre variability of reason to reside (R2R) reporting was based on national data and included >6.6M patient bed-days.
⇒ Standardised data model to form eR2R was based on nationally agreed criteria for each clinical question.
⇒ All admissions >24 hours were included for eR2R performance review, reducing bias.
⇒ eR2R data based on one centre only, although one of the largest National Health Service Trusts nationally serving a diverse population and including >1M patient bed-days.

INTRODUCTION

In 2021, the UK Government published its policy and operating model for hospital discharge and community support within the National Health Service in England (NHSE).[1] This policy responded to concerns about bed capacity during the COVID-19 pandemic.

A National Audit Office report recognised the potential to release acute hospital beds in 2016, finding that older patients no longer needing acute treatment accounted for 2.7 million NHS hospital bed days per year.[2] The report concluded that a lack of planning delayed discharge, recognising research that highlighted adverse outcomes during prolonged hospital stay.[3 4]

The aforementioned policy mandates using set criteria to identify in-patients in whom discharge home, or to a less acute setting, should be considered. These criteria have been referred to interchangeably, as 'Reason[s] to reside' (R2R), 'right to remain' or 'criteria to reside' (see table 1A). Since April 2020, NHS hospitals have been required to provide daily reports on the numbers of people leaving hospital, to where and the

Table 1 Reason to reside (R2R)

1	Requiring Intensive Care (ITU) or High Dependency Unit (HDU) care
2	Requiring oxygen therapy/ Non Invasive Ventilation (NIV)
3	Requiring intravenous fluids
4	National Early Warning Score (NEWS) 2 >3 (clinical judgement required in persons with Atrial Fibrilliation (AF) and/or chronic respiratory disease)
5	Diminished level of consciousness where recovery realistic
6	Acute functional impairment in excess of home/ community care provision
7	Last hours of life
8	Requiring intravenous medication more than twice daily (BD) (including analgesia)
9	Undergone lower limb surgery within 48 hours
10	Undergone throrax-abdominal/pelvic surgery within 72 hours
11	Within 24 hours of an invasive procedur (with attendant risk of acute life-threatening deterioration)

The policy and operating model for hospital discharge and community support within the National Health Service in England states that every person on every general ward should be reviewed on a twice daily ward round to determine whether they meet R2R. If the answer to each question is 'no', the policy states that active consideration for discharge to a less acute setting must be made.[1] In daily data returns, the number of patients to whom this applied were counted at a single, locally defined, time point.

reasons for those remaining in hospital. The proportion of in-patients not meeting R2R criteria and the proportion of patients without R2R discharged that day are also reported. These metrics are considered to be measures of organisational efficiency.

R2R appears to have emerged heuristically from the clinical experience of those involved in its development. A series of questions are posed that might prompt consideration of individual patients for discharge. However, there are no standardised data definitions, there has been no validation of R2R, no investigation of its role as a clinical decision support tool or of its value in evaluating hospital performance. A further barrier to evaluating the performance of R2R is that there is no gold standard definition that identifies patients who could be discharged from hospital against which to compare R2R performance. This lack of a reference standard limits, but does not preclude assessment of the validity of a clinical test, provided a 'fair' measure of performance can be defined.[5] The set of patients actually discharged in the subsequent 24 hours is one potentially 'fair' test of performance of R2R.

In the current study, we show the degree of variation in R2R-associated metrics reported across centres in England. Second, we propose precisely defined, interoperable data definitions corresponding to the elements of R2R. This allows for consistent, generalisable analysis. Third, we evaluate the performance of R2R to predict discharge over the subsequent 24 hours.

METHODS

All studies activities followed the World Medical Association's Declaration of Helsinki. The R2R criteria are as described[1] and are also provided in table 1.

National data

National NHS England data were accessed via The UK Health Facts and Dimensions database[6] for all reporting Trusts in England. Assessment of variability in national R2R reporting included data from 29 November 2021 to 20 February 2022. Online supplemental table S1 provides the names of the Trusts whose data are presented anonymously. Data were collected daily during the censor period for 121 centres, yielding a total of 10 164 potential data points (centre-days). For each of these, the total number of occupied and unoccupied beds, and the number of patients with no right to reside were extracted. The number of patients with no right to reside were submitted once a day by each NHS trust, based on the local hospital interpretation of the definition provided by NHSE.[1] This required none of the criteria to be met at the time of local data collection. The numbers of patients with right to reside were then calculated by subtracting the number with no right to reside from the total number of occupied beds on that day. The number of general and acute beds occupied in any given centre, on any given day (in-patients), was used as a surrogate for the number of patients eligible for evaluation using the R2R criteria. Review of the dataset found some missing and potentially spurious data, which were excluded prior to analysis. This included instances where R2R data were not recorded (n=184 data points), where the total numbers of beds were either zero, missing or clearly spurious (n=37 data points) or where there were more patients with no R2R than the total number of beds (n=3 data points). The national data are shown for the other n=121 centres, excluding UHB.

Local data

In-depth analysis of R2R criteria were performed using data from the Queen Elizabeth Hospital Birmingham (QEHB). QEHB is an NHS, urban, adult, acute hospital in England, which in 2019 had 1269 beds including 80 level 2/3 intensive care unit (ICU) beds, an emergency department that assesses >300 patients per day and a mixed secondary and tertiary practice that includes all major adult specialities except for obstetrics and gynaecology. The electronic healthcare record (EHR) at QEHB (PICS, Birmingham Systems) contains time-stamped, structured records that include demography, location, admission and discharge, comorbidities, physiological measurements supporting NEWS2 and Glasgow Coma Scale, operation noting, prescribing and investigations.

Table 2 Data definitions used to operationalise R2R for EHR

	Flag if…	R2R criterion number
On ITU HDU	listed as being in ITU or HDU ward	1
SNCT level ≥2	Most recent SNCT level in previous 48 hours ≥2	1
SNCT level a	Most recent SNCT level in previous 48 hours=1a	6
SNCT level 1b	Most recent SNCT level in previous 48 hours=1b	6
Oxygen therapy/NIV	Oxygen administration or Non Invasive Ventilation (NIV) documented in observation chart within previous 24 hours	2
Intravenous fluids	Intravenous fluid administration initiated in previous 24 hours or variable rate insulin infusion administered in previous 24 hours	3
NEWS2	If NEWS2>3 within last 24 hours	4
Diminished consciousness	Glasgow Coma Scale value ≤12 in last 24 hours	5
Last hours of life	Comfort observation completed current OR end-of-life medication bundle administered within last 24 hours	7
Intravenous prescription tds current (regular not prn)	Intravenous medication prescribed within last 24 hours and frequency ≥3 times per day for regular medication only	8
Intravenous medication administration tds within 24 hours	Intravenous medication administered ≥3 times within last 24 hours	8
Lower limb surgery within 48 hours	Procedure with relevant OPCS codes in previous 48 hours	9
Thorax-abdominal-pelvic surgery with 72 hours	Procedure with OPCS relevant codes in previous 72 hours	10
Invasive procedure within 24 hours	Procedure with OPCS relevant codes in previous 24 hours	11

The table describes the data definitions used and the R2R criteria they map to.
All OPCS codes used to identify procedures are listed in online supplemental table S2.
EHR, electronic healthcare record; HDU, high dependency unit; ITU, intensive care; NEWS2, National Early Warning Score 2; OPCS, OPCS Classification of Interventions and Procedures code, which is used to identify the coded clinical entry; R2R, reason to reside; SNCT, Safer Nursing Care Tool; tds, three times a day.

The R2R criteria in table 1 were mapped to computable definitions derived from the EHR (see table 2), to generate an electronic R2R (eR2R). The OPCS Classification of Interventions and Procedures codes mapped to criteria 9–11 are described in online supplemental table S2. The concept 'acute functional impairment in excess of home/community care provision' had no direct correlate. Safer Nursing Care Tool (SNCT) levels of care were however available.[7] SNCT levels 2 and 3 correspond closely with the requirement for HDU or ICU.[8] Level 1a identifies patients requiring enhanced nursing reflecting acuity of illness, and level 1b identifies a group with increased nursing dependency. Level 1b is likely to include those who would and would not be considered to require ongoing care in acute hospital. SNCT level 1 was included in the definition of eR2R in two ways, including (eR2Rab) and excluding (eR2Ra) level 1b, to determine if this affected performance.

The primary analysis of eR2R was for patients who had been in hospital for more than 24 hours at midnight. Discharge over the course of the subsequent 24 hours was evaluated. Secondary analyses were undertaken for the set of patients in a bed at 08:00 and at 16:00 to define any change in eR2R performance in these different cross-sections of the in-patient population. Three calendar years were analysed separately to assess the effects of the COVID-19 pandemic.

Statistics

Initially, daily numbers of patients with R2R quantified both as absolute numbers and a proportion of the total number of beds were plotted for national centres and used to calculate between-centre and within-centre variation. These data are analysed as beds occupied at the specified time of day, where the bed inherits the demographics, comorbidities and other qualities of the occupying patient. This represents the in-patient population in cross-section.

For the local analysis of eR2R: the term patient-day was used to refer to a bed with the qualities of the occupying patient at the time of the analysis. The in-patient population is described as means of patient-days thereby representing a cross-section of the group. The performance of eR2R as a predictor of remaining in hospital (or absence of eR2R as a predictor of discharge) was reported as a true positive rate (TPR) and true negative rate (TNR), positive predictive value (PPV), negative predictive value (NPV) and Youden's J statistic (TPR+TNR-1), where positive is remains in hospital and negative is discharge from hospital within 24 hours.

Normally distributed variables are reported as arithmetic means±SD, with medians and ranges used otherwise. Between-centre variation was assessed by analysis of variance. This included a model accounting for day of the week as a fixed effect and the centre as a random effect. All analyses were performed using IBM SPSS V.22 (IBM Corp), with p<0.05 deemed to be indicative of statistical significance throughout.

Patient and public involvement

The research question and topic were agreed following patient/public discussion groups about NHSE discharge policies. Patients/public reviewed the data fields included in the study, with the PIONEER Data Trust Committee providing support for the project (a group of patient/public members who review studies using health data[9]). A patient/public group has reviewed the results and has written a lay summary for study dissemination to patient groups.

RESULTS

R2R reporting in England, November 20–February 21

Across 10 164 available centre-days, accounting for 6 602 706 patient-days, the number of patients reported without R2R as a proportion of in-patients varied significantly between centres (p<0.0001). Individual centre means ranged from 6.7%±2.5% to 59.9%±13.8% (figure 1A). There was also marked within-centre variation (figure 1A), with coefficients of variation (CV) ranging from 8.2% up to 59.3%. Of patients not meeting R2R criteria, the proportion discharged over the following 24 hours, varied significantly between centres (p<0.0001). Individual centre means ranged from 14.0%±7.4% to 85.8%±25.2% (figure 1B). There was also marked within centre variation, with CV ranging from 6.4% up to 83.2%. These data are shown as median and IQR in online supplemental figure S1A,S1B). The proportion of patients without R2R and the proportion of that group discharged within 24 hours were only weakly correlated (R^2=0.12; Online supplemental figure S2).

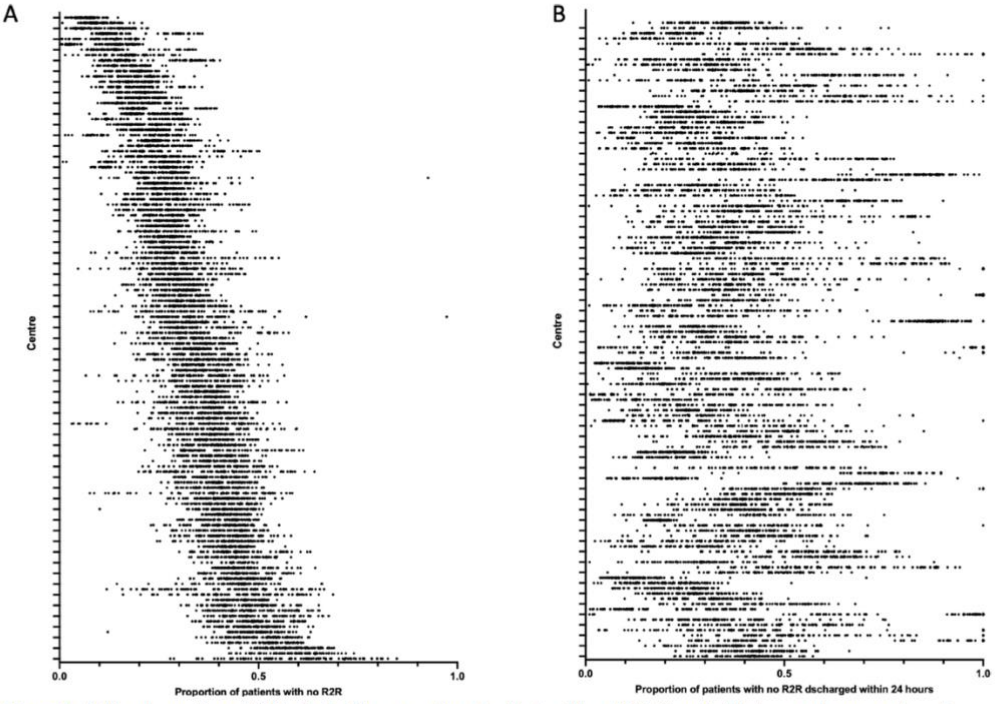

Figure 1 National reporting of R2R criteria. The proportion of patients with no R2R (A) and of that group the proportion of patients discharged within 24 hours (B) reported to Strategic Data Collection Service (SDCS) NHS Digital, UK from 29 November 2021 to 20 February 2022 across 121 centres. Each dot represents result for a single centre-day. We have ordered centres in both A and B according to the median value of proportion of patients with R2R (see online supplemental figure S3 for median and IQRs). R2R, reason to reside.

Table 3 Demographics of patients meeting and not meeting R2R criteria on presentation to QEHB in the censor period

	All QEHB patient days	Meeting eR2Rab	Not meeting eR2Rab
N	1 039 592	919 751 (88.5)	119 841 (11.5)
Age in years*: median (IQR)	68 (53–80)	69 (54–81)	63 (48–76)
Sex* (n, %)			
Female	488 120 (47.0)	434 418 (47.2)	53 702 (44.8)
Male	546 061 (52.5)	484 816 (52.7)	61 245 (51.1)
Not recorded	5411 (0.5)	517 (0.1)	4894 (4.1)
Self-reported ethnicity* (n, %)			
White	784 528 (75.5)	698 573 (76.0)	85 955 (71.7)
Mixed/multiple	12 983 (1.2)	11 023 (1.2)	1960 (1.6)
South Asian/Asian British	114 049 (11.0)	98 903 (10.8)	15 146 (12.6)
Black/African/Caribbean/black British	51 122 (4.9)	43 991 (4.8)	7131 (6.0)
Other ethnic group	19 475 (1.9)	16 623 (1.8)	2852 (2.4)
Not known	57 435 (5.5)	50 638 (5.5)	6797 (5.7)
Co-morbidity count* (n, %)			
None	196 121 (18.9)	164 704 (17.9)	31 417 (26.2)
1–2	474 922 (45.7)	423 200 (46.0)	51 722 (43.2)
3 or more	368 549 (35.5)	331 847 (36.1)	36 702 (30.6)
Morbidities (n, %)			
Hypertension*	492 160 (47.3)	439 930 (47.8)	52 230 (43.6)
Cerebrovascular disease*	159 316 (15.3)	147 676 (16.1)	11 640 (9.7)
Atrial fibrillation*	224 501 (21.6)	204 458 (22.2)	20 043 (16.7)
Ischaemic heart disease, angina, myocardial infarct*	198 480 (19.1)	173 708 (18.9)	24 772 (20.7)
Diabetes (types 1 and 2)*	271 505 (26.1)	242 328 (26.3)	29 177 (24.3)
Asthma*	103 679 (10.0)	91 136 (9.9)	12 543 (10.5)
COPD*	112 731 (10.8)	103 882 (11.3)	8849 (7.4)
Interstitial lung disease*	2533 (0.2)	2380 (0.3)	153 (0.1)
Chronic kidney disease*	198 052 (19.1)	178 284 (19.4)	19 768 (16.5)
Any active malignancy*	215 959 (20.8)	194 419 (21.1)	21 540 (18.0)
Dementia (all types)*	65 272 (6.3)	61 324 (6.7)	3948 (3.3)
English Indices of deprivation			
1	430 114 (41.4)	382 132 (41.5)	47 982 (40.0)
2	222 478 (21.4)	197 999 (21.5)	24 479 (20.4)
3	178 565 (17.2)	158 047 (17.2)	20 518 (17.1)
4	107 747 (10.4)	96 115 (10.5)	11 632 (9.7)
5	75 854 (7.3)	67 296 (7.3)	8558 (7.1)
Not recorded	24 834 (2.4)	18 162 (2.0)	6672 (5.6)
Care escalation to ITU (n, %)	101 017 (9.7)	93 080 (10.1)	7937 (6.6)

Data are number (percentage) of patients in a bed at 00:00. Ethnicity was self-reported. Medical conditions were physician confirmed and checked against admission and linked primary care notes. English indices of deprivation were calculated using postcode.
*Significant difference between meeting and not meeting eR2Rab (p<0.05 in univariate analysis).
eR2R, electronic R2R; R2R, reason to reside.

Performance of eR2R at QEHB

Standardised definitions corresponding to the elements of R2R (table 2) were used to analyse data from QEHB, on 1 214 480 in-patient days, between 1 January 2019 and 31 December 2021. The demographic and clinical details of that population are summarised in table 3, which also shows that those meeting the definition of eR2Rab were older and more likely to have one or more comorbidities than those who did not. Variation in the daily number of patients with or without an eR2R is shown in online supplemental figure S3.

Criteria contributing to eR2R

Given the potential for the COVID-19 pandemic to affect R2R, calendar years were analysed separately. The number of patients meeting any given eR2R criterion are shown in table 4A. The progressive contribution of different elements of the definition of eR2R assessed daily in a modified

Table 4 (A) The number (percentage) of patient-days on which each eR2R data definition was met. (B) A phased analysis undertaken for each day and presented as a modified Consort diagram

(A) The number (percentage) of patient-days on which each eR2R data definition was met			
Year	**2019**	**2020**	**2021**
Criterion	**n (%)**	**n (%)**	**n (%)**
ICU	22 899 (6.1)	20 326 (6.7)	21 305
TAP surgery 72 hours	3783 (1.0)	3010 (1.0)	3974
Lower limb surgery 48 hours	285 (0.1)	252 (0.1)	221 (0.1)
Invasive surgery 24 hours	1861 (0.5)	1613 (0.5)	1988 (0.6)
NEWS2>3 24 hours	93 501 (24.8)	85 123 (27.9)	97 722 (27.3)
O2 treatment 24 hours	77 949 (20.7)	69 355 (22.7)	77 202 (21.6)
Insulin infusion 24 hours	10 951 (2.9)	10 860 (3.6)	12 496 (3.5)
Intravenous fluids 24 hours	79 802 (21.2)	71 376 (23.4)	80 246 (22.4)
Intravenous medication administered in last 24 hours>=three times a day	95 034 (25.2)	81 174 (26.6)	91 573 (25.6)
Intravenous medication prescribed in last 24 hours>=three times a day	21 543 (5.7)	17 866 (5.9)	19 249 (5.4)
SNCT dependency 1 a, 2, 3	99 139 (26.3)	72 226 (23.7)	88 832 (54.8)
COMA score <=12 in last 24 hours	6594 (1.8)	6448 (2.1)	6664 (1.9)
End of Life care definition met in last 24 hours	5359 (1.4)	4747 (1.6)	5075 (1.4)
SNCT dependency 1b	172 659 (45.8)	160 380 (52.5)	179 527 (50.2)
Total number of patient days	376 684	305 254	357 654
(B) A phased analysis undertaken for each day and presented as a modified Consort diagram			
Year	**2019**	**2020**	**2021**
Criterion	**Mean % (SD)**	**Mean % (SD)**	**Mean % (SD)**
ICU	6.1% (0.44)	7.1% (3.10)	6.0% (2.16)
TAP surgery 72 hours	0.7% (0.35)	0.7% (0.37)	0.8% (0.45)
Lower limb surgery 48 hours	0.1% (0.07)	0.1% (0.11)	0.1% (0.08)
Invasive surgery 24 hours	0.2% (0.15)	0.2% (0.18)	0.2% (0.15)
NEWS2>3 24 hours	24.2% (2.28)	27.5% (3.82)	26.6% (3.64)
O2 treatment 24 hours	4.0% (0.61)	3.9% (0.72)	3.6% (0.68)
Insulin infusion 24 hours	0.5% (0.24)	0.6% (0.28)	0.5% (0.23)
Intravenous fluids 24 hours	8.8% (1.09)	9.5% (1.37)	9.6% (1.24)
Intravenous medication admin 24 hours>=three times a day	7.7% (1.05)	7.4% (1.29)	7.5% (1.17)
Intravenous medication prescribed 24 hours	0.7% (0.28)	0.6% (0.29)	0.6% (0.27)
SNCT dependency 1a, 2, 3	8.8% (1.42)	6.7% (1.21)	7.8% (1.12)
COMA score<=12 in the last 24 hours	0.0% (0.05)	0.0% (0.08)	0.0% (0.06)
End of life 24 hours	0.5% (0.24)	0.4% (0.27)	0.4% (0.19)
SNCT dependency 1b	24.5% (1.88)	25.5% (3.53)	25.3% (2.59)
No eR2Rab total	13.3% (1.50)	9.8% (2.29)	10.9% (1.87)
No eR2Ra total	37.8% (2.38)	35.3% (5.08)	36.2% (3.60)

The number (percentage) of patient days on which each eR2R definition was met. The population was in-patients at 24.00 with length of stay ≥24 hours.
The progressive contribution of each element to the definition of eR2R was calculated as proportion of the whole population. These were aggregated by calendar year. The order of the phased analysis was determined by the researchers to be that which was most informative, and which placed objective definitions earlier. SNCT dependency is a global nursing assessment and therefore was placed last.
eR2R, electronic R2R; ICU, intensive care unit; R2R, reason to reside; SNCT, Safer Nursing Care Tool.

Consort table are summarised in table 4B. The proportion of patients not meeting eR2R criteria exhibited relatively little day-to-day variation in 2019 (eR2Rab, CV=11.2%; eR2Ra, CV=6.3%), although somewhat higher in the context of case mix variation consequent on peaks of patients admitted with COVID-19 in 2020 (eR2Rab, CV=23.3%; eR2Ra, CV=14.4%) and 2021 (eR2Rab, CV=17.1%; eR2Ra, CV=9.9%). The criteria contributing most to eR2R status included acuity level (NEWS2>3), SNCT level nursing requirement, being on intensive care and requiring intravenous medications or fluids.

Informedness of eR2R for discharge in the next 24 hours

For the outcome discharge (remain −)/no discharge (remain +) within 24 hours, across the three different years, the eR2Ra TPR lay between 0.63 and 0.65, TNR between 0.46 and 0.47, the PPV was 0.91 and NPV between 0.12 and 0.15; the eR2Rab TPR lay between 0.88 and 0.91, TNR between 0.18 and 0.24,

Table 5 Contingency tables showing the number of patients meeting criteria for (A) eR2Ra and (B) eR2ab

(A)

		Remain		
	2019	Yes (+)	No (–)	Total
eR2Ra	Yes (+)	213382	20845	234227
	No (–)	124874	17583	142457
	Total	338256	38428	376684
	2020	Yes (+)	No (–)	Total
eR2Ra	Yes (+)	177065	18292	195357
	No (–)	93947	15950	109897
	Total	271012	34242	305254
	2021	Yes (+)	No (–)	Total
eR2Ra	Yes (+)	208068	20084	228152
	No (–)	112007	17495	129502
	Total	320075	37579	357654

(B)

		Remain		
	2019	Yes (+)	No (–)	Total
eR2Rab	Yes (+)	297172	29372	326544
	No (–)	41084	9056	50140
	Total	338256	38428	376684
	2020	Yes (+)	No (–)	Total
eR2Rab	Yes (+)	246461	28026	274487
	No (–)	24551	6216	30767
	Total	271012	34242	305254
	2021	Yes (+)	No (–)	Total
eR2Rab	Yes (+)	288384	30336	318720
	No (–)	31691	7243	38934
	Total	320075	37579	357654

The tables show numbers of patients meeting R2R criteria and the corresponding number of patients who remain in hospital over the next 24 hours or do not (were discharged), for the in-patient population at 00:00. For eR2Ra, the TPR varied between 0.62–0.65 and TNR 0.46–0.51, across three different years and three different time points. For eR2Rab, the TPR varied between 0.87–0.91 and TNR 0.18–0.25, across three different years and three different time points. Online supplemental table S3 shows the same data for the in-patient population at 16:00. See online supplemental table S3 for all sensitivity and specificity analysis.
ER2R, electronic R2R; R2R, reason to reside.

the PPV between 0.90 and 0.91 and NPV between 0.18 and 0.20 (table 5). The J statistic for both definitions lay between 0.09 and 0.12. In secondary analyses based on the in-patient population at 08.00 and at 16.00 the J-statistic ranged between 0.10–0.14 and 0.10–0.15, respectively (online supplemental table S3A,S3B).

In-patients not meeting eR2R

The demographic and clinical details of patient who did not meet the eR2Rab definition, stratified by discharge in the subsequent 24 hours, are shown in online supplemental table S5. For patient-days on which discharge occurred within 24 hours, there was significantly higher representation of those with no documented comorbidities 29.2% vs 24.0% (p<0.0001). In those that remained in hospital, 61.2% met eR2R criteria on subsequent days (76% within the next 24 hours). Of all those that remained, 21.9% acquired a NEWS2>3, 32.8% received iv fluids or drugs >3 times/day and 1.9% were admitted to ICU.

DISCUSSION

Assessment of an individual patient's R2R has been promoted as a tool to improve the identification of those who could be discharged from acute hospitals in England. The proportion of in-patients with R2R and their rate of discharge has then been used to evaluate the operational efficiency of acute hospitals and their adjacent health and social care system.[1 10] This paper presents findings to suggest that as currently constituted, R2R is of limited value for these purposes.

The high levels of variation in R2R-related metrics, within and between centres in England, has been attributed to variation in case mix and operational efficiency.[11] However, such extremes of variation are not observed in other metrics that use established data standards. Furthermore, the proportion of patients not meeting R2R criteria correlates poorly with their rate of discharge over the subsequent 24 hours, whereas one might anticipate that such closely related measures of operational efficiency would reflect one another. These findings are most obviously accounted for by the fact that R2R does not constitute a semantic data model. It is therefore susceptible to differing interpretation by individuals and centres. This applies to all the concepts described by R2R, but most obviously those that are necessarily subjective, such as 'acute functional impairment in excess of home/community care provision' and 'diminished level of consciousness where recovery is realistic'.[12 13]

We therefore developed machine readable data definitions corresponding to each concept, allowing consistent analysis of R2R at scale, using data derived from the EHR in our centre. The SNCT is a global nursing assessment of acuity and dependency that was developed to guide workforce deployment. It is regularly recorded within the EHR at our centre. Because level 1b describes a group of patients who are highly dependent on nursing care for daily activities, this was mapped onto the R2R concept

'acute functional impairment in excess of home/community care provision'. However, since the definition of level 1b could include a group of patients suitable for discharge to a less acute setting, two definitions or eR2R were tested, with and without SNCT 1b. Our analysis is therefore likely to represent two extremes of inclusion of patients with acute functional impairment.

Within centre variation in eR2R was low, consistent with it minimising individual interpretation of each data element. eR2R was a poor predictor of discharge within 24 hours.[14] Youden's Index was consistently <0.15 across three calendar years, three different times of day and two eR2R definitions. For a dichotomous test such as eR2R, a Youden's Index >0.50 is generally considered the empirical benchmark for a test to support clinical decision making.[15] eR2R is therefore unsuited to the provision of clinical decision support tool for discharge. It does not define a subpopulation on which to assess discharge performance.[16] The limitations of R2R are not entirely surprising, given the need to interpret concepts that are not semantically defined. Although addressed by eR2R, it nevertheless remains a simple series of binary responses to questions that have not been validated for the purpose of discharge prediction. For example, NEWS2 was validated as an acuity score to quantify physiological instability on initial presentation to hospital.[17] It was not developed and has not been validated, as a triage tool to assess fitness to leave hospital, at any threshold.

Importantly, more than half of those who remain in hospital without eR2R, subsequently acquired eR2R. This group of patients were older and had multiple long-term health conditions, suggesting that there were clinical grounds for that decision, although undefined. This subpopulation requires further study.

There are limitations to our analysis. The eR2R was assessed in only one centre, although one that serves a diverse, multiethnic, urban population, in which more than 1.2 million patient days were assessed. Patients admitted for <24 hours at the time of analysis were excluded to allow clinical decisions to be made and executed. The first day postadmission is a highly dynamic situation, with frequent clinical review, a setting in which this embodiment of clinical decision support is arguably less relevant. Another more intrinsic problem is that there is no gold standard by which to define all patients suitable for discharge so that actual discharge was used as a fair test when evaluating the performance of eR2R.[18] This assumes that patients actually discharged are part of a continuous population of all those who could be discharged. It is also the case that each R2R element could be defined or operationalised in slightly different ways by healthcare professionals when being applied in clinical settings. Our data analysis, with clear definitions for each parameter within the eR2R does not include the 'art' of clinical medicine but does enable consistent comparisons to be made across time and localities.

It is important to validate and evaluate tests within their intended setting. The effects of embedding new care pathways or tools within clinical service delivery, without appropriate evaluation, are increasingly described. There is significant opportunity for unintended consequences to arise from the implementation of poorly considered clinical decision support,[19] particularly when there is competition for clinical resource. This has been recently discussed for NEWS2,[20] sepsis alerting and COVID-19 virtual wards.[21] R2R has been endorsed and adopted but without validation or consideration of the unintended consequences of its application. This is not to contend that a significant number of in-patients could not be discharged earlier, simply that there is no evidence that R2R can support clinical decision making. The collective limitations of R2R identified are likely to account for variation in nationally reported metrics that are difficult to explain.

Our study highlights the need for reproducible standardised data definitions to support both implementation and validation of any tool that purports to support clinical decision making. Further research should focus on building, validating and refining tools to inform clinical decisions.

Author affiliations
[1]PIONEER Data Hub, University of Birmingham, Birmingham, UK
[2]Department of Acute Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[3]Department of Research Informatics, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[4]Renal Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands, UK
[5]Better Care Programme and Midlands Site, HDR UK, Birmingham, West Midlands, UK

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Patient consent for publication Not applicable.

Ethics approval This study used unconsented, anonymous health data, and all study activity was approved by the East Midlands–Derby REC (reference: 20/EM/0158). Specific approvals were provided by East Midlands–Derby REC (reference: 20/EM/0158) to use unconsented, anonymised health data.

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Data availability statement Data are available on reasonable request. The anonymised dataset used for analysis is available on reasonable request from the PIONEER Data Hub on submission of a data request form, see www.pioneerdatahub.co.uk for a copy of the form and processes for data access.

ORCID iDs
Elizabeth Sapey http://orcid.org/0000-0003-3454-5482
Felicity Evison http://orcid.org/0000-0002-9378-7548
Simon Ball http://orcid.org/0000-0001-7410-5268

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Supplementary Table 6.1: The names of the Hospital Trusts included in the national R2R reporting analysis

National Trusts	
•Airedale NHS Foundation Trust	•Salisbury NHS Foundation Trust
•Ashford And St Peter's Hospitals NHS Foundation Trust	•Sandwell And West Birmingham Hospitals NHS Trust
•Barking, Havering And Redbridge University Hospitals NHS Trust	•Sheffield Teaching Hospitals NHS Foundation Trust
•Barnsley Hospital NHS Foundation Trust	•Sherwood Forest Hospitals NHS Foundation Trust
•Barts Health NHS Trust	•Somerset NHS Foundation Trust
•Bedfordshire Hospitals NHS Foundation Trust	•South Tees Hospitals NHS Foundation Trust
•Blackpool Teaching Hospitals NHS Foundation Trust	•South Tyneside And Sunderland NHS Foundation Trust
•Bolton NHS Foundation Trust	•South Warwickshire NHS Foundation Trust
•Bradford Teaching Hospitals NHS Foundation Trust	•Southport And Ormskirk Hospital NHS Trust
•Buckinghamshire Healthcare NHS Trust	•St George's University Hospitals NHS Foundation Trust
•Calderdale And Huddersfield NHS Foundation Trust	•St Helens And Knowsley Teaching Hospitals NHS Trust
•Cambridge University Hospitals NHS Foundation Trust	•Stockport NHS Foundation Trust
•Chelsea And Westminster Hospital NHS Foundation Trust	•Surrey And Sussex Healthcare NHS Trust
•Chesterfield Royal Hospital NHS Foundation Trust	•Tameside And Glossop Integrated Care NHS Foundation Trust
•Countess Of Chester Hospital NHS Foundation Trust	•The Dudley Group NHS Foundation Trust
•County Durham And Darlington NHS Foundation Trust	•The Hillingdon Hospitals NHS Foundation Trust
•Croydon Health Services NHS Trust	•The Newcastle Upon Tyne Hospitals NHS Foundation Trust
•Dartford And Gravesham NHS Trust	•South Warwickshire NHS Foundation Trust
•Doncaster And Bassetlaw Teaching Hospitals NHS Foundation Trust	•Southport And Ormskirk Hospital NHS Trust
•Dorset County Hospital NHS Foundation Trust	•St George's University Hospitals NHS Foundation Trust
•East And North Hertfordshire NHS Trust	•St Helens And Knowsley Teaching Hospitals NHS Trust
•East Cheshire NHS Trust	•Stockport NHS Foundation Trust
•East Kent Hospitals University NHS Foundation Trust	•Surrey And Sussex Healthcare NHS Trust
•East Lancashire Hospitals NHS Trust	•Tameside And Glossop Integrated Care NHS Foundation Trust
•East Suffolk And North Essex NHS Foundation Trust	•The Dudley Group NHS Foundation Trust
•East Sussex Healthcare NHS Trust	•The Hillingdon Hospitals NHS Foundation Trust
•Epsom And St Helier University Hospitals NHS Trust	•The Newcastle Upon Tyne Hospitals NHS Foundation Trust
•Frimley Health NHS Foundation Trust	•The Princess Alexandra Hospital NHS Trust
•Gateshead Health NHS Foundation Trust	•The Queen Elizabeth Hospital, King's Lynn, NHS Foundation Trust
•George Eliot Hospital NHS Trust	•The Rotherham NHS Foundation Trust
•Gloucestershire Hospitals NHS Foundation Trust	•The Royal Wolverhampton NHS Trust
•Great Western Hospitals NHS Foundation Trust	•The Shrewsbury And Telford Hospital NHS Trust
•Guy's And St Thomas' NHS Foundation Trust	•Torbay And South Devon NHS Foundation Trust
•Hampshire Hospitals NHS Foundation Trust	•United Lincolnshire Hospitals NHS Trust
•Harrogate And District NHS Foundation Trust	•University College London Hospitals NHS Foundation Trust
•Homerton University Hospital NHS Foundation Trust	•University Hospital Southampton NHS Foundation Trust
•Hull University Teaching Hospitals NHS Trust	•University Hospitals Birmingham NHS Foundation Trust
•Imperial College Healthcare NHS Trust	•University Hospitals Bristol And Weston NHS Foundation Trust
•Isle Of Wight NHS Trust	
•James Paget University Hospitals NHS Foundation Trust	
•Kettering General Hospital NHS Foundation Trust	
•King's College Hospital NHS Foundation Trust	
•Kingston Hospital NHS Foundation Trust	
•Lancashire Teaching Hospitals NHS Foundation Trust	
•Leeds Teaching Hospitals NHS Trust	
•Lewisham And Greenwich NHS Trust	
•Liverpool University Hospitals NHS Foundation Trust	
•London North West University Healthcare NHS Trust	
•Maidstone And Tunbridge Wells NHS Trust	
•Manchester University NHS Foundation Trust	
•Medway NHS Foundation Trust	

•Mid And South Essex NHS Foundation Trust •Mid Cheshire Hospitals NHS Foundation Trust •Mid Yorkshire Hospitals NHS Trust •Milton Keynes University Hospital NHS Foundation Trust •Norfolk And Norwich University Hospitals NHS Foundation Trust •North Bristol NHS Trust •North Cumbria Integrated Care NHS Foundation Trust •North Middlesex University Hospital NHS Trust •North Tees And Hartlepool NHS Foundation Trust •North West Anglia NHS Foundation Trust •Northampton General Hospital NHS Trust •Northern Care Alliance NHS Foundation Trust •Northern Devon Healthcare NHS Trust •Northern Lincolnshire And Goole NHS Foundation Trust •Northumbria Healthcare NHS Foundation Trust •Nottingham University Hospitals NHS Trust •Oxford University Hospitals NHS Foundation Trust •Portsmouth Hospitals University National Health Service Trust •Royal Berkshire NHS Foundation Trust •Royal Cornwall Hospitals NHS Trust •Royal Devon And Exeter NHS Foundation Trust •Royal Free London NHS Foundation Trust •Royal Surrey County Hospital NHS Foundation Trust •Royal United Hospitals Bath NHS Foundation Trust	•University Hospitals Coventry And Warwickshire NHS Trust •University Hospitals Dorset NHS Foundation Trust •University Hospitals Of Derby And Burton NHS Foundation Trust •University Hospitals Of Leicester NHS Trust •University Hospitals Of Morecambe Bay NHS Foundation Trust •University Hospitals Of North Midlands NHS Trust •University Hospitals Plymouth NHS Trust •University Hospitals Sussex NHS Foundation Trust •Walsall Healthcare NHS Trust •Warrington And Halton Teaching Hospitals NHS Foundation Trust •West Hertfordshire Hospitals NHS Trust •West Suffolk NHS Foundation Trust •Whittington Health NHS Trust •Wirral University Teaching Hospital NHS Foundation Trust •Worcestershire Acute Hospitals NHS Trust •Wrightington, Wigan And Leigh NHS Foundation Trust •Wye Valley NHS Trust •Yeovil District Hospital NHS Foundation Trust •York And Scarborough Teaching Hospitals NHS Foundation Trust

Legend. *Data is presented anonymously*

Supplementary Table 6.2: Codes use to identify surgical interventions

Procedure	**OPCS Codes**
Lower limb surgery within 48hrs	See Online supplement xls.
Thorax-abdominal-pelvic surgery with 72hrs	See Online supplement xls.
Invasive procedure within 24hrs	See Online supplement xls.

Legend. *OPCS=OPCS Classification of Interventions and Procedures code used to identify the coded clinical entry.*

Supplementary Table 6.3a: Contingency tables showing the number of patients meeting criteria for eR2Ra and eR2ab and the corresponding number of patients who remain in hospital over the next 24 hours or do not (were discharged), for the in-patient population at 08.00

	2019	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	214,613	21,333	235,946
	No (-)	128,470	19,270	147,740
	Total	343,083	40,603	383,686
	2020	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	177,852	18,283	196,135
	No (-)	97,119	17,606	114,725
	Total	274,971	35,889	310,860
	2021	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	208,449	19,989	228,438
	No (-)	115,111	19,075	134,186
	Total	323,560	39,064	362,624

	2019	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	301,018	30,176	331,194
	No (-)	42,065	10,427	52,492
	Total	343,083	40,603	383,686
	2020	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	249,964	28,636	278,600
	No (-)	25,007	7,253	32,260
	Total	274,971	35,889	310,860
	2021	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	291,576	30,847	322,423
	No (-)	31,984	8,217	40,201
	Total	323,560	39,064	362,624

Supplementary Table 6.3b: Contingency tables showing the number of patients meeting criteria for eR2Ra and eR2ab and the corresponding number of patients who remain in hospital over the next 24 hours or do not (were discharged), for the in-patient population at 16.00

	2019	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	214,005	19,919	233,924
	No (-)	129,543	18,465	148,008
	Total	343,548	38,384	381,932
	2020	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	178,709	17,343	196,052
	No (-)	98,123	17,692	115,815
	Total	276,832	35,035	311,867
	2021	**Remain**		
		Yes (+)	No (-)	Total
eR2Ra	Yes (+)	211,080	19,105	230,185
	No (-)	116,893	19,616	136,509
	Total	327,973	38,721	366,694

	2019	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	299,551	28,334	327,885
	No (-)	43,997	10,050	54,047
	Total	343,548	38,384	381,932
	2020	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	250,507	27,672	278,179
	No (-)	26,325	7,363	33,688
	Total	276,832	35,035	311,867
	2021	**Remain**		
		Yes (+)	No (-)	Total
eR2Rab	Yes (+)	294,260	30,038	324,298
	No (-)	33,713	8,683	42,396
	Total	327,973	38,721	366,694

Supplementary Table 6.4: The Sensitivity, Specificity and J statistic calculations for Data presented in **Table 6.5** of the main manuscript. A Contingency table showing the number of patients meeting criteria for eR2Ra and eR2ab

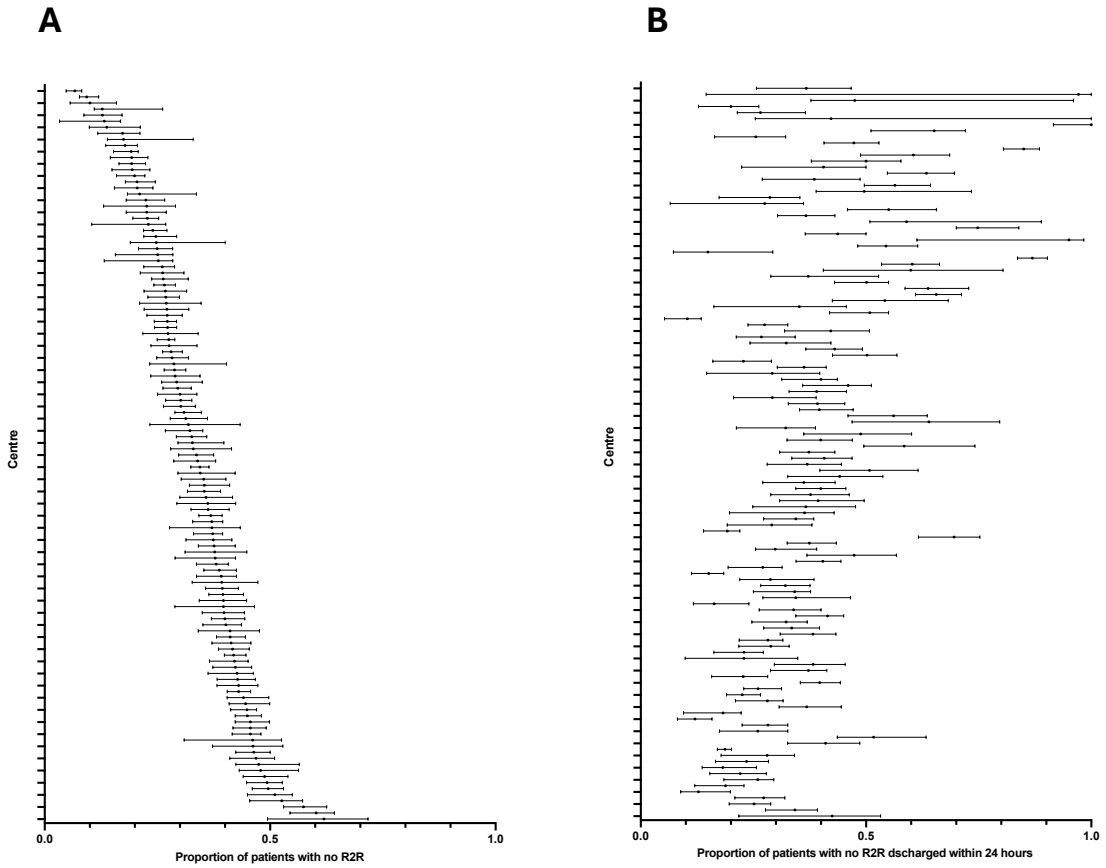
	eR2Ra			**eR2Rab**		
Year	**2019**	**2020**	**2021**	**2019**	**2020**	**2021**
Sensitivity	0.63	0.65	0.65	0.88	0.91	0.90
Specificity	0.46	0.47	0.47	0.24	0.18	0.19
J statistic	9%	12%	12%	11%	9%	9%

Supplementary Table 6.5: Demographics of patients not meeting R2R criteria on presentation to QEHB in the censor period

Population at 00:00	**Not meeting eR2Rab criteria and discharged in subsequent 24 hours**	**Not meeting eR2Rab criteria and not discharged**
n	22515	97326
Age in years: median (IQR)	60(45-74)	64(49-77)
Sex (n, %)	.	
Female	10833 (48.1%)	45345 (46.6%)
Male	11682 (51.9%)	51981 (53.4%)
Self-reported ethnicity (n, %)		
White	15761 (70.0%)	70194 (72.1%)
Mixed/ Multiple	411 (1.8%)	1549 (1.6%)
Asian/ Asian British	2952 (13.1%)	12194 (12.5%)
Black/ African/ Caribbean/ Black British	1274 (5.7%)	5857 (6.0%)
Other ethnic group	567 (2.5%)	2285 (2.3%)
Not known	1550 (6.9%)	5247 (5.4%)
Co-morbidity count (n, %)		
None	6544 (29.1%)	24873 (25.6%)
1-2	10321 (45.8%)	41401 (42.5%)
3 or more	5650 (25.1%)	31052 (31.9%)
Morbidities (n, %)		
Hypertension	9168 (40.7%)	43062 (44.2%)
Cerebrovascular disease	1512 (6.7%)	10128 (10.4%)
Atrial fibrillation	2947 (13.1%)	17096 (17.6%)
Ischaemic heart disease, angina, myocardial infarct	3810 (16.9%)	20962 (21.5%)
Diabetes (type 1 and 2)	4809 (21.4%)	24368 (25.0%)
Asthma	2644 (11.7%)	9899 (10.2%)
COPD	1594 (7.1%)	7255 (7.5%)
Interstitial Lung Disease	24 (0.1%)	129 (0.1%)
Chronic Kidney Disease	3135 (13.9%)	16633 (17.1%)
Any active Malignancy	3968 (17.6%)	17572 (18.1%)
Dementia (all types)	535 (2.4%)	3413 (3.5%)
English Indices of deprivation		
1	9448 (42.0%)	38534 (39.6%)
2	4638 (20.6%)	19841 (20.4%)
3	3888 (17.3%)	16630 (17.1%)
4	2200 (9.8%)	9432 (9.7%)
5	1644 (7.3%)	6914 (7.1%)
Missing	697 (3.1%)	5975 (6.1%)
Regained R2R criteria during stay? (n, %)	N/A	58609 (60.2%)
Reason for regaining R2R criteria?		
ICU		1727 (1.8%)
TAP surgery (72h)		263 (0.3%)
Lower limb surgery (24h)		95 (0.1%)
Invasive surgery (24h)		579 (0.6%)
Acute dependency level (48h)		7452 (7.7%)
NEWS >3 (24h)	N/A	20605 (21.2%)
O2 treatment (24h)		5111 (5.3%)
Intravenous fluids or treatments (24 hours, > tds)		27069 (27.8%)
GCS < or + 12 (24h)		183 (0.2%)
EOL care (24h)		165 (0.2%)
Increased dependency (48h)		10290 (10.6%)

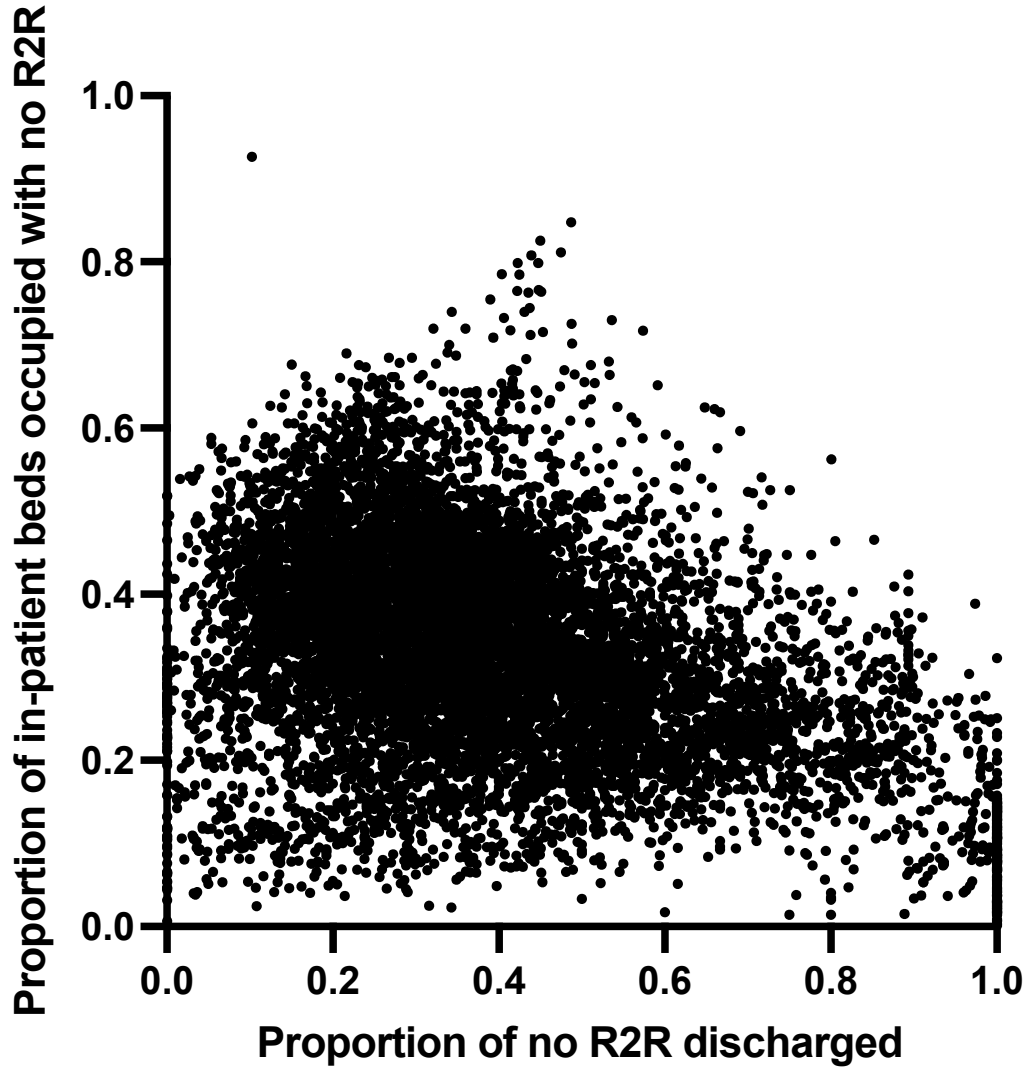
Legend. *Data is number (percentage) of patients in a bed at 00:00 who either were or were not discharged in the subsequent twenty-four hours after eR2R assessment. Ethnicity was self-reported. Medical conditions were physician confirmed and checked against admission and linked primary care notes. English Indices of deprivation were calculated using postcode.*

Supplementary Figure 6.1: The proportions of patients with no right to reside (A), and proportions of these with no right to reside that were discharged within 24 hours (B). Analysis by week.



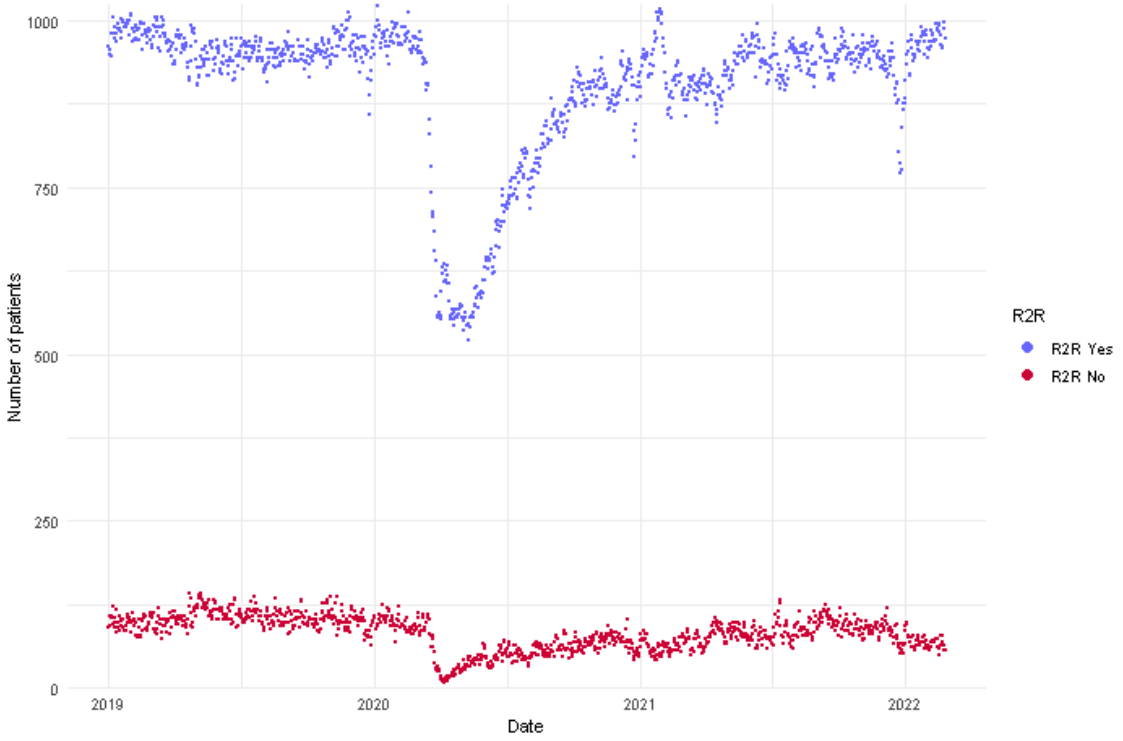
***Legend**. The proportions of patients not meeting the R2R, and the proportions of these patients that were discharged within 24 hours were extracted from daily reports for each national NHS centre. Data is presented as the median and IQR for the reporting period. Centres are arranged in ascending order of the period mean proportion of patients without R2R discharged within 24 hours.*

Supplementary Figure 6.2: The proportions of patients with no R2R and of that group the proportion discharged over the next 24 hours



Legend. *The proportions of patients not meeting the R2R, and of that group the proportion of patients discharged within 24 hours, reported to SDCS from 29 Nov 2021 – 20 Feb 2022 across 121 centres. Each dot represents result for a single centre-day. The two metrics were associated (slope = -0.21, p<0.0001) but the correlation was low (R2=0.12).*

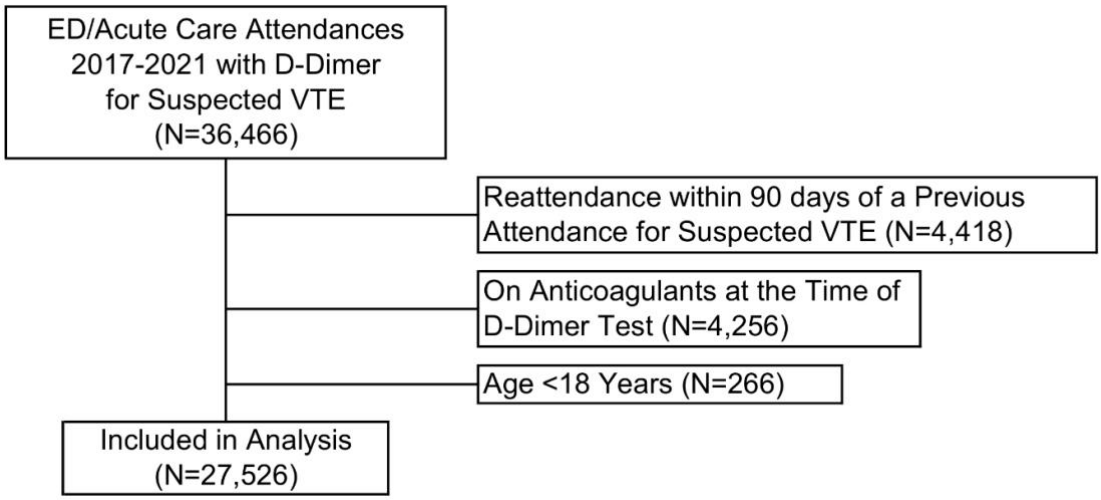
Supplementary Figure 6.3: The number of patients meeting or not meeting eR2Rab criteria 01 Jan 2019 - 31 Dec 2021



Legend. *Number of patients with (red dot) or without (blue dot) eR2Rab at 00:00 on each day of 2019-2021. The first COVID-19 admission to QEHB occurred on 1st March 2020. The first wave of the pandemic was associated with significant changes resulting in reduced bed occupancy and the majority of admitted patients had a diagnosis of COVID-19.*

Appendices for Chapter 7

Supplementary Figure 7.1: Study flowchart



Legend. *ED: Emergency Department, VTE: Venous Thromboembolism*

Supplementary Table 7.1: Classification accuracy of D-dimer thresholds by age

Age (Years)	D-Dimer Threshold	VTE						
		No	*Yes*	Sensitivity	Specificity	NPV	PPV	Accuracy
<50				*p=N/A*	*p=N/A*	*p=N/A*	*p=N/A*	*p=N/A*
(N=12240)	ST							
	<250µg/L	9516	39	87.5%	79.8%	99.6%	10.1%	80.0%
	≥250µg/L	2413	272	(272/311)	(9516/11929)	(9516/9555)	(272/2685)	(9788/12240)
	AAT							
	<AAT	9516	39	87.5%	79.8%	99.6%	10.1%	80.0%
	≥AAT	2413	272	(272/311)	(9516/11929)	(9516/9555)	(272/2685)	(9788/12240)
50-59				*p=0.695*	***p=0.003***	*p=0.810*	*p=0.497*	***p=0.005***
(N=4748)	ST							
	<250µg/L	3203	33	84.5%	70.6%	99.0%	11.9%	71.3%
	≥250µg/L	1332	180	(180/213)	(3203/4535)	(3203/3236)	(180/1512)	(3383/4748)
	AAT							
	<AAT	3330	37	82.6%	73.4%	98.9%	12.7%	73.8%
	≥AAT	1205	176	(176/213)	(3330/4535)	(3330/3367)	(176/1381)	(3506/4748)
60-69				*p=0.169*	***p<0.001***	*p=0.342*	*p=0.084*	***p<0.001***
(N=3973)	ST							
	<250µg/L	2206	10	94.9%	58.4%	99.5%	10.7%	60.3%
	≥250µg/L	1569	188	(188/198)	(2206/3775)	(2206/2216)	(188/1757)	(2394/3973)
	AAT							
	<AAT	2537	18	90.9%	67.2%	99.3%	12.7%	68.4%
	≥AAT	1238	180	(180/198)	(2537/3775)	(2537/2555)	(180/1418)	(2717/3973)
70-79				***p=0.017***	***p<0.001***	*p=0.202*	***p=0.011***	***p<0.001***
(N=3545)	ST							
	<250µg/L	1474	17	93.1%	44.7%	98.9%	11.1%	48.0%
	≥250µg/L	1826	228	(228/245)	(1474/3300)	(1474/1491)	(228/2054)	(1702/3545)
	AAT							
	<AAT	1998	34	86.1%	60.5%	98.3%	13.9%	62.3%
	≥AAT	1302	211	(211/245)	(1998/3300)	(1998/2032)	(211/1513)	(2209/3545)
80-89				***p=0.001***	***p<0.001***	*p=0.102*	***p=0.010***	***p<0.001***
(N=2393)	ST							
	<250µg/L	662	5	97.0%	29.7%	99.3%	9.4%	34.4%
	≥250µg/L	1564	162	(162/167)	(662/2226)	(662/667)	(162/1726)	(824/2393)
	AAT							
	<AAT	1210	22	86.8%	54.4%	98.2%	12.5%	56.6%
	≥AAT	1016	145	(145/167)	(1210/2226)	(1210/1232)	(145/1161)	(1355/2393)
90+				*p=0.617*	***p<0.001***	*p=1.000*	*p=0.084*	***p<0.001***
(N=627)	ST							
	<250µg/L	116	1	97.8%	20.0%	99.1%	8.8%	25.7%
	≥250µg/L	465	45	(45/46)	(116/581)	(116/117)	(45/510)	(161/627)
	AAT							
	<AAT	286	3	93.5%	49.2%	99.0%	12.7%	52.5%
	≥AAT	295	43	(43/46)	(286/581)	(286/289)	(43/338)	(329/627)

***Legend**. The age-adjusted threshold used a value of 250µg/L for those aged <50 years, or age (in years)*5µg/L for those older than 50 years. p-Values are from Fisher's exact tests, comparing the percentages between the standard and age-adjusted thresholds within each subgroup of age; bold p-values are significant at p<0.05.*

AAT= Age-Adjusted Threshold; N(P)PV=Negative (Positive) Predictive Value; ST=Standard Threshold; VTE=Venous Thromboembolism.

Appendices for Chapter 8

Supplementary Analysis 8.1: Statistical results

Two simple examples are the mean μ and variance s^2. The mean is simply a set of sums and counts and may be partitioned into p smaller sums.

$$\mu = \frac{1}{N}\sum_{i=1}^{N} x_i = \frac{1}{\sum_{j=1}^{p} n_i}\sum_{j=1}^{p}\sum_{i=1}^{n_j} x_{i,j}$$

Where $N = \sum_{j=1}^{p} n_j$ and $n_j > 0$

Likewise the variance may for illustrative purposes be written

$$s^2 = \frac{1}{N-1}\left[\sum_{i=1}^{N} x_i^2 - \frac{1}{N}\left(\sum_{i=1}^{N} x_i\right)^2\right]$$

Each sum within the formulation may be partitioned in its own right.

More generally the Fisher-Neyman factorisation theorem may be applied to the likelihood of generalised linear models having errors from the exponential family. Given a sample $\{X_i | i = 1\ to\ n\}$ with probability density $f(x|\theta)$ where θ is a parameter vector, the likelihood of θ given $\{X_i | i = 1\ to\ n\}$ is written.

$$\prod_{i=1}^{n} l(\theta|X_i)$$

Where $l(\theta|X_i) = f(X_i|\theta)$

For data having an exponential family distribution

$$f(x|\theta) = exp[c(\theta).T(x) + d(\theta) + S(x)\ ]$$

The log likelihood is

$$c(\theta)\sum_{i=1}^{n} T(X_i) + n.d(\theta) + \sum_{i=1}^{n} S(X_i)$$

The term $\sum_{i=1}^{n} T(X_i)$ is known as a sufficient statistic for θ. All the information required to calculate θ is contained within $\sum_{i=1}^{n} T(X_i)$. As shown with the mean, sums of quantities are readily federated.

There is no need to demonstrate federation for Bayesian statistics as Bayesian updates may be applied sequentially in any order with the posterior at step n becoming the prior at step $n + 1$.