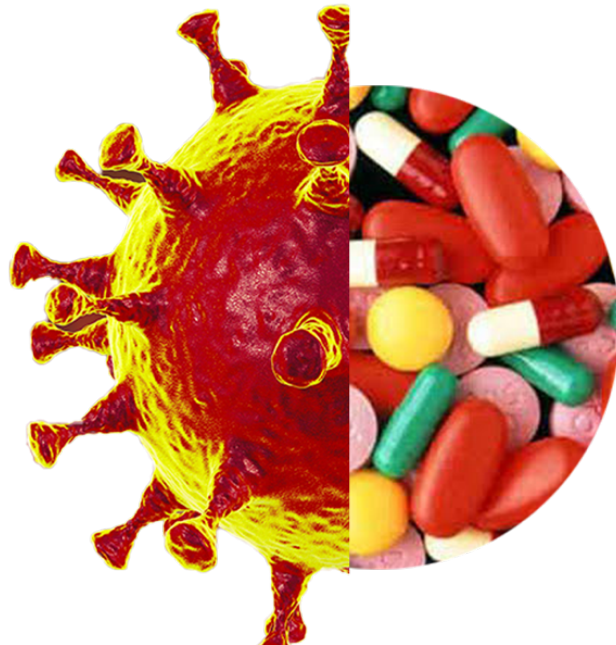# An investigation into factors affecting the implementation of antimicrobial stewardship (AMS) before and during the COVID-19 pandemic in two acute care settings.

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Summary

Background: Antimicrobial resistance (AMR) is a global crisis that requires urgent attention and action. Antimicrobial stewardship (AMS) is a set of actions that aims to promote the effective use of antibiotics. According to the UK report in 2016, it was estimated that, by 2050, 10 million people will die every year due to antimicrobial resistance (AMR). For this reason, the Public Health England (PHE) emphasised the need for AMS implementation in the acute care settings to maintain the appropriate, effective, and safe use of antibiotics. AMS is important to reduce inappropriate antibiotic prescribing and tackle the threat of AMR. It is essential to investigate AMS strategies that could be used effectively in any crisis. COVID-19 challenged all aspects of healthcare, especially appropriate antibiotic use. This research project aims to explore AMS implementation in Bedfordshire Hospitals NHS Foundation Trust before and during the COVID-19 pandemic. It includes three sequential studies.

- **The first study** was conducted last year as a systematic literature review. It aimed to explore AMS interventions before and after the COVID-19 pandemic.
- **The second study** will investigate the practice of AMS implementation in Bedfordshire Hospitals NHS Foundation Trust (Luton and Dunstable hospital and Bedford hospital).
- **The third study** will explore healthcare professionals' (doctors, pharmacists, and nurses') knowledge, attitudes, and perceptions toward antibiotic prescribing and AMS implementation before and during the COVID-19 pandemic.

The proposed measures are to measure AMS implementation using the proportion of inappropriately prescribed antibiotics at the time of admission, 48-72 hours after admission. Additionally, it will review the antibiotic prescribing behaviour of healthcare professionals (HCPs) and identify factors that impact AMS intervention before and during the COVID-19 pandemic. The expected outcomes of this research project are to identify AMS implementation and measures that were used before and during the COVID-19 pandemic based on PHE toolkit of AMS (Start Smart – then Focus), which will provide the gold standards for this research project. Additionally, this research project will help to understand the knowledge, attitudes, and perceptions of healthcare professionals towards antibiotic prescribing and AMS implementation before and during the pandemic.

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Abbreviations

AMS	Antimicrobial Stewardship
CI	Chief Investigator
AMR	Antimicrobial Resistance
PHE	Public Health England
NICE	National Institute for Health and Care Excellence
WHO	World Health Organization
L&D	Luton and Dunstable
RTIs	Respiratory Tract Infections
KPIs	Key Performance Indicators
CINAHL	Cumulative Index to Nursing and Allied Health Literature
MED-LARS	Medical Literature Analysis and Retrieval System Online
EMBSE	Excerpta Medica Database
MIDIRS	Maternity & Infant Care Database
CASP	Critical Appraisal Skills Program
CAG	Confidentiality Advisory Group
PI	Principal Investigator
REC	Research Ethics Committee
UH	University of Hertfordshire
HCPs	Healthcare Professionals
PIS	Participant Information Sheet
MAXQDA	Qualitative Data Analysis Software
NIHR	National Institute of Clinical Research
GCP	Good Clinical Practice
NRES	National Research Ethics Service

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Research Synopsis

Title of Research	An investigation into factors affecting the implementation of AMS before and during COVID-19 pandemic in two acute care settings.
Aims	To explore the factors affecting AMS interventions before/during the COVID-19 pandemic in two acute care settings.
Research Questions	1. How was AMS implemented before and during the COVID-19 pandemic? 2. What factors affect the AMS implementation before and during the COVID-19 pandemic?
Research Objectives	1. To ascertain from the literature, the strategies, tools, and measures used for AMS implementation to decrease the AMR threat. 2. To evaluate AMS implementation before and during the COVID-19 pandemic. 3. To identify AMS intervention strategies used before and during the pandemic. 4. To explore health care professionals' prescribing behaviour, attitudes, perception, and knowledge of AMS practice before and during the pandemic. 5. To make recommendations to support healthcare providers regarding effective AMS intervention to minimise AMR.
Research Design	1. Systematic literature review. 2. Retrospective study from patient medical records after anonymisation of all identifiable data (quantitative study) 3. Prospective online survey study.
Settings	Bedfordshire Hospitals NHS Trust: • Luton and Dunstable University Hospital (L&D) • Bedford Hospital
Duration	September 2022- September 2024
Sample Size	• Hospital: 640 Patients' medical records. • An online survey of about 240 health care practitioners
Resource, Tools, Forms	1. Data collection forms 2. Hospital Antimicrobial Guidelines. 3. Public Health England (PHE), Start Smart - then Focus toolkit of Antimicrobial Stewardship (AMS). 4. NICE guidelines for AMS. 5. British National Formulary (BNF). 6. PHE antibiotic prescribing behaviour toolkit
Pilot study	1. Phase 1 pilot: To maintain the reliability of the data extraction.

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	2. Phase 2 pilot: 5% of the survey respondents to maintain the validity and reliability of the survey. This will be conducted by using IBM statistical package for the social sciences (SPSS) version 22
Data Analysis	● Quantitative data analysis: Descriptive and inferential statistics will be applied in analysing quantitative data. This will be conducted by using IBM statistical package for the social sciences (SPSS) version 22. ● Qualitative data analysis: Data will be organised using NVivo and coded using thematic analysis.
Ethics	1. REC ethical approval 2. UH ethical approval 3. CAG provisional support and approval 4. Implied consent from all survey participants 5. Personal data will remain confidential and anonymous 6. Data will be processed in line with University of Hertfordshire policy

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1- Introduction

The prevalence of antimicrobial resistance (AMR) has risen significantly over the last 40 years, and a few novel antimicrobials have developed [1]. AMR has increased the pressure on existing antibiotics and more significant challenges in treating patients. Inappropriate use of antimicrobials increases the risk of infection with resistant organisms and subsequent transmission to other patients. AMS is an essential element of the UK's five-year antimicrobial resistance strategy from PHE [2]. AMS is a set of actions that aims to promote the effective use of antimicrobials. Such stewardship initiatives aim to contribute significantly to the reductions and spread of AMR. Additionally, AMS intervention strategies seek to improve antimicrobial prescribing and decrease AMR (Appendix 4). The National Institute for Health and Care Excellence (NICE) produced AMS guideline in 2017 and recommended its implementation in acute care settings [1]. Additionally, PHE toolkit of AMS, Start Smart - then Focus provided an impressive outline of evidence-based AMS implementation within the secondary healthcare settings (Figure 1) [2].
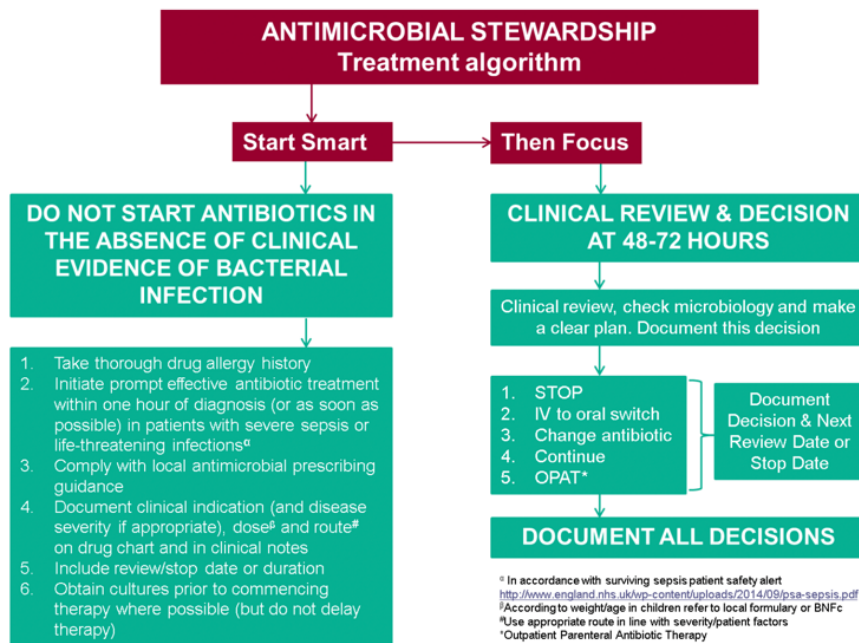
Figure 1 Public Health England AMS treatment algorithm [2]

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Start Smart - this means:

- do not start antimicrobial therapy unless there is clear evidence of infection.
- take a thorough drug allergy history.
- initiate prompt effective antibiotic treatment within one hour of diagnosis.
- avoid inappropriate use of broad-spectrum antibiotics.
- comply with local antimicrobial prescribing guidance.
- document clinical indication (and disease severity if appropriate), drug name, dose, and route on drug chart and in clinical notes.
- include review/stop date or duration.
- obtain cultures prior to commencing therapy where possible.
- prescribe single-dose antibiotics for surgical prophylaxis where antibiotics have been shown to be effective.
- document the exact indication on the drug chart (rather than stating long term prophylaxis) for clinical prophylaxis.

Then Focus – this means:

- reviewing the clinical diagnosis and the continuing need for antibiotics at 48-72 hours and documenting a clear plan of action - the 'antimicrobial prescribing decision'.
- the five 'antimicrobial prescribing decision' options are 1. Stop antibiotics if there is no evidence of infection 2. Switch antibiotics from intravenous to oral 3. Change antibiotics – ideally to a narrower spectrum – or broader if required 4. Continue and document the next review date or stop date 5. Outpatient Parenteral Antibiotic Therapy (OPAT).
- it is essential that the review and subsequent decision are clearly documented in the clinical notes and drug chart where possible, for example stop the antibiotic.

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The COVID-19 pandemic has accelerated the threat of AMR. Inappropriate antibiotic prescribing has increased during the COVID pandemic. The World Health Organization (WHO) discourages antibiotics for mild cases of COVID-19. WHO was concerned about the inappropriate use of antibiotics, particularly during this pandemic [3]. AMR was responsible for 700,000 annual deaths worldwide. In the shadow of COVID-19, antimicrobial resistance (ABR), one of the world's worsening pandemics, has been 'silenced'. Inappropriate antibiotic prescribing within the hospitals has increased as the number of severely unwell COVID-19 patients increased. Diagnostic uncertainty and concern about secondary bacterial infections may have contributed to this adverse change in antibiotic prescribing [4]. It is essential to learn from the COVID-19 pandemic and prepare for any upcoming emergencies or future pandemics. This study will focus on AMS as a practical way to improve the safety and quality of patient care. Additionally, it will contribute significantly to the reduction of AMR (figure 2).
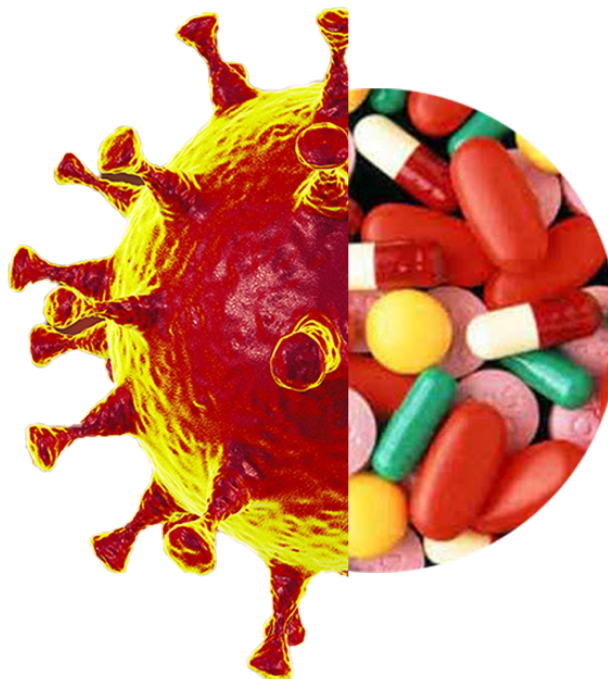
Figure 2 COVID-19 pandemic and antimicrobial resistance (AMR) silent pandemic

2. Research project:

This research project investigates AMS implementation before and during the COVID-19 pandemic. It includes three sequential studies (Figure 3).

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1. Systematic literature review: The first study was undertaken on the published information available in scientific journals and reports to obtain evidence about antibiotic use and AMS intervention in acute care settings. It aimed to explore the practice of AMS in acute care settings before and during the COVID-19 pandemic, using a range of explicit strategies and measures, which showed promising outcomes in improving antibiotic prescribing and maintaining the rational use of antimicrobials, especially during COVID-19. Effective AMS implementation is linked to the improved overall health of adult patients and positively influences reducing AMR. Nonetheless, further studies are required to investigate AMS intervention strategies and the factors affecting AMS implementation in the future.

2. Phase 1: Observational study of hospital retrospective data: It will review the medical records of patients with RTIs or pneumonia who were admitted to Bedfordshire Hospitals before and during the COVID-19 pandemic.

3. **Phase 2: Online survey:** It aims to understand their perceptions, attitudes, practices and identify the factors that affected AMS implementation among Healthcare Professionals (HCPs) before and during the COVID-19 pandemic.

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Systematic Literature Review

To explore the published papers on AMS in the acute care settings before and during the COVID-19 pandemic **(Identifying knowledge Gaps in The Literature).**

Timeline

01/02/2021 to 31/08/2022

Retrospective Study

To investigate AMS implementation in two acute-care settings of Bedfordshire Hospitals NHS Trust. A retrospective review of patients' medical records where antibiotics was prescribed for RTIs or (COVID) pneumonia before and during the COVID-19 pandemic. **(Quantitative Study).**

Timeline

01/09/2022 to 31/08/2023

Prospective Study

To explore the health professionals' perceptions, attitudes and AMS practices. Additionally, this study will identify factors that affected AMS implementation before and during the COVID-19 pandemic. The survey will be used based on PHE antibiotic prescribing and Behavioural analysis in secondary care settings **(Survey Study).**

Timeline

01/09/2023 to 01/09/2024

Figure 3 Description of the research project

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4. Systematic literature review

A systematic review of antimicrobial stewardship intervention before and during the COVID-19 pandemic in the acute care settings

Introduction:

Antimicrobial resistance (AMR) is a global crisis that requires urgent attention and action. More than 1.2 million people died worldwide in 2019 from infections caused by bacteria resistant to antibiotics [9]. COVID-19 challenged all aspects of healthcare, especially the appropriate antibiotic use. AMS is a set of actions to promote the effective use of antibiotics. PHE emphasised the need for AMS implementation in acute care settings to maintain the appropriate, effective, and safe use of antibiotics. It is essential to find out AMS strategies that could be used effectively in any crisis. This systematic review explored AMS implementation strategies in acute care settings before and during the COVID-19 pandemic.

Method: A systematic literature search on MEDLINE, Embase classic, OVID, International Pharmaceutical Abstracts, Psychosocial Instruments, MIDIRS, PubMed, Scopus, Web of Science, CINAHL PLUS, OpenGrey, and Google Scholar was undertaken. The inclusion criteria were: (i) research studies focusing on antibiotic use in acute care settings; (ii) AMS intervention; (iii) AMS implementation strategies during the COVID-19 pandemic; (iv) adult patients of any gender; and (v) studies reported in the English language (Table 1).

Table 1: Inclusion and exclusion criteria of the systematic literature review

	Inclusion criteria	Exclusion criteria
Participants	Studies targeting the public/patients' use of antibiotics. HCPs responsible for prescribing, dispensing, or administering antibiotics (doctors, pharmacists and nurses)	Non-HCPs (patient family or community or nursing or long-term care patients)
Intervention	Studies describe an intervention to improve antibiotic prescribing or AMS implementation strategies as iv- oral switch, and de-escalation, antibiotic review and discontinuation.	Studies that do not describe an AMS intervention.
Comparison	Comparison with a control group/a group that carried out usual care without an AMS intervention.	

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Context	Interventions are carried out in adult inpatient settings in acute care settings.	Interventions are carried out in nursing homes, care homes or long-term healthcare facilities; community settings; pediatric setting/hospital; and animals/veterinary practice.
Outcomes	Primary outcomes: reviewing the effectiveness of AMS intervention and strategies prior to the COVID-19 pandemic and during the pandemic.	
	Secondary outcomes: HCPs' knowledge, attitudes or behaviours related to antibiotic prescribing; rates of AMR; length of stay in hospitals; other measures, metrics, quality improvement, KPIs and COVID-19 pandemic impact on AMS intervention.	
Study design	RCTs, non-randomized trials, CBA studies, interrupted time series designs, case-control studies and cohort studies, cross-sectional studies, qualitative studies	Systematic reviews, meta-analysis, single case studies, case reports, conference abstracts.

Results: Sixteen articles met the inclusion criteria from an initial result of 8,763 identified article titles. A range of AMS interventions was identified based on AMS toolkit that was developed by PHE. Prior to the COVID-19 pandemic, the most reported AMS strategies in 67% of studies were prospective audit, feedback, and AMS Multidisciplinary Team (MDT). AMS education was also reported in 50% of studies. During the COVID-19 pandemic, AMS education and MDT were the most written strategies implemented in 25% of studies. These were followed by antibiotic review, streamlining/escalation and formulary restriction reported in 17% of studies. The antibiotic review was implemented equally before and during the COVID-19 (Figure 4). This systematic review showed the global pharmacists' role in leading AMS implementation in acute care settings (Appendix 6). In addition, it showed some promising new innovative AMS implementation strategies, such as Procalcitonin (PCT) measurements, quality improvement initiatives and antibiotic dashboard that showed promising outcomes in AMS intervention during the COVID-19 pandemic (Appendix 7).
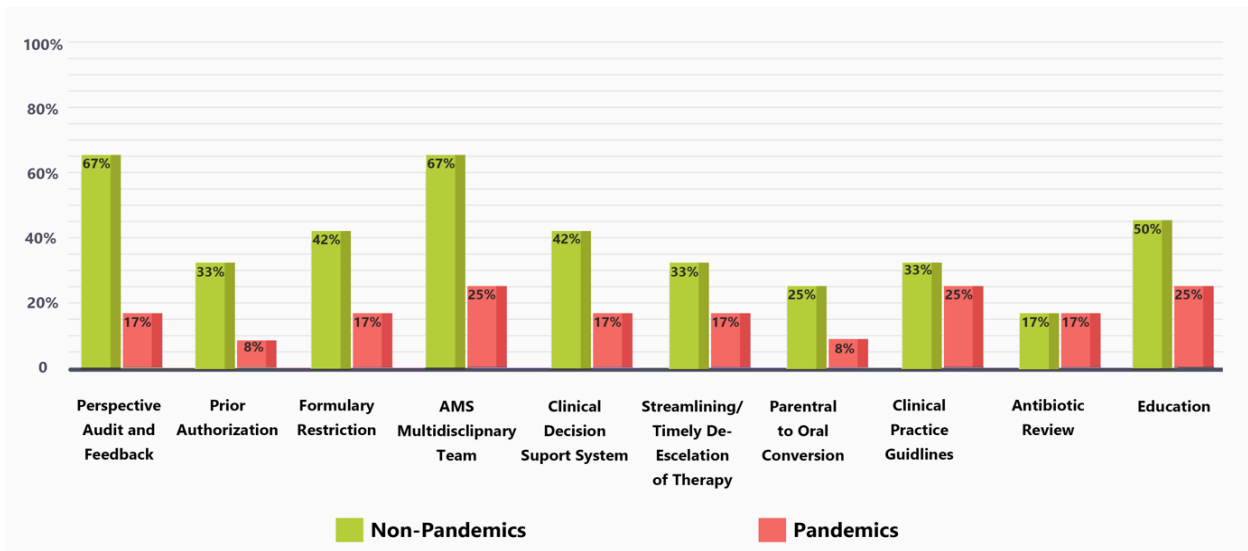
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Figure 4 AMS intervention strategies before and during the COVID-19 pandemic (Total studies 16)

Conclusion: This systematic literature search support findings that show promising outcomes in selecting the right AMS implementation strategies in acute-care settings. The COVID-19 pandemic is a significant and new public health threat, putting tremendous pressure on all HCPs. However, the ongoing global crisis of AMR must not be neglected. Although urgent actions are required to continue measuring AMS implementation and practices during the COVID-19, to be prepared to any future pandemics. Other recommendations include ensuring access to effective antimicrobials and upholding the principles of AMS strategies in the acute care settings. Finally, advocacy for AMS must continue in the post-pandemic era to maintain the safety and quality of patient care.

Results from the systematic literature review have been published at national and international conferences (Appendix 5). A research gap was found to identify how AMS was implemented in the acute care settings during the COVID-19 pandemic. Previous studies did not have the exact AMS toolkits or roadmap that could be used during the COVID-19 pandemic. They did not measure the proportion of inappropriate antibiotic prescribing, and HCPs' perceptions and attitudes toward antibiotic prescribing during the pandemic. This research project will investigate AMS implementation before and during the COVID-19 pandemic based on PHE toolkit of AMS (Start Smart – then Focus), which will provide the gold standards for this research project to identify how AMS interventions were implemented before and during the COVID-19 pandemic.

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5. Retrospective study for the patient medical records

(*Phase 1: Retrospective study at Bedfordshire Hospitals NHS Trust*)

4.1. Aim and Objectives:

This research investigates AMS implementation before and during the COVID-19 pandemic in the Bedfordshire Hospitals NHS Trust (Luton and Dunstable University hospital and Bedford hospital).

Setting:

Bedfordshire Hospitals NHS Trust provides secondary care services for a population of around 400,000 people within the local catchment area covering Luton, South Bedfordshire and parts of Hertfordshire and Buckinghamshire. The hospital became a foundation trust in 2006. There are approximately 742 beds, of which 82 are maternity, and 18 are critical care beds and high dependency beds, with 18 contingency beds over 27 wards. In a twelve-month period, the Trust employed 7,982 (headcount) Health Professionals, the number of inpatient admissions 86,676 and 442,113 outpatient attendances. Permission and support for data collection were sought from the Chief Pharmacist and pharmacy team at Bedfordshire Hospitals NHS Trust.

4.2. Methodology:

This phase will include reviewing medical records of patients prescribed antibiotics for RTIs or pneumonia before and during the COVID-19 pandemic. Data collection will be undertaken at eight-time points, four before COVID-19 as baseline measures and four during the COVID-19 pandemic.

4.3. Inclusion criteria

1. Adult patients 25 years and older.
2. Adult Pregnant women and immunocompromised patients.
3. Patients admitted at Bedfordshire Hospitals NHS Trust.
4. Patient admitted in 2019 and 2020.
5. Patients who were prescribed antibiotics for RTIs or pneumonia.

4.4. Exclusion criteria:

1. Patients who were not prescribed antibiotics.
2. Children and patients admitted for less than 48-72 hours.

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4.5. Data source

Data will be collected from the patient's electronic medical records in Bedfordshire Hospitals NHS Trust by the PhD student/PI according to the study inclusion criteria. The study includes two hospital research collaborators who work at Bedfordshire hospitals. The hospital collaborators will obtain the list of the patients from the coding team first, then communicate with from information governance team according to the study eligibility and the national NHS opt-out act exclusion. Then the PhD student/PI will collect the required study data from the data collection tool. The PI will use the data collection tool to extract the required data for validation and analysis. Each patient's medical record will take about one hour for the PhD student/PI to collect the necessary data.

Process of patient record identification and retrieval

The hospital collaborators for this study are part of the direct patient care team due to their roles within the hospital Trust. Sanil Patel is the lead AMS pharmacist. Patricia Edwards is a lead specialist pharmacist for education and training. Both work across the two Bedfordshire hospital sites, including Luton & Dunstable and Bedford hospitals. Both are part of the direct care team. Sanil Patel is the lead antimicrobial pharmacist who oversees AMS process for all patients. Patricia Edwards is the lead specialist pharmacist for education and training and has the responsibility to oversee all activities related to education and training, including the use of patient data by students who must all have an honorary contract or have employment by the trust.

The PI for this study is Rasha Abdelsalam Elshenawy, who has an honorary contract at Bedfordshire Hospitals NHS Trust. Patricia Edwards and Sanil Patel will contact the coding team to request a list of patient records using the specified codes and criteria for the patient records sample. The coding team will retrieve and produce the relevant patient list matching the study sample codes and criteria and send this to the two hospital collaborators. The coding team will also ensure that the list sent to the hospital collaborators aligns with the NHS opt-out process to ensure that patients who indicated this choice would not be included. The two hospital collaborators will review the patient list to validate its appropriateness with the study sample patient records. Following this process, the patient list will then be made available to the PI/PhD student. The list, which includes identifiable patient information, will be maintained on the hospital computer system and will not leave the hospital system or site in this format.

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4.6. Access to identifiable patients' data during the study

This phase will require assessing patients' data without prior consent. However, for this study, which is mainly retrospective, it will be impractical to obtain consent from the patients whose records are to be assessed due to the time required to seek and obtain consent from the relatively large sample. Patients may have moved residences. However, all data collection and processing will be fair and lawful in line with the principles of the General Data Protection Regulation (GDPR).

The PhD student/PI applied for the Confidentiality Advisory Group (CAG) Committee on 08th Match, 2022, with an application number (22/CAG/0039). CAG committee was provisionally supported, with satisfactory responses to the requests for further information and compliance with the standard and specific conditions of support. CAG is also supported for the duration of the retention of the key between confidential patient information and the pseudonymous study ID. The PhD student/PI will access the patients' identifiable data till the expected end of this study phase 1 which is 28th February 2023. Access to patients' identifiable data will be restricted only to the PI and external collaborators at both hospital sites (L&D and Bedford hospitals). Then the PI will anonymise the data and transfer it to the double secure University of Herefordshire (UH) system for analysis and results. The PI/PhD student who will conduct the data collection is a clinical pharmacist certified in AMS. The PI also obtained training certification in Good Clinical Practice (GCP) from the NIHR. In addition to the training modules in the research, data analysis in the UH, and the training modules in the NHS hospital portal, signed the confidentiality agreement and Honorary contract with the Bedfordshire Hospitals NHS Trust (Appendix 10).

The main ethical issues are data protection, confidentiality, and data anonymity. The PhD Student/PI has signed an honorary contract for the two years of study; the PI has an NHS secure email. In addition, the PI obtained a new user account to access the hospital's electronic system. The PI will protect the confidentiality of data; all patient identifiable data will be stored only in the hospital system under the supervision of the hospital collaborators. Then, the PI will anonymise the extracted data and store it on the University's secured network storage system, which requires a double security check for analysis. The external collaborators (Patricia Edwards and Sanil Patel) are two pharmacists and part of the direct care team with limited capacity to undertake the necessary data extraction process for 640 patients. The PI/PhD student is trained in clinical research and data extraction and has over

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20 years of experience in clinical pharmacy practice, research, data management, patient safety, quality improvement and AMS implementation.

4.7. Confidentiality Advisory Group (CAG) support

Confidentiality Advisory Group (CAG) support is required to allow the disclosure of confidential patient information to the PI, who is not part of the direct care team. CAG support was obtained while extracting a pseudonymous dataset for analysis from electronic patient records at Bedfordshire Hospitals NHS Trust. The CAG support was also assured for the duration between confidential patient information and the pseudonymous study ID. CAG support was retained for the PhD student/PI, who will have access to the patients' identifiable data until the expected end of this study phase 1. The PhD student/PI applied to the CAG Committee on 08th Match, 2022, with an application number (22/CAG/0039) and received the provisional support approval. The Confidentiality Advisory Group (CAG) category set has provisionally supported the following:

1. The CAG application allows the applicant/PI (Rasha Abdelsalam Elshenawy), who is not a member of the direct care team, to access confidential patient information. It will be held at Bedfordshire Hospitals NHS Foundation Trust. The PI will extract a pseudonymised dataset. CAG is provisionally supporting retaining the pseudonymisation key at the Trust. Additionally, CAG's satisfactory response supported the requests for further information and compliance with the standard and specific conditions of support.

2. Support to process the specified confidential patient information without consent is not in effect until a separate outcome letter is issued.

4.8. Data Confidentiality:

The external collaborators from the Bedfordshire Hospitals NHS Trust and part of the direct healthcare will identify the data initially. The data collection will be started after that by the research student. Only the PI will collect the required data from the patients' electronic medical records. The identifiable patient information will be stored only in the hospital system on the hospital. Personal data and clinical records will only be accessed through the PI's secure hospital account with password protection. The data collection will be conducted from the trust computers with a password login protected on the hospital site itself.

4.9. Exit strategy and length of time support required

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This phase obtained provisional support from CAG 's251' support, which refers to section 251 of the National Health Service Act 2006 and its current Regulations, the Health Service (Control of Patient Information) Regulations 2002. The exit strategy for the data extraction element is pseudonymisation. A member of the direct care team (Patricia Edwards) will identify patients who fit the criteria. This member will then review this to ensure patients with NHS opt-out are excluded. Patricia Edwards will then make this data available to the PhD student/PI. The PhD student will then extract the data and pseudonymise it in the hospital sites. The linked data will remain on-site in the custody of a member of the direct care team (Patricia Edwards). Only pseudonymised data will be stored on the university system to facilitate analysis. The PhD student/PI will no longer have access to the patients' identifiable data after the expected end of this study phase 1 – after 31st August 2023.

4.10. Data Anonymisation

1. After receiving the approval from the REC.
2. The PhD student/PI will supply the inclusion and exclusion criteria to the hospital collaborator.
3. The hospital collaborator will contact the 'Coding team' to look for the required list of medical records within the criteria and timepoints of the study.
4. The exported 'excel sheet' list of the patient will be generated for the hospital collaborator.
5. The hospital collaborator will contact the 'Information governance team' to apply the national opt-out act.
6. The hospital collaborator will provide the final list of the identified patient medical records.
7. The PhD student/PI has an Honorary contact in the NHS and will use the hospital computers, secure username and password, for data extraction.
8. Data will be extracted from a total of 640 medical records. Each medical record will take 45 – 60 minutes to extract the data (Appendix 19.

4.11. Data collection:

The PhD student/ PI will collect the data. The PI has an honorary contract in the Bedfordshire Hospitals NHS Trust from December 2021 until the expected end of the research project. As the seasonal variations affect antibiotic prescribing for RTIs or pneumonia. The highest incidence of pneumonia was noted in the winter season, followed by autumn, and spring. However, a low incidence of pneumonia was noted in the summer season [10]. As this study will compare the impact of the COVID-19 pandemic on AMS implementation before and during the COVID-19 pandemic. Randomised data will be

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collected from eight Interrupted time series (four before the COVID-19 pandemic and four during the pandemic) as shown below:

Four-time points before the COVID-19 pandemic
1. 1st week of March (Spring 2019)
2. 1st week of June (Summer 2019)
3. 1st week of September (Autumn 2019)
4. 1st week of December (Winter 2019)

Four-time points during the COVID-19 pandemic
1. 1st week of March (Spring 2020): The first wave of COVID.
2. 1st week of June (Summer 2020): First lockdown.
3. 1st week of September (Autumn 2020): The second wave of COVID.
4. 1st week of December (Winter 2020): Vaccination Rollout.

Data extraction and processing

The PhD student/PI who has access to electronic medical records will extract the data. The PI will protect the confidentiality of data; the patient identifiable data will be stored only in both hospital sites. Data collection and extraction are based on PHE toolkit (Start Smart - then Focus). The PhD student will use the previously mentioned patient list to enable the review of the relevant hospital databases and systems to extract the required information in the data extraction tool based on PHE toolkit for AMS (Appendix 15):

- Demographic information (age and antibiotic allergy).
- Medical diagnosis
- Appropriateness of the antibiotics prescribed upon patient admission (drug initiation, dose adjustment, route of administration, duration and de-escalation).
- Appropriate use of short-duration of antibiotics (<72 hours) versus long-duration of antibiotics (>72 hours).
- Antibiotic(s) used after 48 -72 hours of admission; route, dose, frequency, and duration.
- Appropriateness of oral and IV antibiotics prescribed, antibiotic discontinuation, and antibiotic review
- Other chronic conditions increase the infection prevalence and affect the antibiotic selection, such as hypertension, diabetes, cardiovascular disease, kidney and liver diseases).

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- Diagnostic methods, such as chest X-ray (CXR) and computed tomography (CT) scan.
- Laboratory inflammatory markers, such as procalcitonin (PCT), C-reactive protein (CRP), and Leukocytosis (WBC > 10,000/mm 3) that could indicate infection.
- Red flags for infection, such as fever as an oral temperature >37.8°C (>100.0°F).
- Bacterial culture results interpretation, including the timing of cultures, common culture sites, the potential for contamination, interpreting the Gram stain, use of rapid diagnostic tests, and conventional antibiotic susceptibility testing.

Each patient record will be given a study ID during the extraction process. A list that matches patients' records and their study ID will be maintained on the hospital systems. Patricia Edwards will be responsible for maintaining this list as part of her role. It will be saved as a password-protected document that is only accessible to Patricia Edwards and the PhD student on the hospital sites. The PhD student will only be allowed to export anonymised data to the university's double security data storage system for input into the data analysis software (SPSS). Only patient anonymised data will continue to be fed into the SPSS database until the end of data extraction. Following data extraction, the analysis will then be undertaken. The PhD student will be able to liaise with Patricia Edwards if she needs access to the linked patient record/study ID list. The PhD student will no longer have access to patient identifiable data after the end of Phase 1, which is 31st August 2023.

4.12. Quality checks for data extraction:

A standardised data extraction instrument comprising of an excel sheet based on PHE toolkit (Figure 1), includes all the previously mentioned measures that would help to identify how AMS was implemented before and during the COVID-19 pandemic (Appendix 15). The PhD student/PI and the Sanil Petal, AMS pharmacist lead on the study sites, will independently undertake data extraction from 10 medical records. Inter-rater reliability will be determined by examining the percentage of agreement in the data extracted independently by the two using Cohen's Kappa. Disagreements will be resolved via dialogue. Agreements of ≥80% will be considered as an indicator of the reliability of the process.

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The pilot test will be conducted as follow:

a) The hospital collaborator will select one medical record for every 64 records, for a total of 10 medical records.

b) The PhD student/PI will extract the data from these 10 records in the data extraction form.

c) The AMS pharmacist in the Trust will extract the data from the same 10 records in the data extraction form.

d) Inter-rater reliability will be determined by examining the percentage of agreement in the data extracted independently by the two using Cohen's Kappa.

e) Disagreements will be resolved via dialogue. Agreements of ≥80% will be considered as an indicator of the reliability of the process.

4.13. The Expected outcomes

Primary outcome:

- AMS implementation before and during the COVID-19 pandemic, such as Parenteral-to-Oral switch, antibiotic discontinuation, de-escalation, dose adjustment, and antibiotic review based on the local guidelines.

Secondary outcome:

- Measured the proportion of inappropriately prescribed antibiotics at admission, and after 48 to 72 hours.
- Laboratory and other diagnostic methods, such as chest X-ray (CXR), procalcitonin (PCT), C-reactive protein (CRP), Leukocytosis (WBC > 10,000/mm 3), and fever measured using the proportion of their use in patients infected with RTIs or pneumonia before and during the COVID-19 pandemic.

4.14. Sample size:

The sample size was determined based on the literature and the percentage of inappropriate antibiotic prescribing. According to PHE and the NICE guidelines, at least 20% of all antibiotics are inappropriately prescribed in the UK. The stats package Minitab was used for the sample size calculation. The PI obtained the figures on the total number of inpatient admissions in both hospitals mentioned above, to ensure the feasibility and accuracy of the calculated sample sizes. The Sample size was estimated according to the population size, the margin of error (ME) of 10%, and the confidence interval (CI) of 95 %. Then the sample

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size calculation was verified with the UH statistician. Data will be collected from 320 patient records prior to the COVID-19 pandemic and 320 patient records during the COVID-19 pandemic. Each time series will include the review of 80 medical records. The total sample size for this phase will be 640 patient records. The PhD student/PI will conduct a pilot test for two samples and discuss their results with the academic supervisors to ensure the validity of the data collection and extraction. So data will be collected from 80 records per time point.

4.15. Method of analysis

The process of antibiotic use in the hospital consists of 5-stages, which are (1) prescribing, 2) transcribing and documenting 3) dispensing, 4) administering, and 5) monitoring. The appropriateness of antibiotic prescribing is measured based on the hospital antimicrobial prescribing guidelines. The rest of the antibiotic use process or antimicrobial stewardship will be measured based on Public Health England Antimicrobial Stewardship Toolkit and NICE Antimicrobial Stewardship guidelines.

Quantitative data: Statistical analysis will be performed. Descriptive statistics will be employed to ascertain the distribution of data. Inferential statistics employing parametric (if data is normally distributed) and non-parametric (if data is not normally distributed) tests to explain relationships within data will be performed. Means and standard deviations will be calculated for continuous variables, while percentages and proportions will be computed for categorical variables. Descriptive statistics for interval-level and ratio-level variables will be applied to report the results. Inappropriate antibiotic prescribing percentages prior to the COVID-19 pandemic will be compared with antibiotic use during the pandemic. Additionally, the ratio of AMS implementation strategies will be measured, including AMS strategies, such as IV-to-Oral switch, antibiotic discontinuation, de-escalation, dose adjustment, and antibiotic review based on the local guidelines measured. Further, measure antibiotic utilisation and consumption before and during the COVID-19 pandemic. Laboratory and other diagnostic methods, such as chest X-ray (CXR), procalcitonin (PCT), C-reactive protein (CRP), Leukocytosis (WBC > 10,000/mm 3), and fever in patients infected with RTIs or pneumonia before and during the COVID-19 pandemic among infected patients treated with antibiotics, will be analysed using the ANOVA test for multiple variables.

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5. Prospective Online Survey

(Phase 2: Online Survey at Bedfordshire Hospitals NHS Trust)

Though the first phase of this research study will measure AMS implementation before and during the COVID-19 pandemic, there consequently remains a strong need to determine the antibiotic prescribing behaviours among HCPs. For this reason, this second phase is essential to explore the factors that affect AMS implementation before and during Covid.

5.1. Objectives:

In this phase, the survey will use closed and open-ended questions based on PHE antibiotic prescribing literature review and behavioural analysis [6]. The survey aims to explore the HCPs' perceptions, attitudes towards antibiotic prescribing and AMS implementation before and during the COVID-19 pandemic (Appendix 16).

5.2. Methodology:

This study will use a cross-sectional online survey based on PHE behaviour change and antibiotic prescribing in secondary care settings [6]. A mixed open and close-ended questionnaire survey will be conducted through a secured and UH trusted survey platform, Qualtrics XM. This survey aims to explore perceptions, attitudes, and AMS implementation among HCPs (doctors, nurses, and pharmacists) before and during the COVID-19 pandemic.

5.3. Inclusion criteria:

1. Health Care Professionals (doctors, nurses, and pharmacists).
2. Adults 25 years and older.
3. Registered with the relevant professional regulatory body; GMC, GPhC and NMC.
4. HCPs who were working before/during the COVID-19 pandemic at Luton and Dunstable hospital and/or Bedford hospital and still working in one or two of these hospitals' sites.

5.4. Exclusion criteria:

1. HCPs (doctors, nurses, and pharmacists) who are not currently working at the Bedfordshire Hospitals NHS Trust.

5.5. Study Participants:

After receiving approval from the Research Ethics Committee (REC) and the University of Hertfordshire (UH) ethics, the survey link will be disseminated by the local research office (R&D) to the study participants from HCPs working in the Bedfordshire Hospitals NHS Trust.

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Potential participants will be identified by the hospital collaborator (Patricia Edwards) according to the study inclusion criteria and sample size calculations. The research and development (R&D) office will send the initial original email electronically to the HCPs' secure emails first. This email aims to invite health professionals to participate in the survey. It will include the invitation letter that consists of the Participant Information Sheet (PIS) and the survey link (Appendix 17). After four weeks from the initial email, the R&D office will send the second email, as a reminder, inviting health professionals to participate by clicking on a survey link. Submitting responses after completing the online survey will be taken as implied consent to participate in the survey (Appendix 18). Participants can also decide whether or not to participate as long as the survey link remains live. Participants will be advised on the survey closing date in the reminder email after which an opportunity to participate will no longer be possible as the link will become inactive. Only the research team will have access to this data. All collected data will be anonymised once the submission is completed.

5.6. Access to participants' data during the study

The study will involve a survey of doctors, pharmacists and nurses engaged in antibiotic use and prescribing during the COVID-19 pandemic. The survey is based on PHE antibiotic prescribing behaviour literature review and behavioural analysis. All collected data will be anonymised with no participants' identifiers and all data will be kept confidential in password-protected files. It will not be possible to link any comment to any participant. Only the PI/PhD student will access the respondent's data, analyse, and interpret the results. This anonymised data will be stored on the University's secured network storage system, which requires a double security check.

5.7. Data Confidentiality:

Only the PI/PhD student will access the respondent's data, analyse, and interpret the results. The results interpretations will be discussed with the UH Academic Supervisors (Dr Zoe Aslanpour and Dr Nkiruka Umaru) listed in this protocol. The anonymised data will be stored on the University's secured network storage system, which requires a double security check.

5.9. Expected outcomes

Primary outcome:

- Antibiotic prescribing behaviour of HCPs will be explored using the range of knowledge, attitudes, and perceptions questions.

Secondary outcome:

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- Factors affecting AMS implementation will be explored using the range of AMS implementation before and during the COVID-19 pandemic.

5.10. Sample Size:

To ensure the feasibility and accuracy of the calculated sample size, the PhD student/PI obtained the figures on the total number of employed registered pharmacists as 206, the total number of employed registered nurses as 2,140 and the total number of employed registered doctors as 5,636. Additionally, the PI obtained the total number of health professionals (headcount) which is 7,982. The sample size n and margin of error E are given by:

$$x = Z(^{c}/_{100})^2 r(100-r)$$

$$n = \frac{N\,x}{(N-1)E^2 + x}$$

$$E = Sqrt\left[\frac{(N-n)x}{n(N-1)}\right]$$

Where N is the population size, r is the fraction of responses that you are interested in, and $Z(c/100)$ is the critical value for the confidence level c. The sample size for the survey will be 240, with a margin of error is 5%, a confidence interval is 95%, and a response rate of 20%. All sample size calculations for both phases were verified by the University of Hertfordshire (UH) statistician support.

5.11. Method of analysis

The PhD student/PI will collect, extract, and analyse the results. The academic supervisors will also discuss with the PI the emerging themes, categories, and concepts. An iterative data analysis process will be employed to identify and categorise ideas into key themes and their relationships. The quantitative data will be analysed using Qualitative Data Analysis Software (MAXQDA) to facilitate the categories process. The textual material will be analysed in terms of categories. Any disagreements will be resolved through discussion.

6. Timelines:

This study will start on 01st September 2022: After receiving approval from the NHS and UH ethics.

End of Study: This study will be continued until the required data sample is extracted before 31st August 2024. It will end when the last survey response is received from the last participant.

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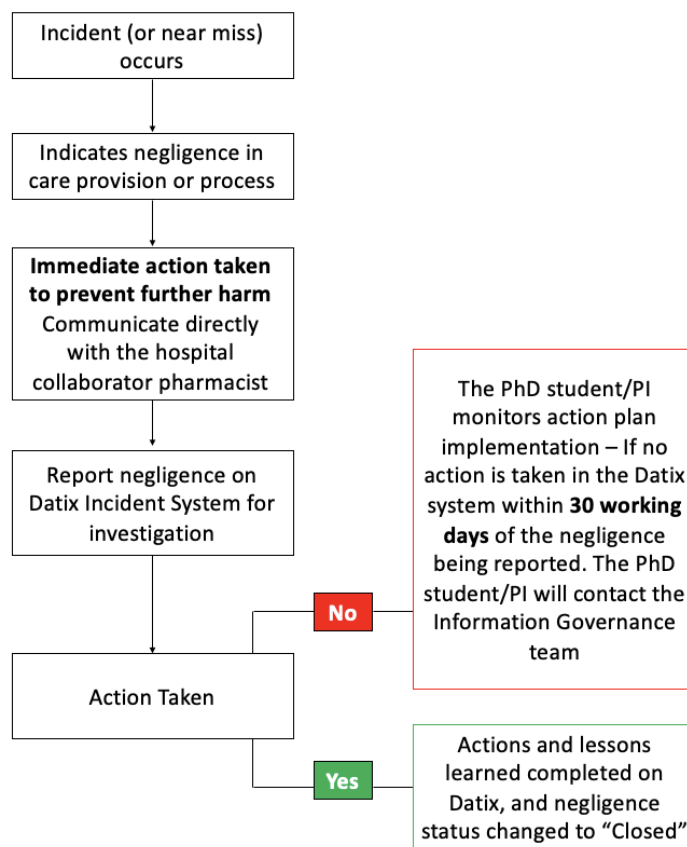## 7. Ethical Consideration in Both Phases:

7.1. Clinical Neglicance:

The research student undertook a training course provided by the National Institute of Clinical Research (NIHR) on Good Clinical Practice (GCP) (Appendix 10).

In line with the learning from the above course, potential harms found in patients' notes in the Trust will first be flagged with the team involved in patients' care if considered reasonably appropriate to do so. This is because any findings of potential harm by the research student, if not handled with diplomacy, may impact negatively on good relationships, which is very necessary for the success of the research at the Trust. Negligence in care provision or process which is also considered as patients' safety related matter of concern due to care provision. A detailed procedure is established, with the proposed guidance for dealing with any clinical negligence or incident. It includes the description of each potential deficiency. Hence the first-place concerns will be raised with the hospital collaborators within the Trust.

The following steps will be considered:

1. If the PhD student/PI discovers any negligence, she will communicate with the hospital collaborators to discuss the negligence issue.
2. Immediate action taken to prevent further harm. The PhD student/PI will communicate directly with the hospital collaborator pharmacist.
3. Report the negligence on Datix System for investigation.
4. The PhD student/PI monitors action plan implementation – If no action is taken in the Datix system within **30 working days** of the negligence being reported, the PhD student/PI will contact the Information Governance team.
5. Actions taken and lessons learned completed on Datix, and clinical negligence status changed to "Closed".

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Figure 5. Negligence Reporting Process Overview Flow Chart

7.2. Risk of Bias:

Bias to data extraction due to the PhD student's professional role as a pharmacist will be minimised by maintaining the selection of samples and quality checks by the hospital collaborators (Patricia Edwards and Sanil Petal) of data extraction.

7.3. Risk assessment

7.3.1. Risk of exposure to patients' sensitive data

CAG was provisionally supported, with satisfactory responses to the requests for further information and compliance with the standard and specific conditions of support. CAG is also supported for the duration of the retention of the key between confidential patient information and the pseudonymous study ID. Access to patients' identifiable data will be only restricted to the PI and external collaborators at Bedfordshire Hospitals NHS Trust (L&D and Bedford hospitals). Data will be saved as a password-protected document accessible to Patricia Edwards and the PhD student on the hospital sites. The PI will anonymise the extracted data

and store it on the University's secured network storage system, which requires a double security check for analysis. Identifiable data will be anonymised before leaving the research hospital site.

7.3.2. Risk of identification of evidence of clinical negligence

Phase 1: In the Retrospective study, the PI will flag any clinical negligence with the hospital collaborators who are part of the direct care team and who will take responsibility for dealing with this issue. They will follow up with the team involved in patients' care in both hospitals. These will escalate information if considered reasonably appropriate to do so.

Phase 2: In the survey study, the PI will be unable to address any survey responses directly because responders' details will be anonymised. However, if there is any notable evidence from the submitted responses, the hospital collaborators will be informed.

7.3.3. Research Ethics Committees

Ethics approval will be sought from the NHS Research and Ethics Committee (REC), the University of Hertfordshire Ethical Committee, and reviewed with Bedfordshire Hospitals NHS Trust Research and Development (R&D) department before starting the study. The PhD student/PI has signed an honorary contract until the end of this research project. The PI received an NHS secure email and a user account to access the electronic system in both hospitals. The PI will protect the confidentiality of data; all identifiable patient data will be stored only in the hospital system. The PhD student will be able to liaise with Patricia Edwards if they need access to the linked patient record/study ID list. The PhD student will no longer have access to patient identifiable data after the end of Phase 1, which is 31st August 2023.

7.3.4 Validity

In Phase 1, the PhD student/PI will extract data from the validated data extraction tool, generated from the literature.
In phase 2, the survey will be validated by piloting the survey among 5% of the sample size (pharmacists, nurses, and doctors), using SPSS program.

7.4. Reliability

In phase 1: Reliability will be determined by the percentage of agreement between the PI/PhD

student and the hospital collaborators hospital collaborators, AMS pharmacist. Abdul

Mohamed will extract data from 10 patients' medical records one week after the first extraction by the PhD student/PI. Agreement in the two extracted data will be ascertained using Cohens Kappa to check the intra-rater reliability. Agreements of ≥80% will be considered an indicator of the instrument's reliability and process. Any disagreements will be clarified via dialogue.

In phase 2: The results from the pilot test will be imported into SPSS software to check for reliability and validity.

8. Data Protection and Confidentiality of Study Data

In both studies, measures will be taken to maintain participant anonymity. The PI will protect the confidentiality of data; the patient's identifiable data will be stored in the hospital system. The anonymised data will be held on the University's secured network storage system, which requires a double security check. CAG supervision was obtained to access the patient's identifiable data in the retrospective study without consent. Then the hospital collaborator will anonymise the data and transfer it electronically to the online double secure University of Herefordshire system for analysis and results. No mobile devices are used for transferring data. The anonymised data will be kept on the University's secured network storage system, which requires a double security check.

9. Regulatory Considerations

All the participants will be treated by the ethical guidelines outlined by the National Research Ethics Service (NRES) and obtain the NHS ethics approval and the Health, Science, Engineering and Technology ECDA (Ethics Committee with Delegated Authority) at the University of Hertfordshire.

9.1. Discontinuation/Withdrawal of participants from the study

Participants have the right to withdraw from the study or not participate without giving a reason before the survey has been completed. Though, once they are completed and submitted, participants will not be able to withdraw, as their data will be anonymised entirely at this stage. Furthermore, the response data of the withdrawn participants will be included in the analysis and dissemination.

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9.2. Approval

The study protocol and all supporting materials, including the participant information sheet, will be submitted to seek Research Ethics Committee approval and the UH Ethics Committee. The Investigator will submit and, where necessary, obtain permission from the above parties for all substantial amendments to the original approved documents. The CI will ensure all the appropriate approvals from participating organisations will be undertaken before the study has been started.

10. Peer Review

The Research Information and Governance team has reviewed the research protocol at the University of Hertfordshire. In addition to the external review to maintain the scientific quality of this research study. The research protocol was reviewed and critiqued by an independent external academic consultant pharmacist from Hertfordshire University (Dr Andrzej Kostrzewski) to assess the quality of this research study. The research team consists of qualified academics considered field experts in pharmacy practice, AMS, and research.

11. Finance

This research is being conducted as part of a doctoral degree (Rasha Abdelsalam Elshenawy). There is no funding for this research project. However, there is no conflict of interest between the PhD student/PI and the study outcomes.

12. Publication Policy

The study results will be submitted for publication in a peer-reviewed journal. The PhD student/PI will prepare the manuscript in collaboration with the research team members, and mutual agreement will determine authorship. Additionally, the publication bias was avoided by publishing this research study in these public databases:

- The study's systematic review was published on the PROSPERO website [9].
- The research project will be published in ISRCTN under the WHO standards for study registration [11].
- This research project will be registered and published in the University of Hertfordshire public database.

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