Study Title: Critical care Atrial Fibrillation Evaluation (CAFE): a scoping review and database analysis.

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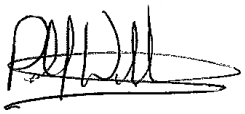

Contents

1. SYNOPSIS

Study Title	Critical care atrial fibrillation evaluation: a scoping review and database analysis.(CAFÉ)
Internal ref. no. / short title	National Institute for Health Research Health Technology Assessment programme: ref 17/71/04
Study Design	Scoping review. Retrospective database analyses.
Study Participants	Adult patients treated in general medical, surgical or mixed intensive care units in the UK and USA with data recorded in the PICRAM, MIMIC-III, NIHR HIC and RISK-II databases.
Planned Sample Size	Approximately 993,000 patients across the databases.
Planned Study Period	01/02/2019 to 31/07/2020 (18 months)
Objectives	To determine in adults who develop new onset atrial fibrillation (NOAF) during treatment on an intensive care unit: ● how do recorded treatments for NOAF compare in short-term effectiveness? ● what are the long-term outcomes of NOAF? ● what are the future research priorities for treatments for NOAF?

2. ABBREVIATIONS

AF	Atrial Fibrillation
ATE	Average Treatment Effect
ATT	Average Treatment effect in the Treated
bpm	Beats per minute (heart rate)
CI	Chief Investigator
CMP	(ICNARC) Case Mix Programme
DARE	Database of Abstracts of Reviews of Effects
HAVEN	Hospital Alerting Via Electronic Noticeboard
HES	Hospital Episode Statistics
HIC	Health Informatics Collaborative
HICF	Health Innovation Challenge Fund
HIPAA	Health Insurance Portability and Accountability Act (USA)
HRA	Health Research Authority
HS&DR	Health Services and Delivery Research Programme
HTA	Health Technology Assessment
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICNARC	Intensive Care National Audit and Research Centre
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive Care Unit
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
MeSH	Medical Subject Headings
MIMIC-III	Multiparameter intelligent monitoring in intensive care III
MIT	Massachusetts Institute of Technology
NHS	National Health Service
NIHR	National Institute of Health Research
NOAF	New Onset Atrial Fibrillation
ONS	Office of National Statistics
PICRAM	Post-Intensive Care Risk Adjusted Monitoring
RISK-II	Risk modelling II study
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions

3. BACKGROUND AND RATIONALE

Research questions

In adults who develop new onset atrial fibrillation (NOAF) during treatment on an intensive care unit (ICU):

1. How do current treatments compare in short term effectiveness?
2. What are the long-term outcomes?
3. What are the future research priorities?

Background

Of 170,000 adults treated on UK ICUs annually, 8,000-18,500 develop NOAF, with clustering in subgroups such as patients with sepsis. NOAF can cause cardiovascular instability and thromboembolic complications. It is independently associated with increased hospital stay and mortality. There is little evidence to guide NOAF treatment in ICUs meaning practice varies. Current atrial fibrillation (AF) treatment guidelines are based on data from patients outside ICU. NOAF in patients on ICU differs in causes of rhythm disturbance, risks and effectiveness of treatments. It is unclear whether NOAF developed on an ICU results in future episodes of AF and stroke, for example in other hospital admissions. Our systematic review found little evidence on avoidable or reversible NOAF antecedents in patients on ICUs (PROSPERO: CRD42017074221).

This study arises from an National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme commissioning call asking for a scoping review and analysis of routinely collected data. The protocol covers: (1) a comprehensive scoping review to investigate the current evidence base; (2) the use of four large anonymised ICU research databases containing routinely collected healthcare data to determine the effectiveness of current treatments for NOAF and the long-term effects of both NOAF itself and treatments for NOAF. The Post-Intensive Care Risk Adjusted Monitoring (PICRAM), Multiparameter intelligent monitoring in intensive care III (MIMIC-III), and NIHR Health Informatics Collaborative (HIC) databases will be used to examine the effectiveness of current treatments. The RISK-II database will be used to examine longer term effects, with a specific goal of determining the place for anticoagulation.

4. AIMS and OBJECTIVES

Scoping review

1. To evaluate the evidence for the effectiveness and safety of:
    a. pharmacological and non-pharmacological (electrical, electrolyte, fluid) NOAF treatments; and
    b. acute anticoagulation.
2. To provide guidance for the database analysis on:
    a. NOAF definitions used in patients on an ICU;
    b. patient subgroups who develop NOAF on an ICU; and
    c. inclusion/exclusion of specific treatments and potential confounders.
3. To determine barriers to future research.

Database analysis

1. To compare the use and effectiveness of pharmacological and non-pharmacological NOAF treatments with respect to heart rate and rhythm control.
2. To assess anticoagulation use, effect on thromboembolic complications and safety.
3. To determine the incidence of short and long-term complications of NOAF and identified treatments.

5. STUDY DESIGN

The study involves a scoping review of existing literature and retrospective analyses of four anonymised databases containing details of patients treated on ICUs in the UK and USA.

These two distinct work packages are described separately.

Work package 1: Scoping review

The scoping review will follow a standard methodological framework (1–3). This will be modified, if required, to ensure we are able to comply with the recently-published PRISMA-ScR reporting guidelines (4).

Searches

We performed an initial MEDLINE search using MeSH and free-text terms to estimate the size of the evidence base. This retrieved 1,292 papers. From a sample of 100 of these, 15 were possibly relevant. After searching other databases we expect to find ~1,500 references. From this, we estimate 200-250 full papers will need assessing.

We will search the bibliographic databases: MEDLINE, EMBASE, CINAHL, Conference Proceedings Citation Index: Science, OpenSIGLE, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effects (DARE) to 2015 and the National Guideline Clearinghouse. We will not use Google Scholar as a preliminary search revealed it was not possible to generate an adequately specific search string. We will search for studies in progress, or completed but unreported, in the clinical trials databases International Standard Registered Clinical/soCial sTudy Number (ISRCTN), ClinicalTrials.gov, the EU Clinical Trials register, additional WHO ICTRP trial databases, and the UK Clinical Trials Gateway. For relevant clinical trials in progress or unreported we will request protocols from the register or Chief Investigator.

We will snowball to identify any further relevant studies. We will track links to other research using Web of Science to determine the source of citations of relevant publications and AMiner to determine other authors associated with authors of identified work. Searches will be performed by an information specialist, without date or language restrictions.

Review eligibility criteria

Given the exploratory nature of scoping reviews, the eligibility criteria may be modified and refined during title and abstract and full-paper screening.

Population

Eligible studies and research protocols will be based in adult (age ≥16 years) general medical, surgical or mixed ICUs. We will exclude studies of cohorts defined by a single disease or narrow disease group not normally admitted to a general ICU (e.g. myocardial infarction) and studies based on service-specific ICUs (e.g. cardiothoracic or neurosurgical). As we expect the evidence base to be limited, we will include studies of conditions commonly associated with admission to an ICU (e.g. sepsis). In line with our experience in our antecedents of AF review, we will report

research into supraventricular arrhythmias if AF constituted at least 70% of arrhythmias. Where these data are unavailable, we will include studies that group AF and atrial flutter if no other arrhythmia types were included (as AF forms the large majority of these rhythms).

Interventions

We will include studies and protocols investigating pharmacological, electrical and other non-pharmacological (including electrolyte and fluid) treatment strategies for treatment or prevention of NOAF and the use of short or long-term anticoagulation.

Comparators

We will extract comparisons with alternative treatment strategies, including no treatment where appropriate.

Outcomes

Eligible outcomes will be rhythm and rate control, length of ICU and hospital stay, mortality (ICU, hospital, 30-day, long term), arterial thromboembolism and adverse treatment effects.

Included study designs

We will include quantitative studies with the following designs: randomised and non-randomised trials, cohort studies, case series with five or more patients reported and trial protocols. We will also include practitioner surveys and opinion pieces (for research recommendations and interventions not otherwise identified).

Data extraction

Data extraction forms will be piloted and developed iteratively. Extracted data will include study characteristics and methods, patient characteristics, intervention and comparator details, outcome measures and results of intervention effectiveness and safety. We will extract information on any recommendations for future research that may be relevant to the review objectives (including any perceived barriers).

Quality and Relevance

Many scoping reviews do not include an assessment of study quality. However, when informed recommendations for research are an important review outcome, some form of assessment (formal or informal) of at least the key studies identified will be necessary. We will therefore make decisions on the methods (and extent) of study quality assessments as we near completion of the full-paper screening phase. As most studies identified in our initial search were of non-randomised design, we are likely to evaluate how tools such as ROBINS-I (5), and the Newcastle Ottawa scale (6) inform our evidence assessment.

Synthesis of findings

We will present extracted data in structured tables and summarise narratively. We will describe the extent, range, quality and nature of the identified research. We anticipate we will divide studies into treatment classes (drug, preventative, electrical, other) and by subgroups of

patients defined by their underlying condition. We will summarise the interest and activity in each of these classes using the number and currency of studies and on-going research. If sufficient studies exist we will summarise the research history and pathway in a graphic, and researcher associations in an ego diagram.

Systematic review of antecedents of NOAF

We will update our systematic review of antecedents of NOAF in the general adult ICU population, incorporating the findings in the final report and in the information for the expert panel (see below). The expert panel will use these findings to facilitate identification of interventions and potential confounders for the database analyses.

Expert Panel

We will convene an expert panel to review scoping review findings to ensure we have identified all appropriate interventions and potential confounders for work package 2 (database analysis). We will use the same expert panel we used in the HICF-funded PICRAM and HAVEN studies (with additional electrophysiological expertise) as the members are all critical care specialists and already familiar with the process.

Work package 2: Database analysis

Data resources underpinning this proposal

We have either developed, or collaborated in the development of, three large anonymised research ICU databases (PICRAM (7), MIMIC-III (8), NIHR HIC critical care (9)) which will be used in this proposal. We have also developed a fourth database (RISK-II), allowing analysis of outcomes for patients treated on an ICU after hospital discharge. Each of these anonymised databases already has the required approvals for secondary research without the need for further ethics applications.

Databases:

1. PICRAM (original funders reference HICF 0510 006): our study generated a detailed research database of all (>18,000) patients treated on both Oxford general ICUs and the Reading (Royal Berkshire Hospital) ICU, from 2008 onward. In addition to all routine ICU clinical data (~650 data items/patient/day) on all admissions it also contains the national ICU audit data (ICNARC Case Mix Programme – CMP data) for each patient.
2. MIMIC-III: contains over 53,000 patient episodes from Beth Israel Deaconess Medical Center ICUs, Boston, USA between June 2001 and October 2012. The database is managed by the Massachusetts Institute of Technology (MIT) Laboratory for Computational Physiology. MIMIC-III includes the patients from the preceding MIMIC-II database. It also contains long-term survival from social service record linkage. As part of our on-going collaboration we have merged MIMIC-III and PICRAM, using the Observational Medical Outcomes Partnership Common Data Model as the common schema. This allows the same analyses to be performed quickly and economically on both databases.
3. NIHR HIC critical care database: we collaborate on this database. It contains limited clinical data (394 items in total) extracted from the computerised information systems for each patient admitted to 10 ICUs in 5 hospitals hosting NIHR Biomedical Research Centres. It currently contains details of 40,000 patients commencing February 2014, but patient numbers continue to expand.
4. RISK-II (original funders reference HS&DR 14/19/06): we developed this 900,000 patient database by matching the patients in the ICNARC CMP database of all ICU admissions in England with their corresponding Hospital Episode Statistics (HES) inpatient data and Office for National Statistics (ONS) mortality data. This dataset covers April 2009 to March 2016.

PICRAM, MIMIC-III and RISK-II are cleaned, anonymised to the US Health Insurance Portability and Accountability Act (HIPAA) standards and research-ready. We have copies of each database in our institutions and expertise in analysing them (7,10). PICRAM and MIMIC-III contain the complete electronic patient record from a patient's ICU admission, including patient demographic data, vital signs data (including heart rate, rhythm and blood pressure recorded hourly), blood test results (including electrolytes that may affect the onset and treatment of NOAF) and pharmacological and non-pharmacological therapies. MIMIC-III has all the data items contained in PICRAM, but in addition includes patients treated with antiarrhythmic drugs not commonly used in the UK (procainamide, intravenous diltiazem). Both contain a large range of potential cofounders. RISK-II contains data on timing and reason for admission, past medical

history, physiology in the first 24 hours of ICU admission, infections and outcome from the ICNARC (CMP) Database. Within RISK-II these data are linked to patients' HES data, for episodes preceding, including and subsequent to the ICU admission. HES data includes details of all NHS admitted patient care, outpatient appointments and Emergency Department attendances in England. Each HES record contains information about diagnoses and operations, age, gender and ethnicity, administrative information and long-term outcomes. A preliminary analysis of a year's data (~1.5M HES records for ~300k patients) revealed a 12% prevalence of atrial fibrillation.

We also have an anonymised copy of the NIHR HIC critical care database in Oxford. The NIHR HIC critical care database only contains data on two pharmaceutical interventions for NOAF, esmolol and metoprolol, and a limited number of potential confounders. This is the least research-mature of the four databases. Our initial assessment suggests we can only use it to explore generalisability of our findings.

Methods - PICRAM/MIMIC-III/NIHR HIC critical care database analysis

Retrospective observational studies of short-term outcomes of NOAF.

Definition of patient group developing NOAF

We will define NOAF as atrial fibrillation or flutter developing during a patient's ICU stay after they were admitted to an ICU with an initial heart rhythm recorded as sinus rhythm. We will exclude patients with chronic atrial arrhythmias or atrial arrhythmias at ICU admission. We will review this definition after the scoping review and refine it if required. We will undertake an exploratory analysis of NOAF labelling/timing/duration within the PICRAM/MIMIC-III databases to ensure the definitions capture the correct patients before proceeding with the full analysis. Unless the scoping review and exploratory data analysis suggests another approach, we will only analyse the first occurrence of atrial fibrillation for each patient admission to ICU.

Definition of comparator group without atrial arrhythmia

The "without atrial arrhythmia" group will be defined as patients admitted to an ICU with no documented preceding history of atrial fibrillation and without an episode of atrial arrhythmia during the ICU admission. The analysis will consider the implications of opportunity for observing preceding history of AF (e.g. through use of 'wash-in' periods) and the handling of multiple admissions within patients.

Determining timing of NOAF and subsequent cardioversion/control

For each patient meeting the definition of NOAF the start of NOAF will be the time of the first record of atrial fibrillation/flutter. The time of cardioversion (if relevant) will be the time of the first subsequent record of sinus rhythm. Subsequent episodes of AF will be similarly timed. The time to rate control will be the first subsequent heart rate recording <110bpm. Our exploratory PICRAM/MIMIC-III analysis will include adjusting the definition of rate or rhythm to manage transient changes.

Determining use, timing and dose of interventions used for NOAF

Likely candidate treatments include pharmacological agents (amiodarone, digoxin, rate-limiting calcium antagonists, beta-blockers), magnesium and potassium supplementation, fluid boluses and electrical cardioversion. A comprehensive list will be developed using the scoping review results, team expertise and the expert panel.

We will record the timing of all pharmacological, electrical and non-pharmacological (including electrolyte and fluid) treatment strategies (alone and in combination) and anticoagulation initiated or dose-adjusted after the first episode of NOAF. We will also record dose and body weight (to allow dose normalisation).

Some treatments (such as magnesium and potassium supplementation, or fluid boluses) occur both as part of maintenance treatment and are used as acute therapies for NOAF. Once the list of treatments is available we will undertake an exploratory data analysis to determine the use of these treatments in patients with NOAF and those without.

Comparators

Interventions will be compared with alternative treatment strategies, including no treatment where appropriate.

Outcomes:

Descriptive data on episodes of NOAF (subject to revision after the scoping review).

1. The proportion of patients with NOAF, with descriptors compared with those not developing NOAF.
2. The frequency distribution of the time to onset of NOAF episodes within an ICU stay.
3. The proportion of NOAF episodes with subsequent cardioversion.
4. The ventricular heart rate first recorded after NOAF, and the change from pre-NOAF values.
5. The blood pressure effect during NOAF and any associated vasoactive therapy use.
6. The change in heart rate and blood pressure after NOAF but prior to treatment (to establish a natural history), subject to data availability.
7. Heart rate variability in the period preceding NOAF.

Primary analyses:

Analysis of the efficacy of interventions (subject to revision after the scoping review).

1. Time from initiation of therapeutic strategy to first cardioversion.
2. Time to heart rate control, expressed as time to first recorded rate <110 bpm (11–13) and as rate reduction per unit time.
3. Rate of change in mean arterial blood pressure after intervention expressed both as time to pre-fibrillation blood pressure and change per unit time.
4. Use of new anticoagulation (during ICU and at ICU discharge) with each intervention.

Secondary analyses: (subject to review after the scoping review).

1. Use of second and subsequent AF intervention.
2. Recurrence of AF in the same ICU admission after cardioversion.
3. Reversion to rates >110bpm after rate control.
4. ICU and hospital length of stay.
5. ICU, hospital, 30-day and one-year mortality.
6. Transfusion requirements (as a surrogate for extra cranial bleeding events).
7. Thromboembolic events (stroke, peripheral emboli).

Statistical analysis

Rather than simply reporting the effects of an intervention in patients who received it, we will use causal inference methodology, such as the GenMatch algorithm (14,15), to match each patient receiving an intervention with a reference patient not receiving the intervention. For first-line treatments, reference patients will be those with NOAF treated with amiodarone (if this remains the most common first-line treatment in preliminary searches of the PICRAM and MIMIC-II databases). For adjuvant treatments, reference patients will be patients with NOAF not receiving the adjuvant treatment but matched on other characteristics, including first-line treatment. The ICNARC risk of death prediction model (NIHR 14/19/06) (16) will be a key matching confounder, adapted to MIMIC-III as required. We will then use appropriate statistical methods for analysis of matched cohort data to estimate marginal odds ratios (for binary outcomes, e.g. mortality) or mean differences (for continuous outcomes, e.g. rate reduction).

Methods - RISK-II database analysis

Retrospective observational study of long-term outcomes of NOAF.

Definitions

The RISK-II database does not contain the granular within-ICU data present in the MIMIC-III and PICRAM databases so a different approach to identifying NOAF is required. We will obtain an approximation of patients suffering NOAF during an ICU admission by selecting patients where an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis of atrial fibrillation (codes I48.0-I48.2, I48.9- I48.91) is present in the HES episode covering the ICU admission, but is not included in the reasons for admission to critical care (from the ICNARC CMP data) and not present in any preceding HES episodes. We will adjust our approach by crosschecking with the incidences of NOAF and chronic atrial fibrillation/flutter identified in MIMIC-III/PICRAM. We will review ICD-10 code usage with field experts in Oxford.

We will determine the incidence of hospital readmission with atrial fibrillation after NOAF by determining the presence of ICD codes I48.0-I48.2 and I48.9-I48.91 in the HES data for admissions after the index admission with ICU care.

We will determine the incidence of hospital readmission with cerebral thromboembolic events by generating an appropriate list of sub-codes for the ICD-10 code I63 (cerebral infarction) and identifying these codes in the HES data for admissions after the index admission with ICU care.

We will determine the incidence of hospital readmission with heart failure by generating an appropriate list of sub-codes for the ICD-10 code I50 (heart failure) and identifying these codes in the HES data for admissions after the index admission with ICU care.

We will determine long term survival for patients with NOAF who were discharged alive from hospital after the index admission with ICU care using the ONS data within the RISK-II data (patients who die during the index admission with ICU care will be identified and analysed using the PICRAM/MIMIC-II databases).

The comparators for all analyses will be patients with no recorded NOAF during a hospital admission including an ICU admission or record of atrial arrhythmia in the CMP data at ICU admission or in previous hospital admissions recorded in HES. As with PICRAM/MIMIC-III, analysis will account for opportunity to observe preceding history of AF and the handling of multiple admissions within patients.

Outcomes

Primary analyses: (subject to review after the scoping review).

1. Incidence of subsequent hospital admission with thromboembolic primary diagnosis.
2. The proportion of patients suffering NOAF, and the demographics compared with those not developing NOAF.

Secondary analyses: (subject to review after the scoping review).

1. Incidence of subsequent hospital admission with atrial fibrillation.
2. Incidence of subsequent hospital admission with heart failure.
3. Time to death.

Statistical analysis

We will use Cox proportional hazards regression to determine the association between NOAF occurring during a hospital admission including ICU treatment and subsequent hospital admission for thromboembolic event, AF or heart failure. We will test if the proportional hazards assumption holds by testing Schoenfeld Residuals, and perform our analysis using logistic regression if the assumption is violated by the data. We will adjust for factors including age, sex, prior heart failure (I50), diabetes mellitus (E10-14), hypertension (I10-15) and prior thromboembolism (I63-4) using appropriate ICD-10 codes (17). We will also undertake an analysis of time to death using similar techniques.

6. ETHICAL AND REGULATORY CONSIDERATIONS

The databases are all anonymised and contain no patient-identifiable data. The UK databases were generated under the following HRA approvals which all allow secondary analysis of the anonymised data:

PICRAM: 11/SC/0440
RISK-II: 15-WA-0256
HIC: 14/LO/103

The MIMIC-III database was generated from data on patients treated in hospitals in Boston USA. Collection of the data was covered by the Beth Israel Deaconess Medical Centre Institutional Review Board (IRB) protocol 2001P001699. Use of the anonymised version of the database does not require specific approval.

7. FUNDING

This study is funded by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme (project reference: 17/71/04). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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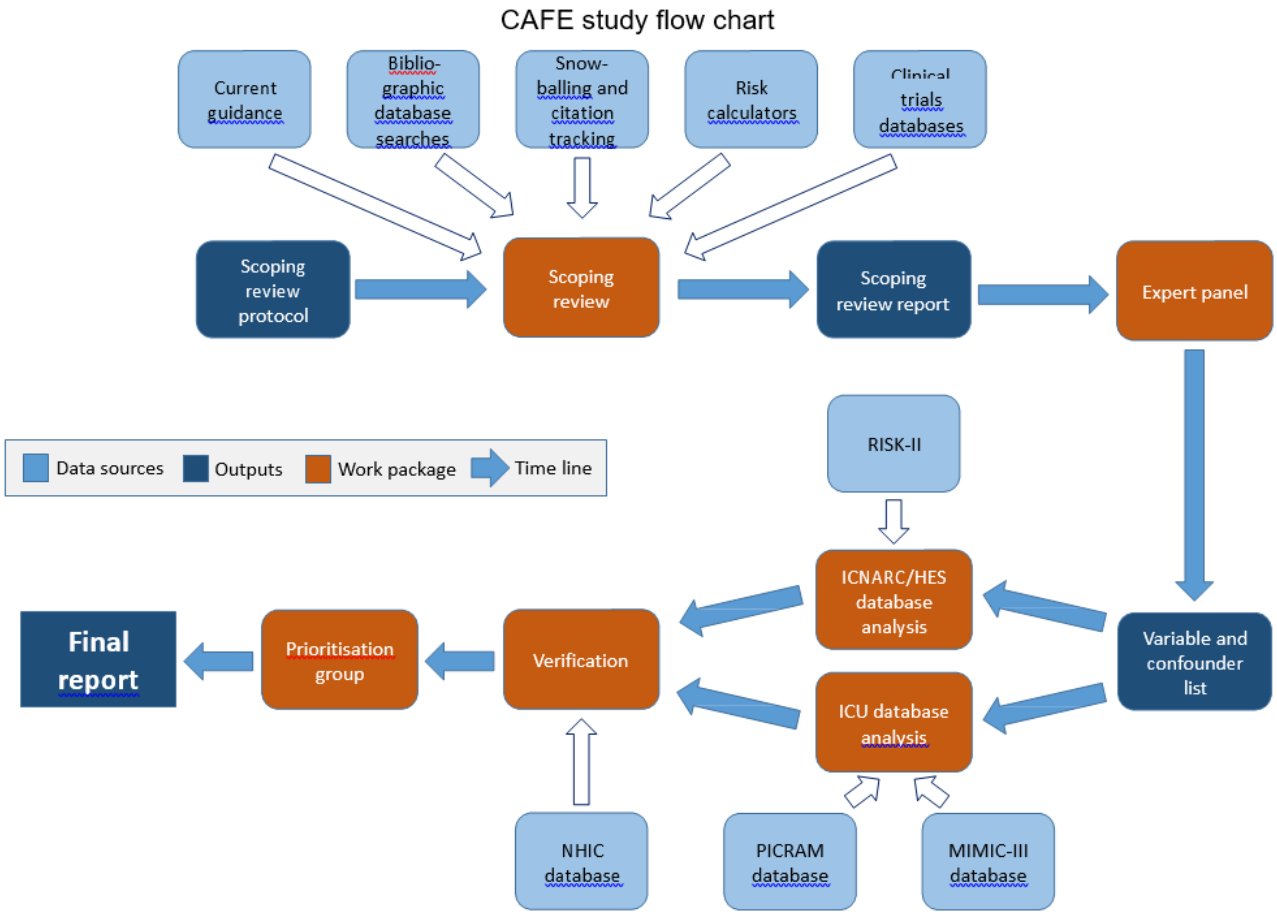
APPENDIX A: STUDY FLOW CHART



APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
Start version	1.0	1st February 2019	JD Young	N/A
1	1a	20th February 2019	JL Darbyshire	Updated NIHR disclaimer & corrected project dates