North Bristol NHS Trust

BRISTOL TRIALS CENTRE

ASPECT

Aspirin after hospitalisation with Pneumonia to prevent cardiovascular Events randomised Controlled Trial

Aspirin after hospitalisation with Pneumonia to prevent cardiovascular Events randomised Controlled Trial (ASPECT)

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Glossary / abbreviations

AE	Adverse event
AR	Adverse reaction
ASPECT	Aspirin after hospitalisation with Pneumonia to prevent cardiovascular Events randomised Controlled Trial
ASPREE	Effect of Aspirin on All-Cause Mortality in the Healthy Elderly
BNF	British National Formulary
BTC	Bristol Trials Centre
CABG	Coronary artery bypass graft
CAS	Chemical Abstracts Service
CI	Chief Investigator
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CTA	Clinical trial authorisation
CTIMP	Clinical trial of an investigational medicinal product
CURB-65	A prediction rule for predicting mortality in community-acquired pneumonia
CV	Curriculum vitae
DMSC	Data monitoring and safety committee
DOAC	Direct oral anticoagulant (also called NOAC)
DSUR	Development Safety Update Report
DVT	Deep vein thrombosis
ECG	Electrocardiogram
HES	Hospital Episode Statistics
HES-APC	Hospital Episode Statistics Admitted Patient Care
HR	Hazardous Ratio
HRA	Health Research Authority
ICD-10	International classification of diseases 10
GCP	Good clinical practice
GI	Gastrointestinal
GP	General practitioner
ITT	Intention to treat
MACE	Major Adverse Cardiovascular Event
MHRA	Medicines and healthcare products regulatory agency
MI	Myocardial Infarction
MRC	Medical Research Council
NBT	North Bristol NHS Trust
NHS	National Health Service
NICE	National Institute for Healthcare and Excellence
NIHR	National Institute for Health Research
NOAC	Novel oral anticoagulant (also called DOAC)
ONS	Office for National Statistics
PCA	Patient controlled analgesia
PCI	Percutaneous coronary intervention
PCR	Polymerase Chain Reaction
PE	Pulmonary embolism
PERR	Prior Events Rate Ratio
PI	Principal Investigator
PPI	Patient and Public Involvement
PIL	Patient information leaflet

RCT	Randomised controlled trial
REC	Research ethics committee
RECOVERY	Randomised Evaluation of COVID-19 Therapy
RSI	Reference safety information
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SOP	Standard operating procedure
SSA	Site Specific Assessment
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TIA	Transient ischaemic attack
TMG	Trial management group
TSC	Trial steering committee
UK	United Kingdom

1. Plain English Trial summary

Pneumonia is an inflammation of one or both lungs, usually caused by infection. Pneumonia is very common with 270,000 patients admitted as an emergency to hospital in England every year. Most people recover completely but some have complications. Two of the most significant complications are heart attack or stroke.

Around 1 in 13 patients (8%) who are admitted to hospital with pneumonia have a heart attack or stroke within three months. These events are thought to occur because the infection attacks blood vessels and causes clots, reducing the blood reaching the heart or brain. Patients who have a heart attack or stroke take longer to recover from pneumonia and are more likely to die. Aspirin has been used for decades to reduce the chance of having a heart attack or stroke in other patient groups. It works quickly with limited side effects in the vast majority of patients. Although aspirin has limited side effects in the vast majority of people, it carries a very small risk of significant bleeding, therefore it is not clear whether or not giving aspirin to everyone with pneumonia will be beneficial overall.

The ASPECT trial aims to test whether aspirin reduces the risk of a heart attack or stroke in patients who are admitted to hospital with pneumonia. This study needs to recruit 6,372 patients to answer this question.

Adults aged 50 years and over admitted to hospital with pneumonia will be invited to take part. Those who agree will be split into two groups. Every person joining the study will have an equal chance of being in either group, so both groups will be made up of the same kinds of people. One group will be asked to take one tablet of low dose aspirin each day for 3 months, after taking a higher dose (2 tablets daily) for 7 days. The other group will be asked to refrain from taking aspirin for 3 months. In all other respects, both groups will have standard pneumonia treatment.

Participants will be followed up at 3 months after randomisation without having to do anything, as data will be collected from routinely available sources. We will assess their recovery, specifically whether they have a heart attack, stroke, deep vein thrombosis (DVT)/pulmonary embolism(PE), transient ischaemic attack (TIA)/unstable angina or any serious side effects of aspirin. We will do this by reviewing the 'usual care' health records of participants held by National Health Service (NHS) hospitals. Following up participants like this has been shown to be robust, reduces the burden on participants and makes the research much less expensive.

2. Background

2.1 Pneumonia and risk of Major Adverse Cardiovascular Events (MACE)

Pneumonia is the commonest cause of emergency hospital admission worldwide, comprising 270,000 admissions to NHS hospitals in England every year (data from custom analysis of anonymised Hospital Episode Statistics (HES) data for the calendar year 2018). The burden on patients and the healthcare system is extensive but pneumonia remains underrepresented in terms of research funding nationally [1]. In recent years there has been increasing realisation that pneumonia causes a short to medium term increased risk of major adverse cardiovascular

events (MACE) such as myocardial infarction (MI) or stroke [2, 3]. Individuals who experience a MACE following pneumonia also have an increased risk of dying subsequently [4].

The mechanism behind this risk is multifactorial. Firstly, the inflammatory response related to the pneumonia, which can persist for several weeks [5], activates inflammatory cells in atherosclerotic plaques making them less stable [6, 7]. Secondly, both animal models and human autopsy studies have demonstrated that *Streptococcus pneumoniae* (the most common cause of pneumonia) can cause cardiac microlesions and atherosclerotic plaque rupture due to direct translocation into the myocardium [8]. Similar studies have also found evidence of cardiac remodelling and scarring after pneumococcal infection [9]. Thirdly, all acute infection states can lead to platelet activation and prothrombotic state within the host which further predisposes to MACE in susceptible individuals [10]. This effect has been shown to persist for several months after the acute infection [11]. Finally, hypoxic stress and increased metabolic demands secondary to pneumonia infection predispose patients to arrythmia which in turn leads to cardiac ischaemia, especially in individuals with occult cardiac disease [12].

The absolute risk of cardiovascular events following pneumonia varies significantly depending on the population studied and severity of the infection. Risk estimates ranged from 5% to 15% in observational studies of patients admitted to hospital with community acquired pneumonia. A recent meta-analysis of observational studies estimated the combined inpatient risk of acute coronary syndrome and stroke as 5.2% [13]. Using Hospital Episode Statistics from 2018, we found the risk of inpatient MACE (MI or stroke or CABG/PCI) in any patient episode (all ages) was 5.7% up to 90 days after admission with pneumonia.

2.2 Evidence for use of aspirin to reduce risk of MACE in pneumonia

Observational studies have shown that patients on aspirin who develop pneumonia have a relatively reduced risk of MACE. Falcone et al prospectively recruited patients presenting to a single centre with pneumonia. Of 1005 patients included in the study, 390 were taking aspirin at the time of hospital admission. At 30 day follow up, the risk of non-fatal MACE and all-cause mortality was higher in the non-aspirin users (Hazardous Ratio (HR) 1.77 and 2.07 respectively)[14]. Other observational studies have found that patients on anti-platelet drugs had reduced rates of MACE, improved mortality and a shorter hospital length of stay [15, 16].

A recent analysis by Hamilton et al focused on primary care pneumonia [17]. It has been previously demonstrated that the primary care population also suffers from a short-term increased MACE risk, albeit with a smaller absolute risk. This analysis used a Prior Events Rate Ratio (PERR) analysis (an approach which compares event rates pre and post an exposure in observational data and has been shown to reduce confounding in observational studies) to compare aspirin users to non-aspirin users. It demonstrated that, despite having a higher average age and risk of co-morbidity, the group of patients taking aspirin at the time of their pneumonia had a reduced risk of MI or stroke (adjusted hazard ratio, HR 0.68; 95%, Confidence Interval 0.55 to 0.83). This study has been selected for an National Institute for Health Research (NIHR) Alert as an important area of future study.

There has been one small randomised controlled trial (RCT) of aspirin in pneumonia. Oz et al randomised patients presenting with pneumonia to 6 Turkish hospitals to receive either 300mg of aspirin for 1 month (n=91) or standard care (n=94). At 1-month follow-up 1 patient (1.1%) had had an acute coronary event in the aspirin group versus 10 (10.6%) in the control group (p=0.015). Although this trial supports our hypothesis, it is at serious risk of several biases due to small

outcome numbers, lack of randomisation within centres, and incomplete results presentation [18]. A recent New England Journal of Medicine review article by an author of the most recent and up-to-date pneumonia guidance in the world concluded that the use of antiplatelets in pneumonia is an area worthy of investigation in a prospective randomised fashion [3].

2.3 Evidence for use of aspirin to reduce risk of pulmonary emboli/deep vein thrombosis

There is a weight of evidence showing that aspirin is effective in the primary prevention of venous thromboembolic events in patients at a higher than baseline risk. The majority of the literature comes from large meta-analyses from the Antiplatelet Trialists' Collaboration who demonstrated that antiplatelet therapy (not exclusive to aspirin) was found to affect a significant reduction in venous thromboembolism (VTE) risk and a favourable trend toward mortality benefit. The Pulmonary Embolism Prevention study randomised 17,000 patients undergoing hip surgery to aspirin or placebo. Aspirin reduced the risk of VTE by 36% (1.6% vs 2.5%) [19].
In the RECOVERY trial, patients hospitalised with COVID-19 were randomised to aspirin (150mg once daily) versus usual care. Despite no impact on mortality, there was a reduction in thrombotic events (4.6% vs 5.3%; absolute reduction 0.6%, SE 0.4%) [20].
VTE occurred more frequently than expected following pneumonia in our initial HES data download, with rates around 3% in the 90 days following randomisation. We have opted to include PE/DVT in the win ratio hierarchy based on the frequency of observed events, prior evidence of aspirin's efficacy in preventing PE/DVT, and the importance of these events given their impact on length of stay, readmission and mortality.

2.4 Evidence for use of aspirin to reduce risk of pulmonary transient Ischaemic attack/ unstable angina

These cardiovascular events were originally not included in our primary outcome of MACE. They are a relatively uncommon event following pneumonia according to our own data (approximately 0.2% in the 90 days following randomisation). However, they often lead to hospital attendance or admission and are important adverse outcomes to patients.

3. Rationale for the study

Around 19,000 fatal and non-fatal MACE occur up to 90 days after admission with pneumonia in English hospitals per year; additional MACE causing sudden death in the community increase this number but to what extent has not been quantified. These events occur whilst the patient is recovering from the infection, thereby lengthening hospital stay or prolonging convalescence and causing significant long-term morbidity and excess mortality. Prospective studies have shown that pneumonia survivors who have MACE have significantly worse mortality and morbidity than matched controls [21, 22].

The high incidence of pneumonia means that there would be about 2,800-3,800 fewer MACE per year if aspirin were to reduce the risk by 15-20% (in England alone). Aspirin is already known to be effective for other groups of patients with risk factors for MACE [23, 24]. Moreover, although the general risk of MACE has substantially reduced in the past two decades, cardiovascular disease still costs the NHS an estimated £9 billion per year in both acute and long-term costs [25].Given the widespread availability and familiarity of aspirin to patients and healthcare professionals any benefit would face few barriers to implementation in standard care for pneumonia treatment in acute care.

4. Aims and objectives

To evaluate the effectiveness of aspirin versus usual standard care in preventing major adverse cardiovascular events (MACE), non-cardiovascular mortality, PE/DVT and TIA/unstable angina in patients ≥ 50 years admitted to hospital with community-acquired pneumonia.

To estimate the difference between randomised groups in:

1) The hierarchical composite of time to cardiovascular mortality, non-cardiovascular mortality, non fatal MI/stroke, PE/DVT and TIA/unstable angina, up to 90 days following randomisation;

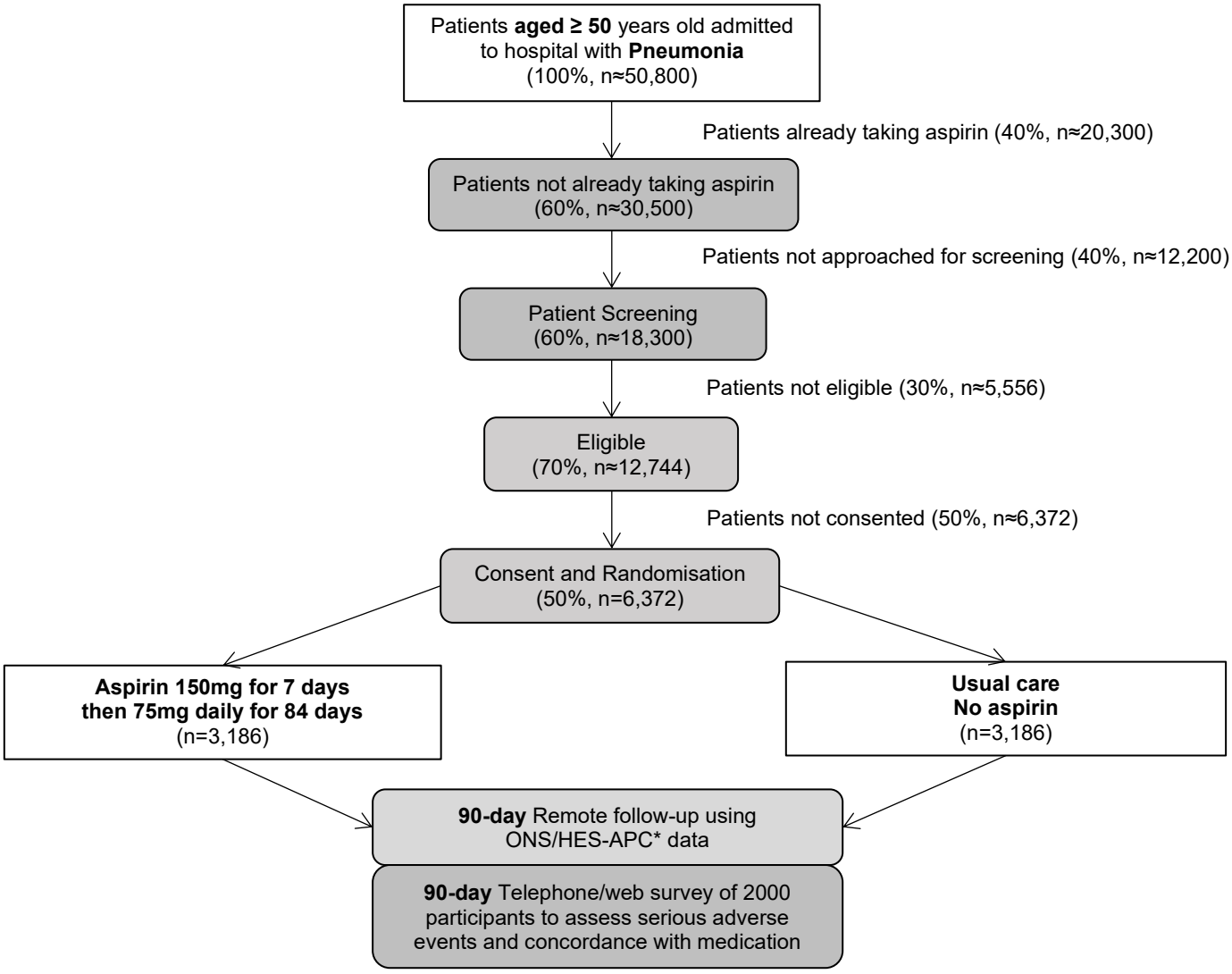
2) secondary outcomes, namely MACE*, all-cause mortality, cardiovascular mortality and major bleeding events up to 90 days following randomisation.

*Composite outcome of any MI, stroke (ischaemic or stroke of unknown type) or cardiovascular mortality.

5. Plan of investigation

5.1 Trial schema

Figure 1. Trial schema



*HES-APC: Hospital Episode Statistics (Admitted Patient Care), ONS: Office for National Statistics

5.2 Trial design

Multi-centre, open-label, parallel group RCT in patients admitted to hospital with pneumonia, with internal pilot and efficient remote outcome measurement.

5.3 Setting

Participants will be patients aged 50 years or older presenting as an emergency to hospital admitted following a diagnosis of community acquired pneumonia.

5.4 Key design features to minimise bias

(a) Bias arising from the randomisation process (selection/allocation bias) (systematic differences between baseline characteristics of the groups that are compared) will be prevented by concealed randomisation. The allocation will be stratified by CURB-65 score (a widely used pneumonia severity score [26]) and the use of novel oral anticoagulants (NOAC) or warfarin to minimise confounding due to these factors (see section 6.1).

(b) Bias due to deviations from intended interventions (performance bias) (systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest) will be minimised by administering the study drug (aspirin) and other procedures undertaken during the trial according to standard protocols and by pre-defining all procedures for participant follow-up and applying the procedures to all participants in the same way. The only difference between groups is that one group is asked to take the study drug and the other is not, all other aspects of care will be the same. The data will be collected from routine data sources which is objective. Adherence to all aspects of the protocol will be monitored (for further details see section 8.2).

(c) Bias in measurement of the outcome (detection bias) (systematic differences between groups in how outcomes are determined) will be minimised by using objective outcomes (further details in section 5.7).

(d) Bias due to missing outcome data (attrition bias) (systematic differences between groups in withdrawals from a study) will be minimised by i) by using routine data sources to collect follow up data, ii) we will be documenting non-adherence to the allocated treatment in a proportion of the patients (see section 6.2.2). The data will also be analysed by intention to treat. In estimating the target sample size, we have not allowed for loss to follow-up as the primary outcome is MACE, which can be obtained from HES data which will be available for every patient.

(e) Bias in selection of the reported result (reporting bias) will be minimised by having pre-specified outcomes (see section 5.7) and a pre-specified analysis plan (section 7).

5.5 Trial population

5.5.1 Inclusion criteria

Participants (**aged ≥ 50 years**) admitted to hospital with pneumonia may enter study if ALL of the following are present:

- symptoms and signs of acute lower respiratory tract infection, and

- radiographic changes in keeping with infection on chest radiograph, CT scan or lung ultrasound scan

5.5.2 Exclusion criteria

Participants may not enter study (i.e. may not be randomised) if ANY of the following apply:

- already taking regular prescribed anti-platelet* medication, including aspirin, clopidogrel, cangrelor, selexipag, cilostazol, dipyridamole, prasugrel, ticagrelor, abciximab, eptifibatide, tirofiban, epoprostenol, iloprost;
- a known allergy, previous important adverse reaction, or contraindication to aspirin;
- at high risk of excessive bleeding (e.g. large trauma or haemorrhage or urgent need for major surgery or uncorrectable coagulopathy) in the opinion of the treating physician;
- hospital acquired pneumonia, defined as related to an inpatient hospital stay within the last 10 days or acquired at least 48 hours after current admission;
- discharged without a 'Decision to Admit' to hospital by urgent care/emergency department**
- unlikely to tolerate/adhere to medication regimen;
- prisoners;
- known to be pregnant;
- life expectancy <3 months due to pre-existing condition (e.g. terminal malignancy);
- presentation more likely due to acute COVID-19 pneumonitis in the opinion of the treating physician. i.e. newly positive Polymerase Chain Reaction (PCR) or similar antigen test for COVID-19;
- enrolment onto another study where the burden on the participant will be too high if they are enrolled onto both. Or, if the enrolment onto both would compromise one or both of the study's objectives.***

*Anti-coagulation medication is **not** an exclusion, however the increased bleeding risk should be considered by the clinician. For more details see section 5.6.8.

**Patients may be approached and randomised within the emergency department provided a decision has been made that they require hospital admission i.e. Decision to Admit.

***To be decided on a case-by-case basis by the local PI and/or CI.

5.6 Trial interventions

Patients will be randomised on a 1:1 ratio to receive;

- Aspirin 150mg once daily for 7 days, followed by 84 days of 75mg daily.

OR

- Usual Standard of Care; patients not prescribed aspirin during admission and advised not to take aspirin unless advised by healthcare professional during follow up period.

There will be no comparator intervention (placebo) for this trial. Instead, patients randomised to receive usual standard care will continue to have normal pneumonia treatment with nothing else about their care changed.

5.6.1 Study drug

Aspirin is the investigational medicinal product (IMP) in this study. Aspirin (CAS 50-78-2) is rapid-acting anti-platelet that, at low-dose, acts by irreversible inhibition of cyclooxygenase-1 preventing the formation of thromboxane A2, thereby inhibiting platelet aggregation for the lifetime of the cell (approximately 14 days) [27]. Equivalent doses of the enteric coated aspirin are not as effective as plain aspirin [28]. No clear clinical benefits in terms of reduction of Gastrointestinal (GI) bleeding or ulceration with enteric coating have been demonstrated [29]. Therefore, non-enteric coated or dispersible preparations would be preferred but not mandated. There are several different manufacturers of generic aspirin in the UK. Because the aspirin will be prescribed using the standard NHS prescribing system, any of the available preparations may be used within the study.

5.6.2 Rationale for dose

Previous literature has shown the peak of the risk for cardiac events occurs during the first 7 days of hospital admission with risk gradually reducing to baseline at 3 months [3]. Given the high risk early after diagnosis we propose an increased dose for the first week after randomisation. A similar regimen has been shown to be feasible by the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, which has randomised over 7351 patients with viral pneumonia secondary to Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to aspirin 150mg once a day until discharge [30]. Although the disease processes are very different, with COVID-19 causing more venous thromboses than would normally be associated with community acquired pneumonia [31, 32], this trial shows that physicians are willing to randomise hospitalised inpatients to this regimen. Aspirin at this dose was associated with a small absolute increase in major bleeding from 1.0% to 1.6% (absolute difference 0.6% Standard Error 0.2%). Eighteen haemorrhagic serious adverse events (SAEs) were adjudged to be related to aspirin (0.24% of the cohort) [30].

After the 7 day course of 150mg daily, patients will continue on aspirin 75mg maintenance for 84 days. The dose of 75mg has been used for decades in primary prevention and is part of the standard treatment following some acute cardiovascular events in the NHS [24, 33]. The dose is familiar to healthcare professionals and patients, with an excellent safety profile. The ASPREE trial randomised 9525 patients over 75 years old to receive 100mg of aspirin versus 9589 who received placebo. After a median of 4.7years on study, there were no significant differences between groups in the risk of haemorrhagic stroke (49 in aspirin arm, 40 in placebo arm, additional absolute rate 0.09%), with a marginal rise in non-stroke bleeding risk (1.4%). This provides reassurance that even over an extended period the rate of major bleeding events is low and not significantly increased with low dose aspirin [34].

5.6.3 Supply and Storage

All aspects of the medicinal product supply, storage, and management of aspirin will be in accordance with standard local policy and practice for prescription medications. Treatment issued to randomised participants will be by prescription.

On randomisation, the participant should be prescribed 14 tablets of aspirin, 2 x 75mg tablets to be taken daily for 7 days. And then, 84 tablets of aspirin, 1 x 75mg tablets to be taken daily for the next 84 days. How the prescription is dispensed will be up to sites and in accordance with their local policies and procedures.

The IMP will not be labelled other than as required for routine clinical use. The IMP will be stored alongside other routine medications with no additional monitoring. No accountability records will be kept beyond those used for routine prescriptions.

The IMP should be stored to local pharmacy procedures. Temperature monitoring will not be required.

5.6.4 Initiation of study drug

The risk of MACE events in pneumonia peaks in the first 7 days from hospital admission. Although there is no mandated time limit on randomisation from admission this is intended to be a time dependent intervention where randomisation within the first 3 days of admission would be optimal, later randomisations will be recorded and monitored but will not be classed as a protocol violation.

5.6.5 Adherence with study drug

The pilot phase of this trial involves the recruitment of 2000 participants over 12 months. Participants in the pilot phase will be contacted by the study team at 90 days post randomisation, either by email, phone or postal questionnaire. The purpose of this is to assess any serious adverse events and adherence with the IMP. Adherence with the IMP will be assessed through a participant-completed questionnaire.

5.6.6 Known side effects and safety information

Full details of aspirin side effects are provided in the section 9.3.

5.6.7 Concomitant medication

There is no concomitant or rescue medication mandated in the Protocol. Treating clinicians may prescribe gastroprotection in those patients randomised to aspirin who are felt to be at the greatest risk of bleeding, but these decisions will be at the discretion of the treating clinician.

5.6.8 Special warnings and precautions for use

Patients already taking an antiplatelet medication will be excluded on the grounds of increased bleeding risk from the addition of aspirin. Patients taking other anti-thrombotic medication, like anti-coagulants, may still be eligible for this trial, as they were in the aspirin group of the RECOVERY trial, but the risk of bleeding would be assessed by the treating clinician.

Examples of anticoagulants (not considered to be an exclusion):

- DOAC
- warfarin
- low molecular weight heparin

These patients are an important group who might significantly benefit from antiplatelet therapy as thrombotic risk is likely to be high. The combination of a DOAC or other anti-coagulant with an antiplatelet is specifically mentioned in the latest National Institute for Healthcare and Excellence (NICE) guidance on ‘Acute Coronary Syndrome’ and where there is an indication for both, dual prescription is warranted [33]. Although not a contraindication, anticoagulation

medication in combination with an anti-platelet medication (aspirin) comes with an increased risk of bleeding. Decisions on balancing bleeding risk with potential benefits of antiplatelet therapy in higher risk patients should be made on a case by case basis by the clinician.

Blood pressure, platelet level or haemoglobin level should also be evaluated and treated with precaution. If any of these levels are at a dangerous level, in the opinion of the treating physician, they will be excluded.

5.7 Primary and secondary outcomes

5.7.1 Primary outcome

All final outcomes will be ascertained from linked, routinely collected data sources (HES-APC and Office for National Statistics (ONS) mortality) at 90 days post randomisation:

The primary outcome was originally time to first MACE defined using validated International classification of diseases 10 (ICD-10) codes for specified diagnoses in hospital or cardiovascular death (deaths with any of the specified ICD-10 codes coded as the underlying cause up to 90 days after randomisation [35, 36]). However, due to challenges with recruitment and an observed lower than expected outcome event rate, the primary outcome was changed from MACE to a combined hierarchical endpoint incorporating the following levels, analysed using the win ratio method:

1. Cardiovascular mortality
2. Non-cardiovascular mortality
3. Non-fatal MI/stroke
4. DVT or PE
5. TIA or angina

The accuracy of MACE coding has been researched by the ASCEND trial. Their secondary analysis confirmed that using routinely collected hospital data and data from the death registry was a reliable method to gather this information without the need to interrogate the patient notes [37]. Myocardial infarction and ischemic stroke resulting in hospitalisation were included in the analysis.

5.7.2 Secondary outcomes

Secondary outcomes will be defined from routine data at 90 days post randomisation:

(a) Time to first MACE
(b) All-cause mortality;
(c) Cardiovascular mortality;
(d) Time to first bleeding event causing hospitalisation;
    i. Any bleeding event
    ii. Gastrointestinal bleeding
    iii. Intracranial haemorrhage
(e) Hospital length of stay

5.8 Sample size calculation

The original sample size for the primary outcome of MACE was 22,600 patients (11,300 in each group) which was determined using anonymised HES-APC data for admissions coded with ICD-10 pneumonia diagnoses (J12-J18) between 01/01/2018 – 31/12/2018. This sample size would be sufficient for a hazard ratio of 0.8 to be detected with 90% power, 5% 2-tailed significance and allowing for 10% crossover in a time to event analysis for:

i. primary outcome frequencies from 6%-10% allowing for deaths from non-cardiovascular causes as a competing risk with frequencies 3.75%-15% and
ii. primary outcome frequency of 5% allowing for deaths from non-cardiovascular causes as a competing risk with frequency 3.75%

The sample size was revised in January 2025 to reflect the new hierarchical primary outcome. Using simulated data, a total of 6,372 participants (3,186 per group) would provide 80% power to detect an effect size of 0.8 at a 5% significance level, accounting for a 5% cross-over rate. This calculation is based on the following assumptions, with all events analysed as time-to-event outcomes:

1. Cardiovascular mortality (10% of all-cause mortality: 6.0% i.e. 0.53% vs 0.67%)
2. Non-cardiovascular mortality (90% of all-cause mortality: 6.0% i.e. 6.0% vs 4.8%)
3. Non-fatal MI/stroke: 2.0% i.e. 1.78% vs 2.22%
4. PE/DVT: 3.0% i.e. 2.67% vs 3.33%
5. TIA/unstable angina: 0.2% i.e. 0.18% vs 0.22%

These estimates are informed by event rates observed in the initial HES data extract, which included 1,299 participants and covered data up to 31 March 2024.

6. Trial methods

6.1 Description of randomisation

Participants will be randomised in a 1:1 ratio, aspirin/standard care, stratified by site, severity of pneumonia using the CURB-65 score (0-1 vs 2-5) and use of NOAC or warfarin. This will be facilitated by a password-protected web-based randomisation platform designed by the Bristol Trials Centre (BTC). This will enable randomisation soon after the consent process reducing burden on research staff.

In the event of technical difficulties meaning the online randomisation platform is not available, sites will be asked to contact the coordination centre. If the coordination centre is also unavailable, a method for manual randomisation will be provided.

6.2 Research procedures

6.2.1 Research assessments; all participants

Patients admitted to a recruiting centre with suspected pneumonia will be approached by the trial or clinical team. Baseline assessment will be completed for consented patients on a web-based platform that also serves as the randomisation module. Baseline assessment will be brief

focusing on basic demographics, comorbidities, focused medication review, smoking history and diagnostic criteria.

All participants will be followed-up 90 days after randomisation using HES-APC and ONS data, by the central trial team.

6.2.2 Research assessments; pilot phase only

The study team will contact the first 2000 participants recruited at 90 days post randomisation. This remote follow-up will focus on recording serious adverse events as well as assessing adherence to their assigned aspirin use, see section 5.6.5.

6.3 Duration of treatment period

Participants randomised to receive aspirin will receive:
a. 150mg of daily aspirin for 7 days and then;
b. 75mg of daily aspirin for 84 days

Participants will have a treatment period of 91 days in total.

Table 1. Schedule of Events

Aspirin taking arm

	Baseline Day 1	Day 1 to 91	Day 90
Consent	✓		
Eligibility	✓		
Randomisation	✓		
Collection of baseline data: Socio-demographic details Co-morbidities Routine clinical measures Diagnostic details	✓		
Aspirin prescription of x98 tablets at 75mg	✓		
Aspirin taken daily[a]		✓	
Follow up questionnaire[b] by central study team; *phase 1 participants only*			✓
Central follow-up using HES-APC and ONS data			✓

[a] Participants course of aspirin.
2 tablets of 75mg to be taken daily for 7 days, then;
1 tablet of 75mg to be taken daily for 84 days
[b] Follow up regarding adherence with IMP and safety events

Adherence and time periods for aspirin taking arm (first 2,000 participants only):

Day 1 – 7. Aspirin course of 150mg daily.

- Participants must take a minimum of one day of 150mg before switching to the 75mg dose. This must be started within 24 hours of randomisation. If the patient does not have the first dose of 150mg aspirin, this will count as a protocol deviation.
- The use of any additional aspirin over and above the expected dose will be ignored for the purposes of calculating the adherence value.
- A minimum of 30% of expected tablets must be taken. Minimum of:
    - 5 tablets of 75mg
- If the adherence value is <30%, it will be considered a protocol deviation. However, if there is a clinical indication to stop early this will not count as a deviation.

Day 8 – 91. Aspirin course of 75mg daily.

- If the participant stops taking aspirin one month early (ending on Day 61 or later) this will not count as a protocol deviation, unless this would total <30% of the tablets taken overall. However, if there is a clinical indication to stop early this will not count as a deviation.
- The use of any additional aspirin over and above the expected dose will be ignored for the purposes of calculating the adherence value.
- Missed pills for longer than a continuous period of 14 days will count as a protocol deviation, up to Day 61. Tablets missed after Day 61 will not be counted as a protocol deviation.
- A minimum of 30% of expected tablets must be taken.
    - Minimum of 26 days of 75mg

  If the adherence value is <30%, it will be considered a protocol deviation.

Control arm (no aspirin)

	Baseline Day 1	Day 1 to 91	Day 90
Consent	✓		
Eligibility	✓		
Randomisation	✓		
Collection of baseline data: Socio-demographic details Co-morbidities Routine clinical measures Diagnostic details	✓		
Refrain from taking any aspirin		✓	
Follow up questionnaire[a] by central study team; *phase 1 participants only*			✓
Central follow-up using HES-APC and ONS data			✓

a Follow up regarding adherence with IMP and safety events

Adherence and time periods for control arm (first 2,000 participants only):

Day 1 – 91

If a participant on the control arm takes 28 days or more of aspirin over any period during the 91 days, this will count as a protocol deviation (unless prescribed by a doctor).

6.4 Definition of end of trial

The trial will end for a participant after they have completed the course of study medication at 91 days post randomisation and completed the 90-day follow-up questionnaire (if one of the first 2000 participants recruited during phase 1). The end of the trial as a whole will be after all trial participants have completed follow up, all data queries have been resolved, the database locked and the analyses completed.

6.5 Data collection

The local research team will use the bespoke study web-based applications for study management and to record participant data (including case report forms, CRFs) in accordance with the protocol. Data will be held in central databases located at the BTC.

In circumstances where there is difficulty accessing the internet or necessary IT equipment, paper CRFs may be required with subsequent data entry by the local research team.

BTC will provide the relevant web-based applications; data access will be controlled by unique usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Where possible, staff will have access restricted to the functionality and data that are appropriate for their role in the study.

6.6 Source data

At baseline, the primary data source will be the participant's medical notes. Where information is collected on the CRFs and not the medical notes, the CRFs may also be source data. For the 90-day follow-up the primary source data is the participants linked HES-APC and ONS data.

For the first 2000 participants recruited in phase 1 the participant completed questionnaires will also be primary source data for the follow up timepoint.

6.7 Planned recruitment rate

Analyses of anonymised HES-APC showed 240,313 adults aged 50 years and over were admitted to hospital with pneumonia (ICD-10 J12-J18 where the diagnosis was recorded within the first episode of the patients' inpatient spell) from 01/01/2018 to 31/12/2018, with a mean number of such admissions in the 80 highest volume English hospitals of approximately 2000 cases. We plan to recruit patients at 65 of these 80 high volume hospitals.

Our original recruitment projections were based on the following assumptions: 60% of potential participants will not already be taking regular aspirin, of whom 60% will be screened (estimate

set conservatively due to the potential workload at a hospital); 70% of these will be confirmed eligible after screening and 50% will consent, giving a projected average recruitment rate of 21 participants per month per site.

These projections were revised in January 2025 to reflect observed recruitment rates of 4.0 participants per site per month during the winter months (November to February), and 2.7 participants per site per month in non-winter months (March to October).

6.7.1 Pilot phase 1: Progression criteria

The pilot phase 1 will recruit in 24 centres over 12 months. The pilot will monitor 1) recruitment rates (proportion of screened patients that are eligible, eligible patients consented and randomised) and 2) adherence to the allocated treatment and 3) follow-up of in the first 2000 patients recruited, see below. If the trial proceeds to phase 2, patients from phase 1 will be included in the final analysis.

Table 2. Progression Criteria

Criteria	Target	Red	Amber	Green
Centres open to recruitment	24	<16	16-23	24
Recruitment target	3276	<2160	2160-3275	3276
Randomisation rate/centre/month	21	<14	14-20	21
Adherence to the allocated treatment (assessed in the first 2000 participants)	>90%	<80%	80-89%	>90%
Follow-up of first 2000 participants	100%	<75%	75-99%	100%

If all criteria are green the full trial will proceed with the same protocol; if one or more criteria are amber, we will propose adaptions to address the short fall; if one or more criteria are red, we will discuss with the trial steering committee whether the full trial is feasible.

6.8 Participant recruitment

Patients admitted as an emergency with community acquired pneumonia will be invited to participate. Potential trial participants will be identified by local teams, both clinical and/or research teams. All potential participants will be given a Patient Information Leaflet (PIL) (approved by the local Research Ethics Committee, REC) describing the study.

Due to the relatively acute nature of the condition and intervention, it is not felt practical to mandate participants have 24 hours or more to consider study entry. However, it is imperative that all participants be given sufficient time (as determined by the participant themselves) for study information to be considered and for questions to be asked. See consent section 10.4 for further details.

6.9 Discontinuation of participation

Participants are free to discontinue from some or all aspects of the study at any time if they wish to do so. In accordance with regulatory guidance, data that have already been collected will

continue to be used. A decision by a participant that they no longer wish to continue receiving study treatment should not be considered to be a withdrawal of consent for remote follow-up.

6.10 Frequency and duration of follow up

With the exception of the first 2000 participants recruited in phase 1 there will be no active follow-up of participants following discharge from hospital. All participants will be followed up remotely to 90-days via HES and ONS.

6.11 Likely rate of loss to follow-up

Loss to follow-up is not expected to be high as all participants will be followed-up through data linkage to HES and ONS. The only losses would be participants who withdraw their consent for follow-up to continue via data linkage (expected to be very small) or those for whom a linked HES/ONS record cannot be found, which is not expected.

6.12 Expenses

There will be no 'research only' visits, therefore participant travel expenses are not required.

7. Statistical analyses

7.1 Plan of analysis

The primary analysis will follow a pre-specified statistical analysis plan and will be in line with CONSORT reporting guidelines for clinical trials. The primary analyses will be by intention to treat. The primary outcome, a composite hierarchical endpoint including cardiovascular mortality, non-cardiovascular mortality, non-fatal MI/stroke, PE/DVT and TIA/unstable angina, will be analysed using the win ratio method [38] stratified by severity of pneumonia (CURB-65 score), use of NOAC or warfarin and site. All levels will be analysed as time to event. An unmatched pairs approach with each individual in the intervention group compared to each individual in the placebo group from the same strata will be used. The estimate of the win ratio and its 95% confidence interval will be calculated.

Secondary outcomes will be compared using Cox's proportional hazards models, adjusted for severity of pneumonia and use of NOAC or warfarin fitted as fixed effects and site fitted as a shared frailty. If the assumptions of the Cox proportional hazard model are violated, alternative methods such as parametric models will be used as appropriate. Treatment comparisons will be presented as hazard ratios (HRs) and 95% confidence intervals (CIs). In the presence of one or more competing risks, outcomes will be compared using competing-risks survival regression and treatment comparisons will be presented as sub distribution hazard ratios (SHRs). If the assumptions of the Cox proportional hazard model are violated, alternative methods such as parametric models will be used as appropriate. Treatment comparisons will be presented as hazard ratios (HRs) and 95% confidence intervals (CIs). In the presence of one or more competing risks, outcomes will be compared using competing-risks survival regression. Treatment effects will be reported with 95% confidence intervals.

7.2 Subgroup analyses

Several subgroup analyses are planned with a focus on populations that are theoretically at higher risk from MACE following pneumonia. Specifically:

- Those with more severe pneumonia as defined by the CURB-65 score of 2 and above at randomisation
- Age (50-64, 65-79, ≥80)
- Sex (M/F)
- Time from admission to randomisation (0-2, 3-6, 7+ days)
- History of atrial fibrillation (Y/N)
- History of COPD (Y/N)
- Any of the following cardiovascular risk factors at baseline (Y/N)
    - On treatment for hypertension
    - History of stroke/TIA/ischaemic heart disease (Y/N)
    - Diabetes (Y/N)
    - Current or ex-smoker

7.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the data monitoring and safety committee (DMSC) at a frequency to be agreed by the DMSC, together with any additional analyses the committee requests.

7.4 Criteria for the termination of the trial

The trial may be terminated early on the recommendation of the trial steering committee (TSC) or DMSC, or if the results of another study supersede the necessity for completion of this study.

7.5 Economic issues

We considered including an economic evaluation but were advised that this would not represent value-for-money, given the low cost of aspirin, i.e. aspirin would be ‘dominant’ if it is found to be effective.

The low cost of aspirin and remote follow-up ensures that the trial itself represents excellent value for money.

8. Trial management

8.1 Trial Oversight

8.1.1 Trial Management Group

The trial will be managed by a trial management group (TMG), which will meet face to face or by video/teleconference approximately every 4-8 weeks for the duration of the study. The TMG will be attended by the Chief Investigator, co-lead and representatives from BTC. Other members of the research team will be invited to attend as required.

The TMG will be supported by the BTC, a United Kingdom (UK) Clinical Research Collaboration registered Clinical Trials Unit. BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the trial progresses, monitor recruitment, manage the trial on a day to day basis and undertake statistical monitoring and statistical analyses.

8.1.2 Investigator Meetings

Investigator meetings will be held approximately every 6-12 months to review study progress and address any issues that arise. All team members, including all study applicants, PIs and lead research nurses will be invited to these meetings.

8.2 Day-to-day management

The study will be conducted at multiple hospitals within the UK. At each hospital, a principal investigator (PI) will be responsible for trial activities but it is envisaged that much of the work will be carried out by medical staff attending patients with pneumonia within the hospital and by hospital research nurses, and other staff with appropriate education, training and experience. The PI may be a doctor or a nurse with suitable qualifications and experience. Sites that have a nurse PI will also need a doctor signed off on the delegation log to work on the study who is delegated to do the doctor-only tasks.

8.3 Training and monitoring of sites

8.3.1 Initiation visits

It is envisaged that given the familiarity and availability of the study drug to clinicians that a wide range of prescribers would be competent and comfortable to recruit and randomise patients to this trial. Prescribers of the IMP would be delegated this responsibility by the local PI and appropriately trained before doing so.

The training aims to allow a broad range of clinical staff to take part whilst maintaining high standards of patient safety and data integrity in keeping with Good clinical practice (GCP). All PI's and Sub-investigators must have a current GCP certificate. All other staff will undergo study training but a GCP certificate will not be required. Staff will also be required to provide a CV or competency questionnaire.

Before recruitment commences at a participating site, training session(s) will be organised by the trial coordinating centre (BTC). These sessions will ensure that personnel at that site fully understand the protocol, CRFs, practical procedures for the study, the informed consent process and key elements of GCP. Those who complete training will be added to a delegation log of personnel who can carry out study procedures.

The sign-off of eligibility can be carried out by medically qualified doctors, advanced nurse/clinical practitioners and physicians associates who have undergone suitable study-specific training that includes targeted GCP and have been delegated this task by the local PI.

8.3.2 Site monitoring

BTC will carry out central monitoring of centres. The study database will have extensive in-built validation and the TMG will review the completeness and consistency of the data throughout the trial. BTC will not check CRFs against the data entered or against source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem).

8.4 Trial Steering Committee and Data Monitoring and Safety Committee

The TSC is made up of representatives of ASPECT TMG, and independent members to be appointed and agreed by the funders.

The DMSC consists of a Medical Statistician and medical experts in this field. Independent members will be appointed by the funder. The Lead applicants will be available as required.

9. Safety reporting

9.1 Definitions

An adverse event (AE) is any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.

An adverse reaction (AR) is any undesirable experience that has happened a subject while taking a drug that is suspected to be caused by the drug or drugs.

A serious adverse event (SAE) is any event which result in death, is life threatening, requires hospitalisation or prolongs hospitalisation, results in persistent or significant disability, incapacity, is a congenital anomaly or birth defect, or another important medical event that may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected to be related to the drug or drugs being taken.

Suspected unexpected serious adverse reaction (SUSAR) is an untoward medical occurrence suspected to be related to the drug or drugs being taken that is not consistent in nature or severity with the applicable product information and is serious.

9.2 Overview

Aspirin was developed more than 100 years ago and has a very well-established safety profile. There is extensive experience of the use of aspirin for both primary and secondary prevention of cardiovascular disease.

ASPECT is adopting the DaRe2THINK approach to safety reporting, which involves a risk-adapted and pragmatic approach to adverse event reporting [40]. ASPECT has made slight modifications to the DaRe2THINK safety reporting approach, due to the safer profile of the IMP being used (aspirin) in this study compared to DaRe2THINK (direct oral anticoagulants (DOAC) or no therapy; choice of DOAC (apixaban, dabigatran, edoxaban or rivaroxaban)).

The rationale for this is: (1) Collection of HES outcomes will only occur on an infrequent basis; (2) Events are captured from routine NHS care coding, meaning that events have already been identified and managed within the NHS; (3) Hospitalisation from cardiovascular and bleeding events and death (specified outcomes in the trial) will be captured with HES data; (4) GPs in England are already experienced in the prescription and monitoring of patients taking regular aspirin; and (5) Aspirin has an established safety profile in patients. This includes RCTs, where aspirin has been extensively studied in numerous large phase IV trials [30], [41].

9.2.1 Operational use within a pragmatic NHS-embedded trial

To limit unnecessary time spent by frontline NHS staff for a class of drug with an established safety profile, ASPECT will operate a risk-adjusted approach to safety reporting. SAEs and SARs will not be reported in an expedited fashion. In particular, major and minor bleeding, hospitalisation (any cause), prolongation of hospitalisation and death will not be reportable SAEs as they are nominated outcomes of the trial. The trial-specific Reference Safety Information (RSI) for ASPECT will be Section 9.3 of the protocol for aspirin. We will be requesting historic HES data to characterise the cohort and to be able to check whether an event is a new event or an old recurring event. Outcomes from HES data will be matched against this list and a summary table of SAEs/SARs will be generated and reported to the DMSC, TSC, Sponsor and MHRA. We do not anticipate that this will be necessary but if requested by the DMSC, more frequent reporting of SAEs can be put in place.

The study database allows local Investigators to directly input a potential SAE for any recruited participant. This entry is then automatically flagged to the trial coordination team to process the potential SAE, with expectedness assessed by the Principal Investigator or delegate. Source data for the SAE form is controlled by the local Investigator.

Paper SAE forms will also be available at all sites and held as part of the Site File content. Training regarding SAE reporting via the study database and via the back-up paper route will be provided to all Investigators as part of site initiation. If a SAE needs to be reported via the back-up route, the Investigator will complete a paper SAE form to the trial coordination team. A copy would also be sent to the Sponsor in an expedited fashion as required (if deemed unexpected and related). All data from both SAE reporting routes will be transcribed and collated (so that there is no risk of identifying patients) into a SAE line listing document.

As with any potential adverse reaction in the NHS, Investigators will be encouraged to complete an MHRA Yellow Card submission when applicable, but these will not be collected as part of trial data.

9.2.2 Reporting of SUSARs

Due to the immense volume of safety data collected aspirin, and its common use in NHS routine practice, it is improbable that new SUSARs will be identified for aspirin in this trial. Data collection in ASPECT will operate entirely from NHS coded outcomes from primary and

secondary care; the purpose of which is to enable a more efficient approach to clinical trials within the NHS. As such, it is not likely that further details of any SAE will be available to the central study team, and any action/outcomes may only be known at the next data collation point. Although this limits the value of expedited reporting from either a safety or regulatory perspective, the processes in place still meet the Sponsor's legal obligations in terms of SUSAR reporting.

All confirmed SUSARs will be reported to the Chair of the DMSC and to relevant regulatory authorities, ethics committees, and investigators in an expedited manner in accordance with regulatory requirements.

Safety information relating to adverse events not subject to expedited reporting that are captured as trial endpoints will be closely monitored by the DMSC throughout the trial. The DMSC will be provided with a report at least annually (unless specified by the DMSC) where study outcomes will be matched against SAEs/SARs.

9.3 Expected adverse events associated with the study drug

This section forms the RSI. The list shown in **Table *3*** has been adapted from the British National Formulary (BNF) for Aspirin 75mg-150mg dose.

Frequency key:

Common	1 in 100 to 1 in 10
Uncommon	1 in 1000 to 1 in 100
Rare	1 in 10 000 to 1 in 1000
Frequency not known	Frequency is not defined by product literature or the side-effect has been reported from post-marketing surveillance data.

Table 3. Expected Adverse Events Associated with the Study Drug

Body system	Adverse event	Frequency
Blood and lymphatic system disorders	Increased bleeding tendencies.	Common
	Thrombocytopenia, granulocytosis, aplastic anaemia	Rare
	Cases of bleeding with prolonged bleeding time such as epistaxis, gingival bleeding. Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures. Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).	Not Known
Immune system disorders	Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock	Rare
Metabolism and nutrition disorders	Hyperuricemia, hypoglycaemia	Not Known

Body system	Adverse event	Frequency
Nervous system disorders	Intracranial haemorrhage	Rare
	Headache, vertigo	Not Known
Ear and Labyrinth disorders	Reduced hearing ability; tinnitus	Not known
Vascular disorder	Haemorrhagic vasculitis	Rare
Respiratory, thoracic and mediastinal disorders	Rhinitis, dyspnoea	Rare
	Bronchospasm, asthma attacks	Rare
Gastrointestinal disorders	Dyspepsia, nausea, vomiting, diarrhoea	Common
	Severe gastrointestinal haemorrhage	Rare
	Gastric or duodenal ulcers and perforation	Not known
Hepatobiliary disorders	Reye's syndrome	Rare
	Hepatic insufficiency, hepatic enzyme increased, hepatic failure	Not known
Skin and subcutaneous tissue disorders	Urticaria, severe cutaneous adverse reactions (SCARs)	Uncommon
	Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme	Rare
Renal and urinary disorders	Impaired renal function, salt and water retention	Not known
Reproductive system and breast disorders	Menorrhagia	Rare

10. Ethical considerations

10.1 Review by an NHS Research Ethics Committee

The research will be performed subject to a favourable opinion from an NHS REC and Health Research Authority (HRA). Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC and HRA for approval prior to implementation.

10.2 Risks and anticipated benefits

The main benefit to participants is the potential to reduce the risk of MACE events following pneumonia which is estimated to be in the range of 5-7%.

The main risks to the intervention are an increased risk of bleeding as noted in **Table *3***.

10.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL. The PIL will be thoroughly reviewed by our Patient and Public Involvement (PPI) panel for readability. The PIL will be translated into several different language to ensure accessibility of

the trial. There will be illustrations accompanying the PIL to aid understanding of the relative/absolute risks involved in taking part.

10.4 Obtaining informed consent from participants

Informed consent will be received by staff members who have been suitably trained and delegated the task by the local PI.

Informed consent will be obtained from each patient before enrolment into the study. Consent can be obtained in person face-to-face.

If a participant has capacity to verbally consent but cannot physically complete the consent form, e.g. too frail to hold the pen, an independent witness e.g. a member of ward staff, can sign the form on their behalf. The independent witness must initial the statement boxes with the participants initials after receiving their verbal consent, then sign their own name in the witness box of the consent form.

Given the urgent nature of the treatment protocol, if the patient lacks capacity to consent due to the severity of their medical condition or prior disease, consent may be obtained from a legally designated representative (i.e., relative or friend or an independent doctor). This can be obtained in person, or verbally over the phone/video call. Should the patient regain capacity at a later time, then confirmatory consent will be sought. Confirmatory consent does not need to be sought once the patient has been discharged.

If infection control protocols or other barriers prevent in-person consent from taking place, verbal consent can be obtained over the phone/video call, or electronically. The consent process will be witnessed by an independent witness, who will also sign the consent form.

10.5 Co-enrolment

Participants will be permitted to take part in other clinical trials including interventional or non-interventional studies (e.g. clinical trials of an investigational medicinal products (CTIMP), non-CTIMPs, observational studies) as long as the burden placed on the patient is reasonable and the other trial protocol permits this. This is to be agreed on a trial by trial basis ensuring that both studies outcomes will not be compromised by the co-enrolment. For non-interventional studies, this decision can be made by the sites PI. Interventional studies will be decided by the CI.

11. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- GCP guidelines
- Research Governance Framework for Health and Social Care
- European Union Directive 2001/20/EC on clinical trials

11.1 Sponsor approval

Any amendments to the study documents must be approved by the Sponsor prior to submission to the HRA/REC/Medicines and healthcare products regulatory agency (MHRA).

11.2 NHS approval

Agreement from the local NHS Trust is required prior to the start of the study at each site, including any provisions of local site capacity and capability confirmation.

Any amendments to the study documents approved by the HRA/REC/MHRA will be submitted to the Trust for information or approval as required, including confirmation of continued capacity and capability.

11.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved by the HRA/REC/MHRA that they receive and ensure that the changes are complied with.

11.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the BTC Standard operating procedure (SOPs), which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor (or BTC) if they have been delegated to monitor see section 8.3.2), the relevant REC and for inspection by the MHRA or other licensing bodies. A monitoring plan will be agreed between the sponsor and BTC.

11.5 Indemnity

This is an NHS-sponsored research study. For NHS sponsored research if there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

11.6 Clinical Trial Authorisation

Aspirin is classed as an IMP and a Clinical Trial Authorisation (CTA) from the MHRA will be in place before starting the trial.

12. Data protection and participant confidentiality

12.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

12.2 Data handling, storage and sharing

12.2.1 Data handling

Data from paper CRFs will be entered into a purpose-designed server database hosted on the University Hospitals Bristol and Weston NHS Foundation Trust network. Data from the follow up questionnaires for the first 2,000 participants will be stored on secure password-protected database hosted on a University of Bristol server. Information capable of identifying individuals and the nature of treatment received will be held in the database with passwords restricted to ASPECT study staff at the participating site, the sponsor site and the co-ordinating centre. Information capable of identifying participants will not be made available in any form to those outside the study, except for information needed for NHS Digital. HES data in will be stored on a secure server hosted by the University of Bristol.
Access to the database will be via a secure password-protected web-interface. Study data transferred electronically to the University of Bristol network for statistical analyses will be pseudonymised and transferred via a secure network. The participants will be identified using their NHS number and unique study identifier on the secure NHS hosted database.

The primary outcome will be assessed remotely at 90-days by the central trial team using the participants NHS number, date of birth, sex and postcode.

Data will be entered promptly and data validation and cleaning will be carried out throughout the trial. The trial instructions will cover database use, data validation and data cleaning. The manual will be available and regularly maintained.

12.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and 10 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial in accordance with North Bristol NHS Trust policy. In compliance with the Medical Research Council (MRC) Policy on Data Sharing, relevant ‘meta’-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic ‘key’ with a unique participant identifier, and key personal identifiers (e.g. name, date of birth, address and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server).

These will be retained because of the potential for the raw data to be used subsequently for secondary research.

12.2.3 Data sharing

Data will be made available for sharing subject to the necessary approvals from NHS Digital. Data sharing will be in line with the University of Bristol, Research data management and open data policy and in agreement with NHS Digital. Any shared data will be available after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be retained for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body. Patient identifiers would not be passed on to any third party.

13. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications (including a full report to the NIHR- Health Technology Assessment programme) and through patient organisations and newsletters to patients, where available.

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Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1	1.1	18th July 2022	2.0	30th November 2022	• Minor typographical corrections. • Co-applicant contact details updated. New team members contact details added. • "CV" added to Glossary. • Removal of the reference of participants doing a "pill count" at the end of the follow up period. • Prescribing of aspirin updated. • Secondary outcomes further defined. • Minimum adherence updated. • Statistical analysis of the secondary outcomes updated. • New subgroup analysis added. • Addition of allowing sites to upload a competency questionnaire in lieu of a CV. • Addition of collecting historical data from NHS Digital.	*17th January 2023*
2	2.0	30th November 2022	3.0	23rd August 2023	• Coapplicant role change. • Time restriction of 14 days to complete follow up has been removed. • Randomisation stratification changed from "use of NOAC" to "use of NOAC or warfarin". • Definitions of primary and secondary outcomes updated to time to first event. • Estimated power for time to event outcomes added. • Description of analysis plan updated to reflect the change of outcome definitions (from binary outcomes to time to first event).	*13th September 2023*

					• Verbal consent has been clarified. • Clarification that regained capacity confirmatory consent only needs to be sought if the patient is still in hospital. • Clarification on where data is stored. • Addition of non-medical research staff to be able to sign-off eligibility. • Clarification on the training and delegation requirements of those who can consent and prescribe.	
3	3.0		4.0		• Change of Trial Manager, Senior Trial Manager and Sponsor Representative • Removal of a co-applicant • Primary outcome changed from MACE to a combined hierarchical endpoint incorporating cardiovascular mortality, non-cardiovascular mortality, non-fatal myocardial infarction/stroke, deep vein thrombosis (DVT)/pulmonary embolism(PE) and transient ischaemic attack (TIA)/unstable angina • Sample size changed from 22,600 to 6,372 to reflect updated primary outcome • Time to first MACE included in the secondary outcomes • Trial Schema for reduced sample size of 6,372 • Added history of COPD to included risk factors within cardiovascular risk subgroup analysis • Removal of electronic consent option	