Does the Principal Investigator (PI) need to be a GP?	In most cases, the site PI will be a GP, but an appropriately-qualified prescribing nurse or pharmacist could also become the PI.
What training is required?	All PIs, will need to have completed **Good Clinical Practice** (GCP) training to carry out study tasks. Free CPD accredited training is available via NIHR Learn or DaRe2THINK specific training can be provided during our Site Investigator Visit meetings. Delegated Investigators or those providing study support will require either GCP training or the PI must confirm that they are aware of the principles of GCP. Before screening any patients, PIs and delegated staff will be required to complete a short **protocol training module** with a member of the trial team.
Who can complete study tasks?	Tasks can be delegated to staff who have been assessed by the PI as having the **appropriate skill set** to carry out the activity, and are named on the **site delegation log**. Study support can be provided by any appropriately qualified and delegated clinical personnel.

Task	**PI: GP or Independent Prescriber (IP)**	**Other Investigators: GPs or IPs**	**Study Support**
Screen patient list	Yes	Yes	Yes
Enrol and randomise patient	Yes	Yes	No
Prescribe the Investigational Medicinal Product (IMP) according to protocol and record prescription on IRSP	Yes	Yes	No
Report Serious Adverse Events (SAEs) and update SAE forms as required	Yes	Yes	Yes
Withdraw patient from trial	Yes	Yes	No
Conduct informed consent discussion, initiate informed consent process via REDCap (enter patient details and forward link to patient)	Yes	Yes	Yes
Confirm patient consent	Yes	Yes	No
Maintain essential documents in the Investigator Site File (ISF)	Yes	Yes	Yes

Can a practice take part in the SAFER study and the DaRe2THINK trial?	**Yes, both studies can be run at the same site**. There is only a small theoretical overlap (men aged 70-73 who are not already anticoagulated). The two trial teams have worked together to use coding to exclude any patients recruited to the other study. We only ask that the PIs and study support personnel are aware, and avoid including SAFER patients in DaRe2THINK and vice versa.
What indemnity do I require as a GP to take recruit patients into the DaRe2THINK trial?	DaRe2THINK is an NHS Clinical Trial with Health Research Authority (HRA) and Research Ethics Committee (REC) approval. It is funded by the Department of Health and Social Government (DHSC) via one of the National Institute for Health Research (NIHR) funding programmes. It has been adopted onto the portfolio of the Clinical Research Network (CRN) which is part of the NIHR and the CRN support all parts of the NHS in the running of research trials. The April 2019 introduction of state indemnity to include cover for GPs and other staff working in Primary Care also included research in its remit, mirroring the indemnity cover that has existed for many years in NHS trusts. This means any adverse events or issues are all covered by NHS indemnity. Anything that falls outside the remit of the state indemnity will form part of the indemnity held by our research sponsor, The University of Birmingham.
What about the bleeding risk for these younger patients in the trial randomised to DOACs?	It is worth remembering that since these are younger patients (55-73 years) and lower risk (they have no or few comorbidities) their bleeding risk score is very low, so bleeding events are unlikely. Bleeding rates are similar between aspirin and DOACs. In randomised trials the rate of bleeding is same including major significant bleeds. Observational trial data is consistent in showing similar bleeding rates between aspirin and DOACs. A recent international study with 3854 patients were treated with a therapeutic dose DOAC (apixaban 5mg BD or rivaroxaban 20mg daily) and 3876 were treated with varied doses of aspirin (81mg [46.9%], 100mg [27.6%], 162mg [18.5%], 243mg [1.9%], 324mg [5.0%], and unknown dose [0.2%]). Our analysis detected no statistically significant difference in major bleeding events (1.27% vs. 1.07%; p=0.4) or clinically-relevant, non-major bleeding events (3.22% vs. 2.65%; p=0.14) between the two groups.
A patient on my list is coded as "AF resolved" do I need to exclude this patient?	The inclusion criteria for DaRe2THINK are **patients with any diagnosis of AF (previous, current or chronic)**. The reason for this is that AF is associated with stroke, thromboembolic and cognitive decline regardless of whether the patient is currently in AF or not. Patients with paroxysmal AF, and those with transient or 'resolved' episodes also have an elevated risk of morbidity and mortality. As seen in the following two papers, this risk remains substantial and may be amenable to treatment with direct oral anticoagulants (DOACs), as tested in DaRe2THINK: BMJ article on 'resolved' AF; EHJ article on 'transient' AF; 2021/22 QOF Guidance. The clinical judgement of the PI is essential here, as there may be patients with resolved AF that are not eligible as they likely have no residual stroke risk (for example, where AF occurred during pregnancy but never again). Here are some examples of patients you would or would not include, assuming all other inclusion and exclusion criteria are met:

	1. Episode of AF two years ago during admission for pneumonia: **Yes, recruit**. 2. Peri-partum AF 30 years ago: **No, don't recruit.** 3. Previous catheter ablation for AF but no longer anticoagulated: **Yes, recruit**. 4. Post-operative AF four years ago treated and resolved: **Yes, recruit**.
A patient on my list is coded as "Valvular AF" do I need to exclude this patient?	The term 'valvular' AF has been largely removed from international guidelines as it is a confusing and inaccurate term. While some forms of valvular heart disease can make AF more common, AF can also lead to valvular incompetence. **Patients with valvular disease can be enrolled in DaRe2THINK**, if they meet the other inclusion and exclusion criteria. Nearly all patients with significant valvular disease and AF will already be anticoagulated by their hospital team, so would not be eligible for DaRe2THINK. Patients with moderate to severe mitral valve stenosis or mechanical heart valves should be receiving warfarin rather than a DOAC.
A patient has not had their kidney function tested in the last 12 months, are we able to include these patients?	If the patients does not have a documented eGFR in the last 12months, and there is no other clinical reason to expect any serious kidney dysfunction, then they are eligible to take part in DaRe2THINK. If the patient is then randomised to the treatment arm and your normal clinical practice is to do a eGFR you can complete this before issuing the prescription.
A patient is currently not eligible to take part in DaRe2THINK, but they may become eligible later, should they be rejected?	If you are unsure about the eligibility of a patient or think that the patient might become eligible to take part in the future, please **do not reject** this patient in thetrial database. Once a patient is mark as rejected, they will not be eligible to be enrolled in DaRe2THINK in the future. Please leave the patient as pre-screened and flag them for review in the future.
What if an invited patient does not want to take part?	You may wish to **speak the patient by phone** to explain the rational for the study (prevention of cognitive decline, strokes and death) and explain the preventive nature of DOAC therapy and its safe use in millions of NHS patients. If an invited patient responds to the invite letter and confirms they do not want to take part, please login to the trial database and **reject that patient** from the trial. You do not need to input any information on the REDCap system.

What if we are unable to get in contact with an invited patient?	We recommend that sites follow up the initial invitation with a phone call or text message. The team recommends practices use the dedicated trial text messaging system (link below), which automates follow-up messaging and streamlines the invitation process. DaRe2THINK Text Messaging System | REDCap If patients still don't respond, we would ask sites to continue to contact patients until every avenue has been exhausted. If still there is no response from the patient then you can reject the patient in the trial database.
Is the informed consent form in other languages?	No – however you wish to use a translator and there is a field for the patient to record if they have completed the form with the **assistance of a translator**. The electronic patient-reported outcomes that participants receive on their mobile phone every six months are available in a range of languages.
Are we limited to one particular DOAC for this trial?	No, investigators can prescribe **any** one for the 4 currently licensed DOACs for AF: Apixaban, Edoxaban, Dabigatran or Rivaroxaban, depending on local experience, policies and your CCG guidance. However, we ask that all patients receive the full licensed dose, with dose reduction only for specific patients (see table below).

DOAC	Usual dose	Reasons for dose reduction	Reduced dose
Apixaban	5mg twice daily	Two out of three indications: weight <60kg, age >80 years, serum creatinine >133mmol/L (or estimated creatinine clearance <30mL/min)	2.5mg twice daily
Dabigatran	150mg twice daily	Patients receiving regular oral verapamil (Consider dose reduction on an individual basis if estimated creatinine clearance 30-50mL/min, in patients with gastritis, esophagitis or gastroesophageal reflux, and others at increased risk of bleeding)	110mg twice daily
Edoxaban	60mg once daily	Any of: weight <60kg, estimated creatinine clearance <50mL/min, or concomitant therapy with potent P-glycoprotein inhibitors	30mg once daily
Rivaroxaban	20mg once daily	Creatinine clearance <50mL/min	15mg once daily

If a patient starts a DOAC in the trial, should I stop their aspirin?	Antiplatelet agents **should be stopped in most patients** when commencing a DOAC, including aspirin, dipyridamole, clopidogrel or prasugrel. This applies to patients who are taking antiplatelets for primary prevention reasons and those with stable coronary, cerebral or vascular disease, where monotherapy with a DOAC is recommended in patients with AF. If a patient with prior acute coronary syndrome or percutaneous coronary stenting receives a DOAC, then in most cases antiplatelet therapy should cease at 12 months after the event, and thereafter the patient should receive a DOAC alone. Cardiologists will have explicitly stated any exceptions to this rule in clinical documentation (for example, patients with unstable complex lesions or plans for further intervention).
Can I prescribe an anticoagulant to a patient in the control arm?	DaRe2THINK is a pragmatic, NHS-embedded clinical trial comparing early use of DOAC therapy with standard-of-care. If your patient develops any indication for anticoagulation in the future (e.g. accumulates 2 or more CHA_2DS_2-VASc risk factors) then they can be prescribed an anticoagulant as usual. Please do not start anticoagulation in patients in the control arm if they do not meet current NICE requirements for AF. If a patient needs temporary anticoagulation (for example due to a DVT or PE), then they can receive this in the control arm as needed for the duration of their treatment. In either case, the patient can stay in the DaRe2THINK trial and **does not need to be withdrawn**. We will automatically capture use of anticoagulants through EMIS prescribing.
How does CHA_2DS_2-VASc work for women?	For women and men, the CHA_2DS_2-VASc score only modestly predicts stroke and thromboembolism; hence the need for DaRe2THINK to see if we can reduce these events by starting DOACs earlier irrespective of CHA_2DS_2-VASc score. The CHA_2DS_2-VASc risk score is particularly difficult to use in women with AF, as female gender is only associated with an elevated risk of stroke or thromboembolism **in the presence of other risk factors**. Women with a CHA_2DS_2-VASc score of 1 (one point only due to their gender) who are aged 60-65 years can be enrolled in DaRe2THINK. Women with a CHA_2DS_2-VASc score of 2 (one point for gender and one point for another factor) who are aged 60-65 years can be enrolled in DaRe2THINK if they are not already receiving anticoagulation and are not being considered for anticoagulation for their AF. Women with a CHA_2DS_2-VASc score of 3 should already be receiving anticoagulation and hence are not eligible for DaRe2THINK.

Does a history of Gestational Diabetes count as a CHA_2DS_2-VASc risk factor?	An episode of Gestational Diabetes in the past should not be taken into account when calculating a patients CHA_2DS_2-VASc risk score.
What happens to participants randomised to DOACs at the end of the study?	In the vast majority of cases, we would expect that DOACs could be continued after the five years of the trial in those patients that wish to do so. Many participants will have accumulated sufficient risk factors by the end of the study to warrant anticoagulation (including advancing age). The MHRA indication for DOACs is ***AF with one or more risk factors***, so at the end of the trial a shared decision by the GP and patient on continuing the DOAC should take place, based on the individual clinical circumstances of each patient and the broad range of risk factors (not just those in the CHA_2DS_2-VASc score). It may also be that DaRe2THINK or other studies advise this decision further – we will keep investigators apprised on any major developments in the field through the newsletter.
Could we have some clinical guidance to assist with the screening question: 'Are there any clinical indications for anticoagulation?'	This includes anything from the BNF indications for DOACs - see here - https://bnf.nice.org.uk/drugs/edoxaban/#indications-and-dose The indications are - Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation, in patients with at least one risk factor (such as congestive heart failure, hypertension, aged 75 years and over, diabetes mellitus, previous stroke or transient ischaemic attack) Treatment of deep-vein thrombosis, Prophylaxis of recurrent deep-vein thrombosis, Treatment of pulmonary embolism, Prophylaxis of recurrent pulmonary embolism Ideally this question is to exclude the likelihood of a patient (albeit unlikely) being invited into the trial and randomised who should already be on it for a compelling reason (e.g. CHA_2DS_2-VASc 2 and above or PE/DVT etc)'
Are we required to do any additional blood tests on patients Randomised to a DOAC?	DaRe2THINK is a 'pragmatic NHS-embedded' trial, and therefore practices are able to follow their standard management procedures for DOACs and long-term conditions.
Can we have one PI looking after multiple sites (for example a PCN)?	Yes, a single PI can be responsible multiple **practices** If this is the case please let the Study team know and they can set this up for you. Please note you will have to identify a Co-investigator as well.

My practice is planning to change software providers. Can I continue to take part?	Unfortunately, we may lose the ability to automatically extract data, and this may mean more work for you and your team. If your practice is planning on changing to Vision or TPP, then **please contact us** as soon as possible so we can develop a practice-specific plan.
How CPRD identifies potentially eligible patients?	In order to select potentially eligible patients to be included for GP review CPRD has created an algorithm to map the trial protocol inclusion and exclusion criteria on to the CPRD primary care database. This has involved the creation of multiple comprehensive code lists that are used in a dynamic detailed search of the primary care health records. For a patient to be deemed eligible for participation in the trial they must meet multiple complex criteria and, depending on the patient, may fall in and out of eligibility over time. There could be multiple reasons why a patient fails to meet the eligibility criteria at a specific point in time therefore it is not feasible to investigate individual patients identified using differing search criteria. The full trial protocol with inclusion and exclusion criteria can be found: For healthcare professionals - University of Birmingham A paper detailing the creation of the code lists and their application in the trial can be found here: Systematic approach to outcome assessment from coded electronic healthcare records in the DaRe2THINK NHS-embedded randomized trial - PubMed (nih.gov)
Do patients need to inform travel insurance of their participation in the clinical trial? Will participation in the clinical trial affect the travel insurance coverage and premium?	*We are pleased to inform you that the Association of British Insurers (ABI) have confirmed to the Health Research Authority that participation in clinical trials does not affect eligibility criteria for travel insurance and has now withdrawn their guidance document "Clinical research trials and insurance".* *ABI agree that taking part in a clinical trial should not affect insurance coverage if the medical condition itself doesn't. Please share the following message with your teams, organisations etc.* *'When individuals apply for travel insurance, insurers will typically ask questions about an individual's health in order to make an accurate risk assessment. This risk assessment takes into consideration the health of the individual and the insurer will often ask questions about any pre-existing health conditions and medical treatments for those conditions. Travel insurers do not typically ask about clinical research trials. Where an insurer does ask an individual about their participation in clinical research trials, the insurer must ensure the question is clear and the individual should answer it accurately and honestly''.*

	If you are aware of instances when participation in a trial is given as a reason for not providing insurance or insurance being an obstacle to participation in clinical trials, please contact ***hrapublicinvolvement@nhs.net*** We would of course recommend the patient notifies their insurer anytime their health/medication changes. In the case of DaRe2THINK, I think it's key to explain to insurers that the trial involves medication that is used widely in the NHS and is a medication these patients will be on in later life anyway.
Patients on anti-inflammatory drugs who are randomised to DOAC, do they need to stop taking DOAC?	Concomitant use of NSAIDS (especially at high doses) with DOACs can increase bleeding risk, particularly GI bleeding. Often it is not necessary to stop the DOAC, and a PPI (lansoprazole 15-30mg/day or omeprazole 20-40mg/day) can be given to reduce bleed risk as per current evidence. We suggest assessing if the patient is at "high" bleed risk based on the following: • History of peptic ulcer disease (especially in last 12 months) or two or more of the following: • Long term NSAID use • Age >65 years • Dyspepsia or GORD symptoms • Concomitant use of other medications known to increase bleeding risk (such as long-term steroid use, SSRIs, etc). • Severe co-morbidity (malignancy, CKD stage 4/5, significant liver disease, NYHA III/IV heart failure) • Heavy alcohol consumption or extensive smoking history If the patient is deemed 'high risk', you might want to consider an alternative to NSAIDs if possible or pursue management of any of the modifiable risk factors above (i.e. weaning/stopping other offending medications, prescribing a PPI, advising reduction of smoking and/or alcohol).
Where can I find answers to common patient questions about DOACs (such as drinking alcohol and taking part in sports whilst on a DOAC)?	**The NHS website has a common question section for each DOAC used within the trial. These can be found through the below links:** **Apixaban:** Common questions about apixaban - NHS **Dabigatran:** Common questions about dabigatran - NHS **Edoxaban:** Common questions about edoxaban - NHS **Rivaroxaban:** Common questions about rivaroxaban - NHS

Further helpful documents and where to find them:

Protocol – on the DaRe2THINK website

Further training or support – book a meeting with the team using the link below

https://calendly.com/dare2think/dare2think-investigator-meeting

Paper consent & SAE forms – in your site file

DaRe2THINK EMIS protocol – on EMIS Now