Oral Anticoagulation with Vitamin K Antagonists (VKAs) for Adult patients within The Oxfordshire Anticoagulation Service

1. Responsibilities	Please note that this Shared care protocol refers only to the agreement between Oxfordshire anticoagulation service and the Oxfordshire CCG. It is noted that there are some practices within Oxfordshire CCG who because of their proximity to the Berkshire border and the haematology laboratory at the Royal Berkshire Hospital, may need to refer patients to the Royal Berkshire anticoagulation service, who can be contacted at rbft.anticoagulantclinic@nhs.net'. Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. ***Anticoagulation Clinic*** • Ensure the patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly • Provide copy of patient information leaflet and anticoagulation card where appropriate • Provide INR results, dosing regime and TTR values (if calculable). • Provide the anticoagulation "dose & post service" informing patients of the dose to be taken • Action and manage raised INR results including arranging for the supply of vitamin K where appropriate. • Actively follow up any patient who does not attend (DNA) for regular monitoring within the agreed recall period. • Accepts referral from initiating clinician (primary or secondary care) • Respond to any concerns raised regarding accepting shared care • Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments • Be available to give advice to GP and patient throughout treatment • Offer virtual 'new patient clinic appointment' for enhanced counselling on warfarin therapy. • Report adverse events via the national reporting system (Yellow Card scheme).

- See patients with difficult venous access or needle phobia for point of care INRs.
- See patients who wish to purchase their own point of care machine for initial training and subsequent machine calibration/parallel testing every six months.
- Provide support and dosing advice for patients who are self-testing using a point of care machine.

GP

- Refer patients to the anticoagulation clinic (ac.referral@nhs.net) if initiating therapy (inpatients will be referred by secondary care team to the anticoagulation clinic).
- Prescribe medication either from initiation (if the referring clinician) or following request for other healthcare specialist (e.g. continuation from initiation in hospital, following transfer of existing patient on warfarin into Oxfordshire etc).
- Ensure all monitoring is completed in accordance with the specific shared care protocol.
- Check recent INRs and TTRs when issuing a repeat prescription of warfarin, but as a minimum at an annual review
- Notify the specialist to any changes in a patient's condition, any adverse drug reactions or failure to attend tests
- Report adverse events via the national reporting system (Yellow Card)
- Provide counselling on warfarin (or other vitamin K antagonist) if required.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Issue repeat prescriptions for warfarin.
- Issue repeat prescriptions for point of care testing strips for those patients who test using a point of care device.
- Inform anticoagulation clinic if situation regarding need for anticoagulation changes.
- Inform anticoagulation clinic if warfarin is stopped using EMIS 'stopping warfarin' proforma emailed to ac.service@nhs.net
- Should a patient have two encounters with the anticoagulation service terminated due to failure to comply or attend the GP practice for blood tests, discuss the ongoing suitability for warfarin and anticoagulation in general with the haematology consultant by emailing HaemostasisConsultant@ouh.nhs.uk

Patient

- Agree to treatment and monitoring after making an informed decision

	• Agree to being under the shared care of the GP and specialist • Attend for blood tests and monitoring when required • Take warfarin as directed by the anticoagulation clinic or GP. • Report any missed doses either during attendance for a blood test and/or discussion with the anticoagulation clinic. • Inform the anticoagulation clinic of any changes to medicines or medical conditions. • Report any side effects to the GP or the anticoagulation clinic. • Attend training sessions, complete a theory test, and sign a self-testers agreement prior to being signed off to self-test (applicable only to patients purchasing their own point of care device). • Attend the anticoagulation clinic for machine calibration and venous parallel testing every six months (applicable only to patients purchasing their own point of care device).
2. Background	Anticoagulant medication is used to prevent or treat thromboembolism predominantly in patients with atrial fibrillation (AF), deep vein thrombosis (DVT), pulmonary embolism (PE) and prosthetic heart valves. All anticoagulants are associated with an increased risk of bleeding and must be used with care. Treatment with warfarin is often long term and patients require regular education and monitoring for adherence and to reduce the risk of side effects. Warfarin has a narrow therapeutic index and regular titration of the dose against the anticoagulant effect, as assessed by the INR, is essential. The patient should be maintained within their therapeutic range, as deviation is associated with an increased risk of haemorrhage (if too high), or thrombosis and increased risk of stroke (if too low). Two other oral anticoagulants require INR monitoring, namely acenocoumarol (nicoumalone) and phenindione. These are occasionally used in patients who cannot tolerate warfarin. This shared care protocol will refer to warfarin only but the same principal will apply for all vitamin K antagonists. **Guidance/supporting information** NICE guidance for AF (NG 196) advises: • Offering anticoagulation to people with a CHA_2DS_2-VASc score of 2 or above, taking bleeding risk into account. Consider anticoagulation for men with a CHA_2DS_2-VASc score of 1. • Discussing the options for anticoagulation with the patient and base the choice on their clinical features and

	preferences. DOACs are the recommended first line option. If DOAC are contraindicated, not tolerated, or unsuitable, anticoagulation with a vitamin K antagonist may be used instead NICE guidance for AF (NG 196) states: • Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation. • Do not withhold anticoagulation solely because of a person's age or their risk of falls. In addition, the guidance advises that patients should have anticoagulation control with warfarin assessed by measuring the time in therapeutic range, TTR, over a maintenance period of at least 6 months. Although NICE guidance NG 196 relates to patients with AF, this shared care protocol recommends that all patients on warfarin are reviewed in a similar manner with the aim of optimising care wherever possible.
3. Indications (licensed)	• Prophylaxis of embolisation in rheumatic heart disease, atrial fibrillation or after insertion of prosthetic heart valve • Prophylaxis and treatment of DVT and PE
4. Locally agreed off-label use	n/a
5. Contraindications and cautions Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.	**Contraindications:** Contraindications include:- • Known hypersensitivity to warfarin or to any of the excipients • Haemorrhagic stroke • Clinically significant bleeding • Within 72 hours of major surgery with risk of severe bleeding • Within 48 hours postpartum • Pregnancy (first and third trimesters) • Drugs where interactions may lead to a significantly increased risk of bleeding Precautions include:- • Bacterial endocarditis (use only if warfarin otherwise indicated) • Conditions in which risk of bleeding is increased • History of gastrointestinal bleeding • Peptic ulcer

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<tr><td></td><td colspan="2">

- Postpartum (delay warfarin until risk of haemorrhage is low—usually 5–7 days after delivery)
- Recent ischaemic stroke
- Recent surgery
- Uncontrolled hypertension

Please see SPC for comprehensive information.
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<tr><td>6. Initiation and ongoing dose regime

Note -
•Transfer of monitoring and prescribing to primary care is normally after the patient's dose has been optimised and with satisfactory investigation results for at least 4 weeks
•The duration of treatment & frequency of review will be determined by the specialist, based on clinical response and tolerability.
•All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician
•Termination of treatment will be the responsibility of the specialist.</td><td colspan="2"><u>Initial stabilisation:</u> this is dependent on indication for VKA and point of therapy (new or continuation).

<u>Maintenance dose (following initial stabilisation):</u> dictated by INR and target range.

<u>Conditions requiring dose adjustment:</u> in general, patients of older age, lower body weight, and those with heart failure or frail are usually more sensitive to warfarin.</td></tr>
<tr><td rowspan="4">7. Pharmaceutical aspects</td><td>Route of administration:</td><td>Oral</td></tr>
<tr><td>Formulation:</td><td>Tablets (standard 1mg, 3mg and 5mg. Those particularly sensitive to warfarin may need to be managed on 0.5mg tablets)</td></tr>
<tr><td>Administration details:</td><td></td></tr>
<tr><td>Other important information:</td><td>Dosage

The usual target INR is 2.5 (target range 2-3). Occasionally a higher target INR e.g. 3.5 (target range 3-4) is indicated. Tighter target ranges (e.g. 2-2.5) are not feasible and overall they do not appear to improve anticoagulant control.

Time to Response

When adjusting doses it should be borne in mind that it takes up to a week for the full effect of any dose change to be seen.</td></tr>
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8. Significant medicine interactions For a comprehensive list consult the BNF or Summary of Product Characteristics. SPC	**The following list is not exhaustive; please see SPC for comprehensive information and recommended management.** Warfarin has a narrow therapeutic range and is well known to interact with a large range of drugs and foods; therefore care is required with all concomitant therapy and ***increased monitoring on starting and stopping medicines is advised 2-3 days after the change in therapy.*** <u>Medicines that increase bleeding risk</u> The following medicines should be avoided, or prescribed with caution to patients taking warfarin. Increased clinical and laboratory monitoring may be required: • DOACs (concomitant therapy is contraindicated except when switching from a DOAC to warfarin) • Antiplatelets • NSAIDs (including aspirin and cox-2 specific NSAIDS) • Dipyridamole • Unfractionated heparins and heparin derivatives, low molecular weight heparins • Prostacyclin • SSRI and SNRI antidepressants • Herbal remedies such as omega 3 fish oils and tumeric Specialists may occasionally recommend one antiplatelet agent such as low-dose aspirin or clopidogrel with anticoagulation. There are instances whereby short term dual antiplatelet therapy (usually aspirin and clopidogrel) are indicated in addition to anticoagulation. This will be a specialist decision and in all cases GPs should receive clear information on duration by the specialists. If this information is not available, GPs should follow this up with the specialists. During the initial treatment of acute VTE, warfarin will be given with a heparin until the INR is in the correct range. Patients on warfarin may also require a heparin for various reasons such as pre & post-operative bridging. <u>Metabolic interactions:-</u> Warfarin is metabolised by different CYP P450 cytochromes. Drugs which inhibit or induce these metabolic pathways may affect warfarin plasma concentrations. In these cases increased monitoring on starting and stopping therapy is advised.

Listed below are some drugs which are known to interact with warfarin in a clinically significant way. Please consult the latest BNF and the SPC for full details of potential interactions.

Examples of drugs which potentiate the effect of warfarin
allopurinol, capecitabine, erlotinib, disulfiram, azole antifungals (for example ketoconazole, fluconazole, and miconazole (including oral gel and possibly vaginal and topical formulations)) omeprazole, paracetamol (prolonged regular use), propafenone, amiodarone, tamoxifen, methylphenidate zafirlukast, fibrates, statins (not pravastatin; predominantly associated with fluvastatin) erythromycin, sulfamethoxazole, metronidazole
Examples of drugs which antagonise the effect of warfarin
Barbiturates, primidone, carbamazepine, griseofulvin, oral contraceptives, rifampicin, azathioprine, phenytoin
Examples of drugs with variable effect
Corticosteroids, nevirapine, ritonavir

9. Baseline investigations, initial monitoring and ongoing monitoring to be undertaken by specialist

Baseline investigations:

If initiated in primary care (e.g. for AF), GP to arrange baseline bloods including full blood count (FBC), coagulation screen (including INR) U&Es and LFTs before referral and patient commencing treatment on warfarin.

AF: The decision about which anticoagulation therapy to start (whether to start treatment with warfarin or a direct oral anticoagulant (DOAC)), should be made after an informed discussion between the GP and the patient about the relative risks and benefits of each agent. For guidance on prescribing DOACs please see 'Primary Care Prescriber Decision Support for Direct Oral Anticoagulants 'DOACs' for Stroke Prevention in Atrial Fibrillation'. GPs should also consider the suitability of on-going monitoring arrangements for each patient. If warfarin is the anticoagulation therapy of choice, GPs should obtain baseline bloods then prescribe 1mg, 3mg, and 5mg tablets of warfarin and inform the patient **NOT** to start taking warfarin until they are contacted by the Anticoagulation Clinic with a dose. All new patients must be referred to the Anticoagulation Clinic to initiate remote postal dosing, as soon as possible after initiating warfarin. Referral forms

	can be found on EMIS or on Clinox and should be sent via email to ac.referral@nhs.net. If initiated in secondary care (e.g. post mechanical heart valve), baseline bloods (as above) to be carried in by responsible team before commencing treatment with warfarin. **Ongoing monitoring:** The Oxford Anticoagulation Service operates a "dose & post" service for most GP surgeries in Oxfordshire. The Service operates 9am – 5pm, Monday to Friday (excluding Bank Holidays). The OUH is responsible for daily dosing of patients under the OUH warfarin service. For patients who are particularly poorly controlled, the OUH telephones the patient to check for recent illness, new interacting medications and adherence. As per 2007 NPSA Alert 18 (http://www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/anticoagulant/) (section 5 on page 5): it is the responsibility of the prescriber supplying the repeat prescription, in this case the GP, to ensure that the warfarin is indicated, and that anticoagulation control overall is safe and reviewed as to effectiveness: *"In many cases, the healthcare professional who issues repeat prescriptions for anticoagulants, for example the general practitioner, is not the same practitioner who monitors and adjusts the dosage of the therapy, for example the anticoagulant clinic practitioner. It is for the prescriber supplying the repeat prescription to ensure that it is safe to do so. Repeat prescriptions of anticoagulants should only be issued if the prescriber has checked that the patient is regularly attending the anticoagulant clinic, that the INR test result is within safe limits, and that the patient understands what dose to administer. Reviewing the patient-held record when the repeat prescription is requested, and discussing the anticoagulant treatment at this time, is one method of doing this".*

10. Ongoing monitoring requirements to be undertaken by primary care. See section 10 for further guidance on management of adverse effects/ responding to monitoring results.	Monitoring	Frequency
	The time in therapeutic range (TTR) is an effective way of establishing the quality of anticoagulation control over at least a 6 month timeframe and is an important predictor of bleeding and thrombosis. TTR will be provided with each INR result (if calculable) to help assess anticoagulant control for	Minimum annually

	all patients under OUH warfarin service. GPs are therefore advised to check recent INRs and TTRs when issuing a repeat prescription of warfarin, but as a minimum at an annual review Anticoagulation should be reassessed for a person with poor anticoagulation control ***shown by any*** of the following: • Two INR values > 5, or one INR value > 8 within the past 6 months • Two INR values < 1.5 within the past 6 months TTR less than 65% (calculated over a maintenance period of at least 6 months).***Actions for GP to take when anticoagulation control is poor:*** Anticoagulation should be reassessed taking into account and if possible addressing: • Patient education • Cognitive function • Adherence to prescribed therapy • Illness • Interacting drug therapy • Lifestyle factors including diet and alcohol consumption If poor anticoagulation control on warfarin cannot be improved, and is not due to poor adherence, evaluate and discuss the risks and benefits of a DOAC. Note that whilst DOACs are licensed for stroke	

	prevention in non-valvular AF and for secondary prevention of VTE, they are contraindicated for patients with metallic heart valves. DOACs should not be prescribed for patients with triple positive antiphospholipid syndrome or for any patients requiring warfarin with a higher INR range than the standard 2-3. For guidance on prescribing DOACs please see Primary Care Prescriber Decision Support for Direct Oral Anticoagulants for Stroke Prevention in Atrial Fibrillation or Direct Oral Anticoagulants for Treatment and Secondary Prevention of Deep Vein Thrombosis and Pulmonary Embolism in Primary Care.	
11. Adverse effects and managements **Any serious adverse reactions should be reported to the MHRA via the Yellow Card scheme** www.mhra.gov.uk/yellowcard	Result	Action
	INR above target range	Anticoagulation service to action by reducing dose of warfarin, temporarily holding warfarin and/or supplying vitamin K for reversal.
	TTR less than 65%	GP to review and discuss with patient to optimise anticoagulation.
12. Advice to patients and carers The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.	**The patient should be advised to report any of the following signs or symptoms to their GP without delay:** • Blood in your vomit or sputum • Passing blood when you go to the toilet • Passing black coloured faeces • Less severe bleeding (e.g. nosebleeds which stop easily after one or two minutes) • Severe or spontaneous bruising **Pre-operative assessment**	

	Patients due for elective procedures in OUH are usually assessed in Pre-operative Assessment Clinic (POAC). At this appointment their anticoagulation should be discussed and the patient should be advised when to stop their warfarin prior to procedure. POAC should notify the anticoagulation team or inform the patient to notify the anticoagulation team of upcoming procedures, the desired INR prior to the procedure, and of any other instructions. Some patients may require pre-operative bridging, and the responsibility for prescribing dalteparin pre-operatively belongs to the department carrying out the procedure.
13. Pregnancy, paternal exposure and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review but the ongoing responsibility for providing this advice rests with both the GP and the specialist.	**Pregnancy:** • Based on clinical experience warfarin causes congenital malformations and foetal death when administered during pregnancy. • Warfarin is contraindicated in pregnancy in the first and third trimester. • Women of child-bearing age who are taking warfarin tablets should use effective contraception during treatment. • Women who become pregnant on warfarin should be switched to a LMWH immediately and referred to the Silver Star Service at OUH. **Breastfeeding:** • Warfarin is excreted in breast milk in small amounts. However, at therapeutic doses of warfarin no effects on the breast-feeding child are anticipated. Warfarin can be used during breast-feeding.
14. Specialist contact information	Role and specialty: OUH Anticoagulation & Thrombosis Team Daytime telephone number: 01865 857555 Email address: ac.service@nhs.net Alternative contact: OUH Anticoagulation Optimisation Support Service doacsupport.ox@nhs.net Out of hours contact details: Haematology Registrar on call via switchboard
15. Additional information	Where patient care is transferred from one specialist service or GP practice to another, a new shared care agreement must be completed.

16. References	1. American College of Cardiology, Atrial fibrillation toolkit http://www.acc.org/tools-and-practice-support/clinical-toolkits/atrial-fibrillation-afib 2. British National Formulary (BNF online). Last updated 09/07/2021. https://bnf.nice.org.uk/ 3. Summary of Product Characteristics (SPC) for warfarin 0.5mg, last updated on eMC 11/04/2018, accessed via https://www.medicines.org.uk/emc/ 4. NPSA Alert 18, Actions that can make anticoagulant therapy safer - Patient Safety Alert - 2007-03-28-V1http://www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/anticoagulant/ 5. Medicine Information Leaflet - Initiating oral anticoagulation with vitamin K antagonists (VKA) in adult patients Volume 5, No. 8. Oxford University Hospitals NHS Foundation Trust. 6. Atrial fibrillation: diagnosis and management. NICE guidelines [NG196]. Published: 27 April 2021 Last updated: 30 June 2021. Accessed 10/8/2021 7. Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. NICE guideline [NG158] Published: 26 March 2020. Accessed 10/8/2021
17. To be read in conjunction with the following documents	• RMOC Shared Care Guidance • NHSE/NHSCC guidance – items which should not be routinely prescribed in primary care: guidance for CCGs • NHSE policy- Responsibility for prescribing between Primary & Secondary/Tertiary Care
18. Local arrangements for referral Define the referral procedure from hospital to primary care prescriber & route of return should the patient's condition change.	See responsibilities above