SIGN Prevention and management of venous thromboembolism in COVID-19

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Invited reviewers			**Type of response and declared interests**
AO'P	Ms Alison O'Prey	Specialist Pharmacist Critical Care and Major Trauma, Queen Elizabeth University Hospital	*Individual response.* *Non-financial personal interests* – planning to undertake research to investigate what is optimal venous thromboembolism (VTE) prophylaxis regimen for non-COVID critically ill patients.
GMcP	Mr Gordon McPherson	Person with lived experience or caring experience	*Individual response.* Nothing declared.
HH	Mr Harry Hall	Person with lived experience or caring experience	*Individual response.* Nothing declared.
JH	Ms Joanna Hutchison	Lead Respiratory Pharmacist, Royal Infirmary of Edinburgh	*Individual response.* Nothing declared.
MK	Dr Mohammed Khan	Consultant Haematologist, Aberdeen Royal Infirmary	*Individual response.* Nothing declared.
RW	Ms Rosemary Wilkie	Person with lived experience or caring experience	*Individual response.* Nothing declared.
RCGP		Dr Gail Allsopp, Clinical Policy Lead – submitting comments on behalf of the Royal College of General Practitioners	*Group response.* *Nature and purpose of your group or organisation* –

			charity supporting GPs. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity* - the Guidance is applicable to all GPs and primary care teams. If there are changes to current pathways we would consider creating e learning and rapid educational updates for our 53,000 members to help disseminate the guidance.
RR	Dr Ryan Rodgers	Consultant Haematologist, Glasgow Royal Infirmary	*Individual response.* *Personal financial interests* – not relating to this topic. Bleeding disorders – speaker fees, advisory board, funding to attend Takeda, Roche, NovoNordisk, Sobi and Bayer meetings.
SC	Ms Sarah Connelly	Principal Pharmacist (Clinical Services), University Hospital Monklands, Airdrie	*Individual response.* Nothing declared.
TC	Dr Thomas Craven	Consultant in Critical Care, Royal Infirmary of Edinburgh	*Individual response.* Nothing declared.
Open consultation			**Type of response and declared interests**
AC	Ms Angela Cunningham	Midwifery Clinical Lead, Maternity and Children Quality Improvement Collaborative, Healthcare Improvement Scotland	*Individual response.* Nothing declared.
CMacL	Dr Catherine MacLean	Consultant in Acute Medicine, NHS Forth Valley	*Individual response.* Nothing declared.
DW	Professor David Wilson	Personal Chair of Paediatric Gastroenterology and Nutrition, Child Life and Health, Centre for Inflammation Research, University of Edinburgh	*Individual response.* Nothing declared (emailed response).
JS	Dr Jeyakumar	Consultant Physician and Lead for VTE, Forth Valley Royal	*Individual response.*

	Selwyn	Hospital, Larbert	Nothing declared.
NHSGGC TC		NHS Greater Glasgow and Clyde Thrombosis Committee	*Group response.* *Nature and purpose of your group or organisation* – The NHSGGC Thrombosis Committee is a committee of multidisciplinary representatives from cross sector and cross speciality in the Greater Glasgow and Clyde health board, whose purpose is to develop, support and audit best practice for the prevention, diagnosis and management of VTE. The views put forward in this questionnaire are a collective response of the whole committee who attended the NHSGGC Thrombosis Committee on 17 September where this guideline was discussed (31 attendees) and the response written in this questionnaire was ratified by 15 members of the committee, excluding the Chair, and there were no objections. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity* – the NHSGGC thrombosis committee agree with the recommendation to consider therapeutic dose low molecular weight heparin (LMWH) for prevention of VTE in hospitalised patients with moderate COVID disease as defined in the guideline. However, this recommendation for patients with moderate and severe COVID-19 infection will be a significant clinical governance issue for our health board, which will require the development of a number of risk mitigation strategies.
PH	Dr Philip Hodkinson	Associate Medical Director, NHS Ayrshire and Arran	*Individual response.* Nothing declared.
RCPE		Dr Sue Pound, Vice President – submitting comments on	*Group response.*

		behalf of the Royal College of Physicians, Edinburgh	*Nature and purpose of your group or organisation* – Medical Royal College. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity* – no response.
RCP&S		Mr Richard Hull, Honorary Secretary – submitting comments on behalf of the Royal College of Physicians and Surgeons of Glasgow	*Group response.* *Nature and purpose of your group or organisation* - membership of healthcare professionals. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity* - the college support the need for a guideline and our reviewers considered it a well-balanced document.
SG		Ms Laura Boyce, Professional Advisor for Midwifery and Perinatal Care – submitting comments on behalf of The Scottish Government	*Group response.* *Nature and purpose of your group or organisation* - Scottish Government advisors. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity* - the guidance will have no impact on the function of my organisation but it may subsequently impact commissioned pieces of work for the future.
SW	Dr Simon Watson	Medical Director, Healthcare Improvement Scotland	*Individual response.* Nothing declared (emailed response).

Section		Comments received	Development group response	Editorial response
General				
	SW	Main comment is that a lot of it seems to overlap with standard recommendations for VTE. You have to read quite a lot of what looks like standard VTE guidance to spot the bits where COVID-19 really does necessitate doing something different. Might it be possible to produce something much more focussed that complements existing VTE guidelines by highlighting where COVID-19 really does present a 'special case' requiring different guidance. That might be a good model for rapid guidance anyway – ie build upon what we have with 'exceptions'?	The guideline key questions reflect areas of clinical uncertainty, so the recommendations for management along existing pathways are helpful learning. Where no specific advice was identified for management in the context of COVID-19, the guideline development group (GDG) noted this and reflected established advice on prevention and management of VTE. The GDG considered that a document containing only 'exception recommendations' may not be suitable for a wide multidisciplinary audience as it assumes that all users of such a guideline would be aware of all default existing national recommendations on VTE for people without COVID-19. However, we have collected the recommendations which represent the most divergence from standard practice in VTE management into the 'key recommendations' section.	
	DW	As a paediatrician, I note that all patients under 16 years of age are excluded; this group has a much lower risk of VTE in the community or when infected with COVID. Response - a very comprehensive guideline on which I have no comments.	Noted. Thank you.	
Section 1				
1.1	PH	I agree we need a guideline.	Noted. Thank you.	
	JS	Very clearly defined the need and happy with this. Being a stroke physician, I have personally seen patients with COVID-19 infection with no risk factors	Noted. Thank you.	

		at all. Young and fit with stroke disability, disheartening to see. We regularly audit /quality improvement projects (QIP) to see the prescription of LMWH in medical patients and COVID -19 (moderate) patients. It was poor among medical and getting better. COVID-19 patients - it is so good! It is an ongoing QIP in Forth Valley Royal Hospital (FVRH).		
	MK	Agree.	Noted. Thank you.	
	RCGP	Completely agree for the need for this guidance. From a primary care perspective, many questions are asked regarding community patients who take to bed with COVID-19 and whether prophylaxis is required.	Noted. Thank you.	
	RCP&S	The college support the need for a guideline and our reviewers considered it a well-balanced document.	Noted. Thank you.	
	AC	I agree a guideline is required.	Noted. Thank you.	
	RCPE	The college notes that this is an area of practice with scant good quality evidence, which therefore leaves decision making to the personal judgement of clinicians. This draft guideline presents a reasonable synopsis, however College Fellows have noted that the 'Key Recommendations' section is yet to be completed in this draft. To fully comment on the utility of the guideline to a busy frontline clinician, it is essential to see the key recommendations as this will be the most referred to section in the guideline.	Noted. Thank you. This section was completed once the recommendations were finalised and it is included in the published version.	
	AO'P	The need for this guideline is very clearly defined and the introduction clearly highlights the potential consequences for patients if VTE prevention is not managed appropriately. Also very well written, easy to navigate and a good flow through the sub topics.	Noted. Thank you.	
	RW	Some of the terminology used would be too scientific for non-medical professionals. Patients and carers would need a simplified version,	Agreed. As this is a rapid guideline which does not include a full pathway of care, we will not be following the process used in standard SIGN	

		which is clear and concise, without advanced medical terminology.	guidelines, ie developing a complete patient booklet after the guideline publication (the guideline may be withdrawn more quickly than standard SIGN guidelines). We will develop and publish a summary of the key messages for patients at the same time as the clinical guideline publication.	
	RR	Good overview and is clear that there is still facts that we don't know about the pathophysiology of thrombosis in COVID. It highlights the important need for such a guideline and that evidence is continually being published.	Noted. Thank you.	
1.2.1	PH	Correct remit.	Noted. Thank you.	
	SG	It states this doesn't cover COVID-19 in pregnancy why is this not inclusive of pregnancy – VTE is the biggest cause of maternal mortality If it will not be reconsidered for inclusion can it clearly state they advise that 'this should not delay treatment and liaison with multi-professional team is imperative'. We would like to see signposting to the maternal critical care COVID-19 position statement as previously issued by SIGN and Royal College of Obstetricians and Gynaecologists (RCOG) guidance for this cohort as a standalone paragraph if not included in the main guidance.	The remit of this rapid guideline reflects the four areas of greatest clinical uncertainty during the COVID-19 pandemic, rather than a comprehensive overview of recommendations for this subject. Prevention and management of VTE in pregnancy during COVID-19 was not included in the guideline because of: lack of evidence, availability of other specialist guidance, for example, the SIGN maternal critical care guidance and the RCOG guideline on Coronavirus in Pregnancy and that the pregnant group represents a small proportion of overall at-risk population. We have added hyperlinks to the existing specialist guidance for this group.	
	JS	I am the PI for the RECOVERY Trail in FVRH and I see the most sickest patients in Acute Assessment Unit (AAU) and not in intensive care unit (ICU)! This objective is very unambiguous.	No change required.	
	MK	Agree.	Noted. Thank you.	
	RCGP	Excellent summary and very pleased to see community care included as this is often forgotten in COVID guidance.	Noted. Thank you.	
	AC	Concerned over the limitation of objectives as it does not cover all “adults" in Scotland.	See above for comment about pregnancy. The guideline text has been changed to “non-pregnant	

			adults" for clarity.	
	RW	Appropriate but written from the perspective of care providers from professional medical sector.	Noted. Thank you.	
	RR	Clear explanation of objectives and highlights guideline not specific to diagnosis.	Noted. Thank you.	
1.2.2	PH	No issues with the target.	Noted. Thank you.	
	JS	No concern at all.	Noted. Thank you.	
	MK	Agree.	Noted. Thank you.	
	RCGP	Agree. No comments.	Noted. Thank you.	
	RCP&S	The evidence base is fairly limited and we should largely follow the guidelines for prophylaxis and treatment of VTE in other higher risk groups.	Noted. Thank you.	
	AC	Agree.	Noted. Thank you.	
	RW	Medical professionals - yes. Not suitable for patients and carers. A simpler, much shorter booklet with the main facts around risk, treatment and aftercare is appropriate.	Agreed – see response to comment from RW in section 1.1	
	RR	List of users is appropriate but for in particular list it should be all general physicians rather than just critical care as patients may deteriorate while inpatients.	Agreed – changed to "physicians in primary and secondary care".	
	HH	As patients and carers are also target users, it would be helpful to have a short summary of the salient points in a simpler form that would be readily understood by non-medical readers.	Agreed – see response to comment from RW in section 1.1	
1.3	PH	No issues.	Noted. Thank you.	
	JS	Very clear and explanatory.	Noted. Thank you.	
	MK	Agree.	Noted. Thank you.	
	RCGP	The clinic diagnosis of COVID-19 can be made based on symptoms alone and since there is still a significant false negative result with PCR testing, we would ask that clinical diagnosis also include the	Agreed – We have revised the wording here to reflect the common symptoms (clinical case definition) of COVID-19 and linked to NHS Inform.	

		typical symptoms described by our Public Health England (PHE) colleagues and not limit the diagnosis to hospitalised patients with abnormal blood tests and X-ray. If the guidance I to include community care patients, the definitions used in the guidance should ideally also include those clinically diagnosed in the community.	A negative PCR result is very likely to reflect non-infectivity.	
	AC	Agree.	Noted. Thank you.	
	AO'P	It could be useful to define moderate and critical or severe COVID-19 disease at this point rather than later in the document.	Agreed. The definitions in section 4.1 have been copied to here.	
	RW	Fine.	Noted. Thank you.	
	RR	Happy with definitions.	Noted. Thank you.	
Section 3				
General	PH	No additional comments.	Noted. Thank you.	
	SG	We would like the inclusion of maternity/pregnant community in this section or signposting to the appropriate guidance for RCOG/maternity critical care guidance recognising the increased need for community surveillance in this population group with already increased risk of VTE.	Agreed – see response to comment from SG in section 1.2.1	
	JS	Very difficult unless patients seek the help of a practice. We have to increase the public awareness to let the clinician to be aware. We only see the patient admitted with shortness of breath (SOB) and requiring oxygen. There are many numbers confined to bed at home due to COVID-19 and high risk of VTE. This guideline will increasing the awareness among clinician and it has to be published well.	Noted. Thank you.	
	MK	Agree - need to await data from ongoing trials before recommendations can be made for patients in	Noted. Thank you.	

		primary care.		
	TC	Not best place to review.	Noted. Thank you.	
	AC	Excludes pregnant women, who are particularly susceptible to COVID-19 at this time due to the lag time in confirming vaccines as safe. Also due to miss information on social media.	Agreed – see response to comment from RW in section 1.1	
	RW	I personally don't feel reassured by this statement. As someone with a strong family history, I would not like to be further down the line of high risk patients who have heart valve issues etc. As a lay person I would like it recognised that all hospitalised patients are at risk of VTE, the stats are known, and more so for certain groups of people beyond heart patients. It is quite obvious to me that patients with moderate lung affected COVID would struggle with a pulmonary embolism (PE), but that would surely be the case for all moderate lung problems, outwith COVID-19. If this is the thinking for COVID-19, it might be useful to be rolled out in all respiratory patients.	Noted. There are many risk factors for thrombosis and a comprehensive listing is not possible. Noted. This section refers to individuals who are not in hospital. The first sentence of section 4 expresses the risks of VTE in hospitalised patients. We have revised the text to: "The most commonly identified indications for ***pharmaceutical prevention of thrombotic events in the community*** are non-valvular atrial fibrillation and ***mechanical*** heart valve ***replacement***."	
	RR	The indications of non-valvular atrial fibrillation (AF) and heart valve transplant are not for VTE prophylaxis. They are anticoagulated to prevent arterial stroke. They are the most common indication for thrombotic anticoagulation but not VTE.	Agreed. See above	
3.1	PH	Accurate - no issues.	Noted. Thank you.	
	GMcP	I note family history is not considered here as a risk factor although it is later in the draft guideline.	This information reflects the design of the study cited here, rather than a comprehensive listing of known risk factors. We did not identify a reference to family history later in the guideline.	
	JS	Very clear.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	TC	Not best place to review.	Noted. Thank you.	
	AC	Pregnancy excluded though high risk for this group.	Noted – see response to comment from RW in	

			section 1.1	
	RW	Glossing over the family history risk, just because it was not included in this one study is rather foolish and downright dangerous. If one study does not cover other angles, then refer to another. Family history, previous medical history and other mitigating factors could be included - such as pregnancy, recent surgery, recent long haul flights etc. For a paper focussing on VTE, I feel a broader look at VTE risk would be safer for patients.	Noted. A comment that other risk factors exist has been added.	
	RR	Agree with the stated risk factors. I'm not clear how often the thrombosis calculator is used in clinical practice though. Important to stress that other patient factors, e.g. bleeding risk, co-morbidities, is stressed.	Agreed – see above	
	HH	The small number of patients with family history of VTE recorded could be partly due to this information, although well known, not being placed on their file. I know also, from the bitter experience of loss, that this question is not always asked at the point of diagnosis and is even more important in these current COVID times.	Noted. Thank you.	
3.1.1	PH	Accurate – no issues.	Noted. Thank you.	
	JS	Self explanatory.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	TC	Not best place to review.	Noted. Thank you.	
	RW	This is aimed more at patients re: lifestyle and work behaviours. Good practice for patients and carers to instil less VTE risk on an ongoing basis. Risk factors from obesity and immobility will be well known to medical professionals.	Noted. Thank you.	
	RR	Happy with additional risk factors.	Noted. Thank you.	
3.2	PH	No additional comments.	Noted. Thank you.	
	JS	Should be considered if they are confined to bed.	Noted – no evidence was identified on this. We	

		I have come across three stroke patients with COVID-19 with no risk factors. It is all likely due to COVID-19 and no doubt.	note that patients who are confined to bed are likely to be frail and have additional comorbidities which may also influence COVID outcomes. SIGN 122 notes immobility to be a risk factor for VTE, therefore the guideline notes “Where there may be clinical concern, primary care practitioners should seek advice from their local specialist team.” This can facilitate a more comprehensive risk assessment, which would consider a range of factors, including mobility.	
	MK	Agree.	Noted. Thank you.	
	RCGP	We welcome the clarity, with the addition of clinical judgement and advice from experts.	Noted. Thank you.	
	TC	Not best place to review.	Noted. Thank you.	
	RCP&S	Pharmacological prophylaxis against VTE in COVID-19 patients should not be “routine” in the community. Existing indications such as atrial fibrillation or valve replacement are appropriate.	Noted. Thank you.	
	NHSG GC TC	The committee would like clarification in the guidelines whether recommendations made for VTE prevention in patients with COVID-19 who are managed in the community, also applies to those patients who attend emergency or acute receiving units and are discharged without admission.	Thank you – we are not aware of evidence that patients presenting to ED or medical assessment unit, and subsequently not admitted, are at different levels of risk from patients in the wider community setting. The advice in this section to not “routinely” prescribe anticoagulation for individuals in community settings would therefore apply equally to these groups.	
	RW	This seems reasonable. Given that blood thinning medication also carries risks, it is good to assume all COVID patients would not receive this, and only those with additional risk factors should be given consideration for treatment.	Noted. Thank you.	
	RR	Agreed that thromboprophylaxis should not routinely be considered in the community but additional risk factors should be considered.	Noted. Thank you.	
Section 4				

General	PH	No overall concerns. Clear section.	Noted. Thank you.	
	SG	Propose the addition of recognising that pregnant women with COVID-19 are at increased risk of morbidities, particularly in the third trimester of pregnancy and as such any pregnant woman admitted should have her ongoing care/treatment planning discussed as part of a multi professional team with her obstetric/anaesthetic team involvement.	Noted. Information on the increased risks associated with pregnancy compared with non-pregnant women with COVID-19 has been added. Pregnant women admitted to hospital will be eligible for the recommendations in this section. Care of hospitalised pregnant women with COVID-19 is described in more detail in the RCOG guideline which has been hyperlinked in this section.	
	JS	Very clear.	Noted. Thank you.	
	MK	Comprehensive review of the available data.	Noted. Thank you.	
	RCP&S	Prophylaxis against VTE in COVID-19 patients should be “routine” for those who are hospitalised.	Agreed – this is stated in section 4, para 4	
	AC	Pregnancy not included though this group at high risk, no sign posting to other resources i.e. RCOG or indeed SIGN Maternal Critical Care Guideline.	Agreed – see above	
	AO’P	'More recent case series have reported a trend for lower incidence of VTE (7–14%) in ICU settings'.17-20 - I think this statement is a bit unclear, a lower incidence than compared to what? Non-ICU patients or just lower than previously reported?	Agreed – we will clarify wording to show that the comparison is with the meta-analyses reporting higher rates of VTE, from the first wave at a time when some ICU treatments were not available.	
	RW	I'm interested to know how this compares with general stats for VTE in patients. Are COVID patients at same or greater risk than all patients in critical or ICU? The study doesn't differentiate. I think the more interesting statement is that VTE is a serious issue for all inpatients. What role do compression stockings play? Are all patients wearing them or only the ICU patients?	Not known. This was not searched for in this guideline which relates to COVID-19 patients only. Not in the remit of this guideline. Mechanical prophylaxis methods do not have a role in the management of medical inpatients, unless there are contraindications to drug therapies. Section 1.2.1 has been revised to: “This guideline provides recommendations based on current evidence for best practice in the *pharmacological* prophylaxis and management of	

			thrombotic complications of COVID-19."	
	RR	Clearly describes the increased risk of VTE in patients requiring ICU. Introduces the potential need for higher doses of prophylactic anticoagulation.	Noted. Thank you.	
4.1	PH	Ok with this.	Noted. Thank you.	
	SC	I think the first paragraph could be worded more clearly to demonstrate that each of the drugs should be adjusted to account for patients' weight and renal function. Enoxaparin can now be used at a dose of 1 mg/kg twice daily for treatment of patients with VTE with a risk factor.	Agreed – the text has been revised to: "Prophylactic-dose anticoagulation in medical patients is considered to include any of the following regimens: unfractionated heparin (UFH) 5,000 units every 8–12 hours, enoxaparin 40 mg once daily, dalteparin 5,000 units every 24 hours, or fondaparinux 2.5 mg once daily. ***All of these medications require doses adjustment to account for patients' weight and renal function.*** The additional treatment dose of enoxaparin has been added, in line with BNF advice.	
	JS	Happy with this.	Noted. Thank you.	
	MK	The authors may wish to include Dalteparin 200 u/kg when discussing the various regimens for therapeutic anticoagulation.	Agreed – this has been revised to: "Therapeutic-dose anticoagulation is considered as the dose used to treat acute venous thrombosis and would include any of the following regimens: […] dalteparin 200 units/kg once daily (banded dosing – see British National Formulary[10] or local protocols), …"	
	TC	I am not familiar with the following modality of organ support: ≥20 L/min invasive or non-invasive ventilation This could be simplified to invasive or non-invasive ventilation. Non-invasive ventilation does not include continuous positive airway pressure (CPAP) which I recommend is listed separately for clarity.	Noted. No change. While we agree that CPAP often sits outwith the classification of non-invasive ventilation, these definitions of respiratory or cardiovascular organ support are derived from the studies used in support of this section of the guideline and are retained verbatim to align the recommendation to this evidence.	

	AO'P	Enoxaparin 1 mg/kg twice daily should be included in the therapeutic definitions -it is a licensed dose for treatment of VTE in patients with additional risk factors It's also unclear where high dependency patients will fall in terms of moderate or severe or critical COVID-19 disease, many of these patients will be on some form of organ support and fall into the definition of critical or severe but some patients may not but will still be unwell enough to require critical care. For the definition should it be critical care level respiratory or cardiovascular organ support rather than ICU level? High flow and vasopressors can be offered in high dependency.	Agreed – see response to comment from SC above. Agreed. However, these definitions were derived from the mpRCT protocols, in order to allow the recommendations to be applied directly based on this evidence. "ICU-level" has been changed to "critical care-level"	
	RW	Of no interest to patients and carers. Medical professionals only.	Noted. Thank you.	
	RR	Treatment dose of Dalteparin is 200 units/kg not 150. Is there a low risk group - patients at home OR patients in hospital with another condition who are found to have COVID on hospital screening?	Agreed – see response to comment from MK above. Individuals who are found to have COVID-19 on hospital screening are at lower risk of VTE than those admitted with a diagnosis of COVID-19, although there are no data to measure risk of VTE in patients with COVID-19 in the community. (see Ho FK, Man KKC, Toshner M, Church C, Celis-Morales C, Wong ICK, et al. Thromboembolic Risk in Hospitalized and Nonhospitalized COVID-19 Patients: A Self-Controlled Case Series Analysis of a Nationwide Cohort. Mayo Clin Proc. 2021 Oct;96(10):2587-2597.) AI hospitalised patients will be offered standard pharmacological thromboprophylaxis on receipt of positive COVID-19 screening result.	
4.2	PH	Agree with this.	Noted. Thank you.	
	JS	No ambiguity.	Noted. Thank you.	
	MK	Liver disease with INR >2 - this could be considered a caution as opposed to a contraindication.	Agreed – this has been designated as a caution.	

		Coagulopathy of liver disease is complex and there is not only an increased bleeding risk in these patients but they are also at increased thrombosis risk, due to depletion of naturally anticoagulants.		
	AO'P	Trauma with a high bleed risk isn't always a contraindication particularly if it is a major trauma patient since their VTE risk may still be higher than their risk of bleeding. What is the definition of 'recent' in terms of intracranial bleeding?	Noted, thank you. However, the BNF notes major trauma with high bleeding risk as a contraindication, so we have clarified this further in this guideline. We are not aware of any definition - clinical judgement is implied, but the BNF specifies "recent cerebral haemorrhage".	
	RW	As above.	Noted. Thank you.	
	RR	Does within 12 hours of procedure relate to both before and after procedure? - routinely give prophylactic dose LMWH 6 hours post-surgery. - if on treatment dose wouldn't want to procedure until 24 hours after.	Each heparin has distinct pharmacokinetics and cannot be used interchangeably with other heparins. We have added a sentence to advise users to refer to the summary of product characteristics for specific advice on appropriate timing of administration.	
4.3.1	PH	Seems reasonable based on evidence.	Noted. Thank you.	
	JS	Clear.	Noted. Thank you.	
	JH	Lack of information about dosing in extremes of weight. Obesity is known risk factor for both COVID-19 complications and VTE. Some of the trials referred to (eg. ref 30) have different dosing schedules based on weight which is what is routinely seen in practice although off-label. The guidance in renal failure is very specific while comparatively there is little on dosing in obesity.	The guideline notes in section 4.1 that several heparins require dose adjustment to account for patients' weight and renal function. This is achieved by board-level protocols. The information about renal failure in section 4.3.2 is more specific as it reflects the additional complications resulting from dose adjustment when using LMWH in patients with abnormal renal function which can be avoided by using UFH. UFH is not cleared via renal excretion. This difference does not apply to individuals at extremes of body weight.	
	MK	Nil to add.	Noted. Thank you.	
	TC	The two systematic reviews are old. Are there any	The literature searches for this question carried out	

		newer summaries of observational evidence that can give a more modern update?	in April 2021 identified 3 systematic reviews. As one did not find any evidence on the topic it was not included in this guideline. The remaining 2 systematic reviews are referenced. These were published in October 2020. Due to the rapid development methodology used for this guideline it has not been possible to carry out update searches.	
		The INSPIRATION study (Sadeghipour et al. JAMA March 21) directly asked what is the effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit and recruited 562 patients but is not included here.	This study was identified in our literature searches but excluded as it did not meet the inclusion criteria for key question 1 which compares anticoagulation at therapeutic dose with standard prophylactic-dose or enhanced intermediate-dose anticoagulation. We have added a description of the results to section 4.5 to reflect that the trial showed no significant benefits for intermediate-dose anticoagulation compared with standard-dose anticoagulation.	
		The two small trials are given too much weight in the text.	We do not agree with this interpretation. The trials are clearly labelled as having small sample sizes. In addition, limitations in the studies are described, for example problems with applicability, and there is a statement that “Confidence in the collective quality of evidence is limited by a range of factors affecting individual studies such as small sample sizes and risk of confounding.”	
		The mpRCT is clearly the best source of evidence to date. The majority of patients from severe stratum came from REMAPCAP who actually compared therapeutic anticoagulation with either intermediate or standard prophylaxis. They were understandably pragmatic in this regard. The question of intermediate vs standard is being addressed in their follow up domain - although this is a similar question to that in INSPIRATION. A separate focus on thrombotic events (in addition to OSFDs) is perhaps	Agreed.	

		distracting unless searching for thrombotic events was systematic. The remaining issue which might be worthy of addressing under the subtitle dose is anti-Xa monitoring and the seemingly real phenomenon of heparin resistance in COVID. Most published work uses weight based dosing strategy or fixed dose strategy. An alternative strategy is anti-Xa guided strategy such as initial weight based strategy then adjusted to meet an anti-Xa level which is in the prophylactic range. We find augmented/intermediate dosing is required to maintain a prophylactic target. To the best of my knowledge there is only observational data in this regard. A recommendation for fixed dose thromboprophylaxis might be met with resistance at my institution for example.	We agree that the published evidence we have reported refers to fixed dose strategies (with dose adjustment in specific circumstances). Anti-Xa guided strategies were not investigated in this guideline, however may be indicated in local thrombosis protocols at health board / hospital levels. We did not find evidence comparing intermediate dose with therapeutic dose anticoagulation and have included this as a research recommendation. Details of the INSPIRATION trial results (intermediate v standard-dose anticoagulation) have been added to section 4.5	
	RW	As above. A simple version of treatment recommendations are required for patients and carers.	Noted. See response to the original comment by RW in section 1.1	
	RR	Good and accurate review of the data, highlighting the conflicting data published.	Noted. Thank you.	
4.3.2	PH	Agree.	Noted. Thank you.	
	SC	It is standard practise to use 20 mg enoxaparin daily for patients with creatinine clearances less than 30 ml/min. It could be noted that the manufacturer advises to avoid in creatinine clearance less than 15 ml/min but in my experience it would be unusual to use unfractionated heparin in these cases.	Noted. The guideline has noted that dose alteration is required in cases of renal abnormality in section 4.1 and in this section. We agree that 20 mg enoxaparin is the standard dose alteration of that individual LMWH but are aware that boards and ADTCs determine preferred choice of anticoagulant drugs at more local levels. Here we are emphasising that as each LMWH has a different dose alteration requirement for patients with renal failure, in the context of COVID-19 where rapid reversal of anticoagulation may be required in high-pressure environments, there may be an advantage in defaulting to use of unfractionated heparins for these patients which would remove the requirement for anticoagulation dose alternation.	

			We have revised the recommendation to clarify that either dose-adjusted LMWH or dose-adjusted UFH are options.	
	JS	Each hospital it varies and Area Drug and Therapeutics Committee (ADTC) will review and recommend this in individual hospitals and happy with this.	Noted. Thank you.	
	JH	Many boards across Scotland have moved away from using unfractionated heparin as VTE prophylaxis and continue to use LMWH with anti-Xa levels where appropriate. This is in both downstream wards and critical care areas. It may be challenging implementing different prescribing policies for different patient cohorts. In section 5.1.1, it is advised that for the treatment of VTE in patients with CrCl <15 LMWH can still be used, whereas the cut off for prophylaxis in this section of the guidance is 30 ml/min.	Noted. While some LMWHs are not recommended (in SPC) for use in patients with CrCl <15 ml/min, we are aware that in practice, dose-adjusted LMWH is the standard approach. We have revised paragraph 6 in this section and changed the recommendation to support use of either UFH or LMWH with appropriate dose adjustment. Anti-Xa monitoring was outwith the remit of this guideline. This paragraph in section 5.1.1 specifically refers to the DOACs apixaban and rivaroxaban. We have revised the paragraph to: "In patients with renal failure, the summary of product characteristics (SPCs) for apixaban and rivaroxaban should be followed. If creatinine clearance <15 mL/min, these medications should not be used and the patient should be anticoagulated with off-label dose-adjusted LMWH, or dose-adjusted UFH ± VKA according to local prescribing protocols.."	
	MK	Nil to add.	Noted. Thank you.	
	RCGP	We agree with the choice of anticoagulant and it is important to note that once the patient is transferred to primary care, there may be a local prescribing pathway preferentially choosing an alternative anticoagulant. The clarity here is very helpful for primary care.	Noted. Thank you.	
	TC	Dalteparin can be dose adjusted down to CrCl <10 mL/min especially if safely coupled with anti-Xa monitoring. A recommendation to use unfractionated	Noted. See response to JH above.	

		heparin (UFH) will lead to more heparin-induced thrombocytopenia (HIT) and given its complexity of use inevitably leads to episodes of prolonged under-dosing (and to a lesser extent periods of overdosing).		
	AO'P	The short half-life of enoxaparin is probably more problematic in critically ill patients since they are immobile 24 hours a day. The half-life of enoxaparin would suggest that the effects of VTE prevention would wear off before the end of the dosing interval. This is not as problematic in non-ICU patients since they will be mobilising for part of the day. There are suggestions from the literature that ICU patients (non-COVID) would benefit from twice daily enoxaparin to provide full 24 hour VTE prophylaxis cover. This is something that needs to be investigated further but since this is a consideration I don't think stating that shorter acting LMWH are preferable in critically patients should be included.	Noted. Health boards maintain thrombosis protocols which determine the preferred choice of anticoagulant agent based on local factors. We note that enoxaparin is a commonly used LMWH for this indication in Scotland. Noted. In this case, "shorter-acting LMWH" refers to a comparison with fondaparinux, rather than a shorter-acting agent within the LMWH class. The text has been revised to clarify this point.	
	RW	As above.	Noted. Thank you.	
	RR	Agree with recommendations though LMWH can be used with lower glomerular filtration rate (GFR) (than 30) if appropriate anti-Xa monitoring is used. Depends on local protocols and familiarity in this patient group.	Noted. Thank you.	
4.4	TC	Not reviewed.	Noted. Thank you.	
	RCP&S	Our reviewer considered full dose anticoagulation should not be routine practice for COVID-19 hospitalised patients unless VTE is proven. The words "Consider" therapeutic dose in hospitalised patients with moderate COVID-19 seems reasonable but some clinicians may read this as a subtle recommendation rather than neutral guidance.	Noted. Thank you. The recommendation for prophylactic dose anticoagulation in those with severe COVID-19 is a strong recommendation based on two RCTs, one multiplatform RCT (mpRCT) and two systematic reviews of observational data. While the evidence was noted to be inconsistent, the largest and most methodologically robust studies were consistent in showing that therapeutic dose anticoagulation did not show benefit in that group, leading to a strong	

			recommendation in this guideline. For patients with moderate COVID-19, the evidence is also inconsistent, however the evidence base consists of the same mpRCT and a further RCT. The larger and more powered mpRCT demonstrated benefits in some outcomes while the smaller RCT did not show benefits, however this trial used a statistical method that was difficult to interpret and used DOACs rather than LMWH which may have additional anti-inflammatory and antiviral effects. This introduces further uncertainty in the strength of the findings as a comparator to the mpRCT and on balance weighing up the benefits and harms of the evidence base as a whole, the guideline development group felt that a conditional recommendation in favour of therapeutic anticoagulation in patients with moderate COVID-19 was justified.	
		Risks of bleeding should be factored into the decision to use therapeutic doses in the absence of proven VTE and it may be worth stating this on page 13.	Noted. Standard VTE and bleeding risk assessment should be routinely carried out for all hospitalised patients on admission and this will inform anticoagulation choices. A good practice point has been added to section 4.4.1 – “Bleeding risk should be considered when making decisions regarding intensity of anticoagulation.”	
	AO’P	The use of UFH in patients with renal impairment in ICU is not always standard practice. Often with UFH it is difficult to maintain patients in the appropriate APPTr range, this is even more difficult with COVID - 19 patients. Also in ICU there are often issue with access since patients are on a significant number of infusions therefore LMWH can be more practical. For patients on renal replacement therapy in units that use citrate anticoagulation, LMWH will be the choice of VTE prophylaxis despite patients having an GFR < 30ml/min.	Noted. See response to JH in section 4.3.2	
	RW	As above.		

	RR	Consider is never the best term to use in a guideline. Patient factors and bleeding risk need to be taken into account especially when the outcome data only shows benefit in OFSD rather than overall mortality.	Noted. “Consider” is a term used to reflect a conditional recommendation where there is likely to be an important variation in the decision that informed persons are likely to make. A good practice point has been added to section 4.4.1 – “Bleeding risk should be considered when making decisions regarding intensity of anticoagulation.”	
4.4.1	PH	I think this section needs work. The recommendation seems juxtaposed to the preceding paragraph. The reading of the data suggests possible benefit of therapeutic LMWH but not enough to recommend its use - suggest this should be consider instead. Duration unclear also.	Noted. The formatting has been corrected to separate the recommendation from the text. Agreed – the wording of the summary has been revised to clarify the judgement around evidence which shows benefits and evidence which does not. Agreed – we have added a further recommendation in line with the duration of anticoagulation in the mpRCT.	
	SC	I think the second recommendation refers to moderate COVID-19 and not critical or severe as documented. Again it would be unusual to use unfractionated heparin and again a reduced dose of low molecular weight heparin (with anti-factor Xa monitoring for accumulation) is standard practise.	Thank you – the typo in this recommendation has been corrected. The recommendation has been revised to offer a choice of either dose-adjusted UFH or dose-adjusted LMWH in patients with renal impairment and COVID-19.	
	JS	We do this in our hospital. Those with high BMI, the dose of LMWH should be prescribed correctly otherwise no use!	Noted. Thank you.	
	JH	Lack of information about dosing in extremes of weight. Obesity is known risk factor for both COVID-19 complications and VTE. The guidance in renal failure is quite specific while comparatively there is little on dosing in obesity.	See response to JH in section 4.3.1	
	MK	Nil to add.	Noted. Thank you.	
	CMacL	"Consider use of a therapeutic dose of unfractionated heparin in hospitalised		

		patients with critical or severe COVID-19 and renal failure (CrCl <30 ml/min) and/or those considered at very high risk of bleeding where anticoagulation needs to be terminated very quickly." In practice, given the unfamiliarity across the multidisciplinary team with the use of unfractionated heparin infusions and the timeline between sampling and actioning of results, the use of unfractionated heparin in a general medical setting often results in significant periods of over or under anticoagulation. While patients in high dependency/ intensive care have higher staffing ratios able to reliably deliver UFH infusion, this is often not the case for patients in a general ward setting. My understanding of the referenced paper is that decision between LMWH or UFH was based on normal local protocols for anticoagulation in renal impairment. Was there a consensus or evidence to explain why the guideline recommends UFH rather than therapeutic anticoagulation according to local protocol?	Noted. See response to JH in section 4.3.2. The recommendation has been revised to offer a choice of either dose-adjusted UFH or dose-adjusted LMWH in patients with renal impairment and COVID-19.	
	NHSG GC TC	This recommendation may have implications regarding a need to alter supplies of LMWH to ward areas in hospitals. For example, in Greater Glasgow and Clyde (GGC), dalteparin is used for treatment of VTE and enoxaparin for prevention of VTE. The health board will need to determine which of the following policies carries the least risk; all patients receive enoxaparin for thromboprophylaxis, but at different doses depending on whether they have COVID-19, or patients with COVID-19 receive therapeutic dose dalteparin for VTE prevention, as the appropriate size syringes for therapeutic dosing will already be in ward stock, and healthcare staff will be familiar with calculating therapeutic dose dalteparin.	Thank you. Choice of anticoagulant should continue to be made according to local prescribing protocols with reference to the dosage recommended in this guideline. We understand that a shortage is unlikely to be an issue. There is a lot of flex in the supply chain to cover peaks of usage. This can be addressed through national procurement arrangements.	

		Either strategy has risk as there will not be the usual 'one size fits all' thromboprophylaxis policy for all hospitalised patients that healthcare staff are familiar with. In addition to this, the SIGN guidance recommends that patients with COVID-19 infection, who deteriorate and require critical care, should receive a dose reduction in LMWH, with possibly an associated change in product type.	This issue was not addressed in the evidence reviewed. Management of patients transitioning from standard to critical care remains a clinical decision, and would depend on the patient improving, with no evidence of VTE, which would trigger a return to standard prophylactic dosing.	
		Given the above, there will be a significant requirement for additional staff education, at a time when all departments are very busy both as a result of short staffing, due to absences resulting from COVID infection, and the ongoing high admission numbers to hospital for patients affected by COVID. Dispensing services, prescribers and those that administer LMWH will need to be made acutely aware of the above changes and will require ongoing reminders and support, so they are fully aware that patients with moderate severity COVID-19 disease require a different dose of LMWH to non-COVID patients and possibly a different product. Finally it is essential that strategies are in place to clearly differentiate between patients with COVID-19 disease who are receiving LMWH with the intent of treating a VTE, as opposed to using a treatment dose for prophylaxis purposes. Such identification is essential to avoid dispensing inappropriate treatment dose anticoagulation post discharge for those patients who have not experienced a VTE. Perhaps the writing group could suggest a standardised set of words to address this as it has the potential to be a significant clinical governance issue.	Noted. We agree with this observation. Agreed – a Good Practice Point has been added "For all patients hospitalised with COVID-19, it is important that both anticoagulation dose and purpose of anticoagulation are recorded in the patient's notes, medicines chart or appropriate local system in order to differentiate individuals receiving therapeutic doses of anticoagulation for different indications."	
		Although the committee appreciate that the writing group are most likely referring to hospitalised patients who have symptomatic COVID-19 disease, clarity is recommended regarding whether there should be any change from standard prophylactic	Asymptomatic patients admitted for other reasons should follow pathways for general medical inpatients. On positive screening for COVID-19 they should receive either standard thromboprophylaxis if they remain asymptomatic,	

		dose LMWH for those patients who are admitted to hospital and are incidentally found to be COVID-19 positive on PCR screening. Furthermore, the writing group should provide clarity regarding whether patients with moderate COVID-19 disease should be stepped down from therapeutic dose LMWH to standard prophylactic dose as they recover and if so, at what time point e.g. when they are no longer dependent on supplementary oxygen Taken together, introducing this recommendation for patients with moderate and severe COVID-19 infection will be a significant clinical governance issue for Health Boards which will require risk mitigation strategies. Thromboprophylaxis policies will need to be updated and highlighted to frontline healthcare staff. Finally, these recommendations have implications for LMWH supply nationally, given that there are approximately 1000 patients, hospitalised with COVID-19 at the current time, most of whom are not in critical care and therefore would be eligible for therapeutic dose LMWH to prevent VTE. The use of therapeutic dose of LMWH will therefore increase across Scotland significantly until the number of patients hospitalised with COVID-19 disease falls significantly.	or may be considered as a candidate for therapeutic anticoagulation if they develop moderate symptoms of COVID-19 (eg oxygen requirement). Agreed – a paragraph has been added to indicate that no evidence has been identified to support intensification of anticoagulation dose in patients recovering from severe COVID-19 to moderate COVID-19 See above.	
4.5	PH	Agree with this.	Noted. Thank you.	
	JS	Something is better than nothing! As long as why and justified the dose.	Noted. Thank you.	
	MK	Agree - insufficient evidence to make any recommendations.	Noted. Thank you.	
	TC	Comments as per 4.3.1.	See response to TC in section 4.3.1	

	AO'P	There may be no evidence comparing enhanced and standard VTE prophylaxis regimens but most critical care units in Scotland will have been using enhanced regimens for the last 18 months. Following discussions with colleagues I think it will be very difficult to get units to move back to using standard VTE prophylaxis since after introducing the enhanced protocols a reduction in the incidence of VTE was seen and renal replacement filters clotted less frequently. We also did not seen an increased incidence of bleeding. Continuing with our current practice would be considered a significant departure from a national guideline (as stated in this document) therefore would it be possible to have more of an acknowledgement about current practice included? In ICU many of the treatments we use are based on clinical experience and not evidence from large trials and I think most ICU staff will see this in the same way. They will not see a lack of trial evidence as a reason to change practice.	The question reviewed by this guideline compared standard (prophylactic) or intermediate (enhanced) dose anticoagulation with therapeutic dose. No evidence was identified to inform this question. We did not investigate standard compared with enhanced dose anticoagulation. We note this was the remit of the INSPIRATION trial which concluded that: "Among patients admitted to the ICU with COVID-19, intermediate-dose prophylactic anticoagulation, compared with standard-dose prophylactic anticoagulation, did not result in a significant difference in the primary outcome of a composite of adjudicated venous or arterial thrombosis, treatment with extracorporeal membrane oxygenation, or mortality within 30 days. These results do not support the routine empirical use of intermediate-dose prophylactic anticoagulation in unselected patients admitted to the ICU with COVID-19." A summary of the results from this trial has been added to this section. The GDG acknowledges that in the absence of evidence to support or refute it, use of intermediate-dose anticoagulation might be provided based on locally determined prescribing protocols. As an off-label use, in line with standard practice, prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility. GMC notes that when prescribing a medication off label, doctors should: • be satisfied that there is no suitably licensed medicine that will meet the patient's need	

			• be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy • take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so • make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine. While there is no evidence to support intermediate-dose anticoagulation in critically ill patients this remains an area of active research.	
	RW	Only of small interest to non-medical professionals.	Noted. Thank you.	
	RR	Highlights the know lack of data though this a practice that appears to have been commonly adopted during COVID.	Noted. Thank you.	
Section 5				
General	PH	Agree.	Noted. Thank you.	
	SG	Again the addition of recognising that pregnant women with COVID-19 are at increased risk of morbidities, particularly in the third trimester of pregnancy and as such any pregnant woman admitted should have her ongoing care/treatment planning discussed as part of a multi professional team with her obstetric/anaesthetic team involvement.	Noted. Pregnant women (with or without COVID-19) are at additional risk of VTE and we refer the reader in section 1.2.1 to specialist advice on management of this group from other sources.	
	JS	No concern.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	TC	Not best placed to review.	Noted. Thank you.	

	AC	Where is the mention of pregnancy in this? Currently increased number of this group in hospital with COVID-19.	See responses to SG in sections 1.2.1 and 5.	
	RW	It seems to be suspected that COVID patients may be at higher risk, given that clotting has an association inherent in the virus or viral response in the body. Although conjecture mostly, it seems reasonable and reassuring that patients with COVID will have some extra consideration.	Noted. Thank you.	
	RR	Good clarifying statements.	Noted. Thank you.	
5.1	PH	Agree.	Noted. Thank you.	
	JS	As mentioned, as per the approval by ADTC in an individual hospitals.	Noted. Thank you.	
	MK	Agree.	Noted. Thank you.	
	TC	Not best placed to review.	Noted. Thank you.	
	RW	For medical professionals.	Noted.	
	RR	Agree, quoting up to date National Institute for Health and Care Excellence (NICE) guidance.	Noted. Thank you.	
5.1.1	PH	Agree.	Noted. Thank you.	
	SC	I think the ISTH suggests that apixaban and rivaroxaban may be considered rather than recommends they be used. This section advises using LMWH for creatinine clearance less than 15 ml/min which contradicts the previous sections which recommend unfractionated heparin.	Agreed. The text has been revised to reflect the conditional status published by ISTH and we have also altered our recommendation to conditional status: “Consider apixaban or rivaroxaban using the licensed dosing regimens as first-line anticoagulation for hospitalised patients with confirmed VTE.” This has been clarified to be an off-label use of LMWH and should be used with support from local prescribing protocols. Section 4.3.2 has been updated to clarify use of LMWH with respect to renal function.	

	JS	Should be as per guidelines like other aetiology.	Noted. Thank you.	
	JH	In section 5.1.1, it is advised that for the treatment of VTE in patients with CrCl <15 LMWH can still be used, whereas the cut off for prophylaxis in section 4.3.2 of the guidance is 30 ml/min.	This paragraph specifically refers to the DOACs apixaban and rivaroxaban. We have revised the paragraph to: "In patients with renal failure, the summary of product characteristics (SPCs) for apixaban and rivaroxaban should be followed. If creatinine clearance <15 mL/min, these medications should not be used and the patient should be anticoagulated with off-label dose-adjusted LMWH, or dose-adjusted UFH ± VKA according to local prescribing protocols.."	
	JH	Other clinical scenarios where direct oral anticoagulant (DOAC) may not be appropriate treatment choice eg significant drug interactions.	Noted. Thank you. While we agree, this point is true for all drug recommendations in guidelines, where clinical judgment is required to avoid use of medications which may cause significant interactions.	
	MK	Agree.	Noted. Thank you.	
	TC	Not best placed to review.	Noted. Thank you.	
	RW	As above - simple recommendation for patients required.	See response to RW in section 1.1	
	RR	Good review of the data. Especially the up to date guidance regarding dosing in weight extremes with apixaban and rivaroxaban. In recommendation states to use LMWH or UFH if CrCl <15 but early recommendation in document said not to use LMWH if CrCl <30. Need to marry up recommendations.	Noted. Thank you. This has been clarified to be an off-label use of LMWH and should be used with support from local prescribing protocols. Section 4.3.2 has been updated to clarify use of LMWH with respect to renal function.	
5.2	PH	Agree.	Noted. Thank you.	
	JS	AS PER OTHER CAUSES AND GUIDELINES.	Noted. Thank you.	
	MK	Agree.	Noted. Thank you.	
	RCGP	Can the committee consider adding that the agreed duration of anticoagulant be clearly articulated in the discharge summary? This will prevent primary care	The GDG noted that duration of anticoagulation should be recorded, where possible, in the discharge summary. While most reviews will	

		having to contact the hospital at the 3 months review mark to decide whether to discontinue the medication.	happen in secondary care, they discussed that there is regional variation in the settings where medication review may take place. A good practice point has been added to clarify this – "To ensure clear communication between secondary and primary care, the discharge summary should state how long anticoagulation should continue and how the patient's anticoagulation will be reviewed at 3 months after discharge."	
	TC	Not best placed to review.	Noted. Thank you.	
	RCP&S	Clinical decisions on anticoagulation duration and agent should be made on an individual basis taking into account thrombotic and bleeding risks.	Thank you. This reinforces the reference and good practice point in this section, however an initial treatment period of at least 3 months is established clinical practice.	
	RW	Seems reasonable to follow standard protocol for standard patients. As long as the fewer who would benefit from long term medication, are not missed.	Noted. Thank you.	
	RR	Agree with 3 months and review, as per non-COVID practice.	Noted. Thank you.	
Section 6				
General	PH	There is no convincing data here. Agree.	Noted. Thank you.	
	JS	This information is sensible.	Noted. Thank you.	
	RW	I would like to see the long term riskier patients (outwith heart disease) considered too.	Noted. No action required. The guideline notes the relevance of significant comorbidities, and congestive heart failure and COPD are provided as examples, although not the only risk factors. Formal VTE risk assessment is not included in the scope of this guideline.	
	RR	Highlights the lack of evidence for COVID patients. Makes reference to previous non-COVID trials but they are not referenced.	Thank you. A reference to a systematic review and meta-analysis of RCTs of extended thromboprophylaxis has been added.	
6.1	PH	Agree.	Noted. Thank you.	
	JS	Individual risk assessment and duration.	Noted. Thank you.	

	MK	Nil to add.	Noted. Thank you.	
	TC	Not best placed to review.	Noted. Thank you.	
	RW	Earlier in the paper it was noted that COVID-19 has a thrombotic element to its nature, yet here the findings rather dispute this, by placing risk squarely on hospital admission. From the info here it seems that COVID patients are not any additional risk and protocols are the same as all hospitalised patients. Given that so much data in relation to COVID is unknown, we all have to recognise that we live through a trial and error phase with this.	No evidence was identified which reported VTE risk in patients who were not hospitalised for COVID-19, however this does not mean that this group is not at risk. The complexity of measuring risk in a homogenous community dwelling population and linking this to confirmed COVID-19 diagnosis while recording the varying range of risk factors, severities and durations across individuals may prevent robust risk assessment.	
	RR	Happy with description of processes.	Noted. Thank you.	
6.1.1	JS	No issues.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	RW	Risks from bleeding internally are referred to as being inherent. But risks from bleeding due to eg slip and fall with head trauma could be included particularly in informing patients and carers. Being on blood thinning medication required care and attention from a work and lifestyle perspective too. I was grateful for such advice when I was receiving treatment as a variety or sports and weekly activities increase chance of accidental bleeding.	Noted. Section 7.1 on provision of information includes the advice to “Provide written or online information to patients and their family about the benefits and risks of VTE prophylaxis” for individuals discharged from hospital who may be considered to be at sufficient risk of VTE to warrant extended thromboprophylaxis.	
	RR	Clear review of published work.	Noted. Thank you.	
6.1.2	MK	Nil to add.	Noted. Thank you.	
	RW	Shorter would be better.	Noted. The guideline text will be reviewed before publication to optimise the content.	
	RR	Clear review of published work - is suggested greater consideration for discharge thromboprophylaxis.	Noted. Thank you.	
6.1.3	JS	Very clear too.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	

	RW	The more realistic information. We don't know - carry on as best you can and assess risk individually.	Noted. Thank you.	
	RR	Clear review of published work.	Noted. Thank you.	
6.1.4	PH	Agree.	Noted. Thank you.	
	JS	No issues.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	RCP&S	Clinical decisions on anticoagulation duration and agent should be made on an individual basis taking into account thrombotic and bleeding risks.	Thank you – this reflects the good practice point in this section which states: “The use of extended thromboprophylaxis should be based on clinical judgement taking into account the balance between the patient’s risks for venous thrombosis and bleeding.”	
	RW	Bit shorter would be better, info towards bottom is more relevant.	Noted. The guideline text will be reviewed before publication to optimise the content.	
	RR	Descriptive work on lack of good data to definitive drive the decision.	Noted. Thank you.	
6.2	PH	Agree.	Noted. Thank you.	
	JS	Should be decided by the treating clinician considering the co-morbidities and level independence with ADL. Nursing home patient? Again to be decided by the clinicians.	Noted. The guideline states that “the choice of agent and duration of treatment be decided on a case by case basis after discussion between the patient and the clinician.”	
	MK	Nil to add.	Noted. Thank you.	
	TC	Not best placed to review.	Noted. Thank you.	
	RW	For medical professionals. Patients only need brief outline of medication risks.	Noted. Thank you. A plain language summary of the key messages for patients will be published with this guideline.	
	RR	Leaves it individually for each patient and clinician to decide.	Noted. Thank you.	
Section 7				

7.1	PH	No comments.	Noted. Thank you.	
	JS	Clear.	Noted. Thank you.	
	JH	“People hospitalised with COVID-19 and no confirmed VTE” Discusses the evidence that the use of heparin can significantly reduce the risk of VTE. Described as anticoagulation throughout the rest of this section rather than heparin.	Agreed – “heparin” has been replaced by “anticoagulation”.	
	MK	Useful.	Noted. Thank you.	
	RCGP	This is excellent.	Noted. Thank you.	
	AC	No mention of RCOG or SIGN Maternal critical care guidance.	See response to SG in section 1.2.1. These sources of specialist advice have been added to the introduction of the guideline.	
	RW	From reading this paper it is unknown if COVID patients are at any higher risk of VTE than all patients, so better to focus on the risk of PE in an already acutely ill patient. But this is an awareness all severely ill patients/relatives should have, particularly respiratory patients. How will anyone know if the patients develops VTE due to COVID? Only long term data can make sense of that in amongst the patients who develop VTE due to immobility, age, family history (sadly lacking in mention in this paper) or other mitigating factors. Patients would be better to be informed of long term risks of further clot development rather than viewing it as an isolated incident. It may be for some but not everyone.	Noted. Thank you. The guideline includes a section on modifiable risks particularly relevant to the COVID-19 pandemic which help to inform choices on behavioural changes that can reduce the individual’s VTE risk. These will also be communicated in a summary of the key messages for patients which will be published with the guideline.	
	RR	This is a good checklist. Will generic leaflet be created to provide to patients?	Noted. Thank you. A patient summary will be published with this guideline.	
7.2	PH	No comments.	Noted. Thank you.	
	SG	Addition of documents pertaining to maternity community to be inclusive of RCOG and SIGN Maternity critical care guidance already issued during the COVID-19 pandemic and RCOG	See response to SG in section 1.2.1. These sources of specialist advice have been added to the introduction of the guideline.	

		guidance on VTE in pregnancy.		
	JS	Very good.	Noted. Thank you.	
	MK	Useful.	Noted. Thank you.	
	AC	Same as comment on section 7.1.	See response to SG in section 1.2.1. These sources of specialist advice have been added to the introduction of the guideline.	
	RW	Only 3 - perhaps a more comprehensive list would be better for all professionals and non-professionals.	These sources of information were nominated by clinical and lay representatives in the guideline development group. We note that no additional specific sources have been suggested by peer reviewers.	
	RR	Good sources including charity.	Noted. Thank you.	
Section 8				
8.1	PH	Good review.	Noted. Thank you.	
	JS	Well done to those involved.	Noted. Thank you.	
	MK	Comprehensive review of the available information/evidence.	Noted. Thank you.	
	RW	For professionals.	Noted. Thank you.	
	RR	Appropriate sources and reviewing method.	Noted. Thank you.	
8.2	JS	Should always be there.	Noted. Thank you.	
	MK	Agree.	Noted. Thank you.	
	RCGP	We welcome the call for community care research to determine if prophylaxis is beneficial.	Noted. Thank you.	
	AO'P	I think this should include research into comparing enhanced and standard VTE prophylaxis in critically ill patients with COVID-19 disease. This is currently standard practice but the authors were unable to find published literature on this comparison, would this not warrant further investigation?	The question reviewed by this guideline compared standard (prophylactic) or intermediate (enhanced) dose anticoagulation with therapeutic dose in patients with COVID-19. We did not investigate standard compared with enhanced-dose anticoagulation. We note this was the remit of the INSPIRATION trial which is now published and has been cited in the guideline.	

	RW	For professionals.	Noted. Thank you.	
	RR	Happy with this.	Noted. Thank you.	
8.3	JS	I agree.	Noted. Thank you.	
	MK	Agree.	Noted. Thank you.	
	RW	Fine.	Noted. Thank you.	
	RR	Happy with this.	Noted. Thank you.	
Abbreviations				
General	PH	Good section.	Noted. Thank you.	
	JS	No issues.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	AC	Very helpful list.	Noted. Thank you.	
	RW	Fine.	Noted. Thank you.	
	RR	Appropriate.	Noted. Thank you.	
Annex 1				
General	PH	Nothing to add.	Noted. Thank you.	
	MK	Nil to add.	Noted. Thank you.	
	RW	For professionals.	Noted. Thank you.	
	RR	Appropriate questions asked.	Noted. Thank you.	
Annex 2				
	MK	Nil to add.	Noted. Thank you.	
	AC	No comment on this. However excluding pregnant woman with no onward signposting is concerning. Venous Thromboembolism is a leading cause of maternal mortality in confidential enquiries. COVID-19 is an additional risk to this group. There are in the region of 50,000 women a year pregnant in Scotland, many un vaccinated at this time. Guidance that does not	See response to SG in section 1.2.1. These sources of specialist advice have been added to the introduction of the guideline.	

		refer to them or sign post is in contradiction to the recently published Woman's Health plan for Scotland which clearly states the needs of women must be taken into consideration. I see no reference that the RCOG were contacted or had any input into this guidance.		
	RW	For professionals.	Noted. Thank you.	
	RR	Clear tables used.	Noted. Thank you.	