European Medicines Agency

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR PROPHYLAXIS OF HIGH INTRA- AND POST-OPERATIVE VENOUS THROMBOEMBOLIC RISK

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	ISTF	
2	EFPIA	
3	BMS	
4	Roche	
5	Pr H.R. Büller	

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Table 2:Discussion of comments

GENERAL COMMENTS - OVERVIEW

(1) Cfr. the ISTF Protocol circulated by Mia van Petegem to CHMP members February 2006. Some of the sections from the ISTF Protocol have been implemented in the current CHMP draft but there are still important issues that need to be addressed. It is of vital importance that the Authorities, the Industry and those that handle the patients accept the Guideline on anticoagulant drug development. The draft still reflects a view that is historical i.e. that only venous thrombosis is taken into account and quantified by radiological screening methods. This is in disharmony with current scientific knowledge (we are dealing with systemic thrombotic events) and with surgeons perception of surrogate markers i.e. that they do not believe reflect real-life and thus not believe in the thromboprophylaxis recommendations that are largely based on radiological screening studies.

(2,4) As a minimum reference to two guidelines/regulations should most likely be included :

- **Paediatric regulation** in cardiology area (warfarin, heparins, enoxaprin etc) are listed in the EMEA charts for deep vein thrombosis and or thrombosis indications as well as ICH E11

- **Investigation on gender differences** (co-medication, hormonal status etc.) is recommended to be included as per reflection paper on gender differences in CV diseases (EMEA/CHMP/EWP/498145/2006) which refers to a consensus paper of the European Society in Cardiology which states that possible gender differences should be addressed in clinical trials. It is recommended to reference this more pronounced in section 4.2 Pharmacokinetics and section 4.6 special populations.

  Although in principle this is captured in paragraph 2.1 it would be beneficial to emphasize this aspect stronger so that present efforts such as EMEA/CHMP/EWP 498145/2006) are adequately captured.

(5) The EMEA guideline revision process is important but it involves a tremendous amount of work and is unlikely to lead to recommendations that are significantly different from what is generally considered the gold standard of recommendation, i.e. the ACCP. A close involvement of this group of experts is warranted in or to be efficient and evidence based.
The current document has outlined many of the current controversies in the area of thromboprophylaxis. It offers no solutions to these controversies because ther inadequate evidence to do so.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Title (1)	This is historical and does not take into account what is stated in the	Not accepted. The guideline integrates European and ACCP

[1] Where applicable

	ISTF protocol i.e. that we are dealing with all kind of thrombin driven complications that affect the whole vasculature Proposal: Delete: VENOUS	recommendations for treatment of venous thromboembolic events; therefore, VENOUS in the title will be kept.
Scope (1)	Major orthopaedic surgery induces systemic procoagulant activity. Subclinical DVT as a main outcome of a compound efficacy in phase II and III studies may still be a good approach. However, these studies have traditionally been used to achieve an official drug license and also used for drug marketing. Further, Guideline committees and their recommendations have used it as basis information. The surgical community do not believe in this surrogate DVT markers and thromboprophylaxis is consequently not applied properly in many regions. Surgeons have for years requested studies on sole clinical endpoints that reflect the clinical advantages and disadvantages of a compound. In accordance with recent research, all vascular events on the arterial and venous side should be implemented. Vascular complications in an elective Hip replacement population accounts for about 5% during a 3-month postoperative time-period. The overall death is dominated by prothrombotic vascular events. There is reduced low relative survival that lasts for about 4 weeks after hip replacement and the absolute reduced survival lasts for 2-3 months. Thus, ISTF strongly recommend that this guideline also should include recommendations on clinical studies that up to know have been post-marketing studies. If we are going to reduce vascular mortality (the main cause of death) after major orthopaedic surgery we need pure clinical studies on top of the current phase II and II studies and focus on simple postoperative endpoints like overall mortality and vascular morbidity.	Not accepted. Proximal DVT, PE and death are believed to be the relevant clinical endpoints. Large scale morbi-mortality trials are considered unfeasible in the pre-MA setting.

1 INTRODUCTION

Line no. + para no.	Comment and Rationale	Outcome
Paragraph 2 (1)	... fatal and non-fatal, usually resulting from proximal DVT of the lower limb venous system. Distal DVTs are considered less serious unless propagating proximally Comments:	Comment taken into consideration. Indeed, PE may appear from any segment of the collecting veins. However, it is considered that clinically important events will be captured with assessing proximal DVT, as PE usually results from proximal DVT.

	This may not be true in surgical patients cfr FUT and 99-TC plasmin tests: clots were coming and going. Venography is only a photographic snap shot if this dynamic process. A clot that is present at one time point may have disappeared on next venography etc. Studies on clinical and radiological confirmed DVT and PE in THR and TKR patients showed that those events appeared independently of each other (Bjørnaå B et al JBJS 2006). Thus the pathopysiological pattern differs from medical patients were a steady thrombus growth from distal to proximal veins may finally embolize. In surgical patients the PE may appear from any segment of the collecting veins (Haas SB et al JBJS 1992)	
Paragraph 2 (2)	Distal DVT if untreated can migrate and lead to PE Modify "Distal DVT are considered less serious unless propagating proximally" to read: "*Distal DVT may be less serious, but may in some circumstances propagate proximally"*. Add the following sentence "*Depending upon its location and clinical presentation, distal DVT if untreated may propagate and lead to PE"* after "Distal DVT may be less serious, but may in some circumstances propagate proximally". Add also after the end of second § "A secondary aim is to prevent or limit the occurrence of the post thrombotic syndrome (PTS)"	Partly accepted. The text will read: "Distal DVT are considered less serious, but may in some circumstances propagate proximally". The sentence: "A secondary aim of thromboprophylaxis is to prevent or limit the occurrence of the post thrombotic syndrome" will be added.
Paragraph 2 (2)	Add after the end of second §: "A secondary aim is to prevent or limit the occurrence of the post thrombotic syndrome (PTS)" (because quoted in the definitions, but not in the text even if it is stated that PTS is out of scope of this guideline.) The whole 2nd § should read: "The primary aim of thromboprophylaxis, in clinical practice, is the prevention of PE, both fatal and non-fatal, usually resulting from proximal DVT of the lower limb venous system. *Distal DVT may be less serious, but may in some circumstances propagate proximally. Depending upon its location and clinical presentation, distal DVT if untreated may propagate and lead to PE. A secondary aim is to prevent or limit the occurrence of the post thrombotic syndrome (PTS)*"	Partly accepted. The text will read: "Distal DVT are considered less serious, but may in some circumstances propagate proximally". The sentence: "A secondary aim of thromboprophylaxis is to prevent or limit the occurrence of the post thrombotic syndrome" will be added.
Paragraph 3	"DVT is approximately 40 – 60% following major orthopaedic surgery;	Accepted. The text will specify that the prevalence of asymptomatic

(1)	up to one third of these thrombi involve the proximal deep veins) the formation of a thrombus in a deep vein predisposes patient to symptomatic DVT and PE (which may be the initial clinical manifestation of a DVT) and fatal PE" Comment: As written above, the term "high risk" is not appropriate today when the overall mortality corresponds to moderate to low risk according to the traditional risk criteria. The relative early mortality after THR is 0.2% and after TKR 0.15% (Lie SA et al Acta Orthop 2002)	DVT was assessed by venography
4th paragraph (2)	It is noted that "The risk stratification to three (high-moderate-low) or to four (very high-high-moderate-low) VTE risk levels allows for the implementation of group-specific VTE prophylaxis at each risk level: It is suggested to delete the "very high" VTE risk level as it has not been defined in the draft guideline. The sentence should read "*Risk stratification to three (high-moderate-low) VTE risk level*s allows for the implementation of group-specific VTE prophylaxis at each risk level:"	Accepted.
(2)	The classification of VTE risk into three risk levels (high, moderate and low) as based on the surgical procedure alone may be misleading. Predisposing patient-related factors have to be considered especially for the moderate & low risk surgeries where patient could still have a high VTE rate depending on patients –related risk. The moderate and low VTE risk surgeries are too broad and too difficult to generalise and their classification need to factor in the patients risk as already stated. Trauma may be associated with a VTE risk as high as 20% and should not necessarily appear in the moderate VTE risk class. Modify "Predisposing patient-related factors have to be considered especially for the moderate & low risk surgeries where patient could still has a high VTE rate depending on patients –related risk" to read "***Predisposing patient-related factors for VTE are important considerations especially for the moderate or low risk surgeries, and may place individual patients at a higher risk for VTE relative to their***	Comment taken into consideration. As it was decided to focus only on patients undergoing surgery with high risk for VTE, patient-related risk factors during moderate or low risk surgery will not be discussed.

	perioperative risk alone".	
(5)	If the primary aim is to provide appropriate thromboprophylaxis to patien the simpler the risk stratification the better. We do know little (in quantitative sense) about the value of complicated stratification schemes in the present setting of surgery and medicine. We would favour either no or a two category stratification.	Partly accepted. The guideline focuses only on high risk surgery.
8th paragraph (1)	…. thrombin formation by inhibiting the activation of the factors involved in the coagulation cascade Comment: The aim of chemical thrombopropylaxis should be to reduce total mortality by reducing overall vascular deaths (Dahl OE Thromb Haemost 2005)	It is true that cardiovascular events are frequent in patients undergoing high risk surgery (myocardial infarction, arrhythmia, hypertension). However, arterial thrombosis is mainly related to platelet activation and antithrombotic agents, given for venous thromboprophylaxis, have few direct effects on platelets. Therefore, the reduction of total mortality by reducing overall vascular deaths is not an appropriate aim for thromboprophylactic agents. In addition, such aim would be impossible to demonstrate anyway in the pre-MA setting.
2.		
Line no. + para no.	**Comment and Rationale**	**Outcome**
2.1 3rd paragraph (1)	In the majority of trials performed up to now patients with VTE and/or bleeding risk were almost systematically excluded. This does not reflect clinical reality … ... patient screening log . Comments: Good	No specific comment given.
2.1 4th paragraph (2)	Further clarification is required for ……" it is recommended that a sufficient number of patients with high surgery-related VTE risk level and with intrinsic risk factors for VTE (i.e. cardiac disease, infection/inflammation, cancer other than that to be operated), be evaluated in clinical trials in order to permit an adequate benefit/risk assessment at the optimal dose of the drug in these sub-populations due to the heterogeneous nature of VTE predisposing factors" It is noted that … "sufficient number of patients" … and "adequate benefit/risk assessment…" have not been quantified in the draft guideline."	

	In addition, trials are not always powered for statistically significant results in subgroups analyses but their results should be consistent with the overall trial results. The below sentence is proposed <u>to be added at the end of page 4 after the last sentence finishing with "predisposing risk factors":</u> "Benefit/risk assessment in these sub-populations ***should be consistent with the overall results***".	Accepted.
2.1 5th paragraph (2)	Screening logs are rarely comprehensive and it is very difficult to get reliable screening log from investigators. We propose to <u>change the wording of this § to read</u>: *" It is important to establish that the patient population was selected without bias. One approach could be a record of patients who were considered for enrolment but were not included, e.g. a patient screening log"*.	Accepted.
2.3 2nd paragraph (1, 2)	The 2nd paragraph refers to the use of aspirin in patients with atherosclerotic disease. It is mentioned that "the use of aspirin should not be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding. Stopping aspirin in such patients immediately prior to surgery will not reduce peri-operative bleeding (because the antiplatelet effect of aspirin lasts a week) and carries the risk that aspirin may not be represcribed after surgery". This is not in accordance with practice in orthopedic surgery in Germany: typically, the orthopedic surgeons are terminating the aspirin therapy 10 days before surgery in order to avoid the before mentioned long lasting antiplatelet effect due to fear of bleeding. The recommendation for not interrupting ASA & NSAID should remain an investigator judgement and should be based on an individualized B/R assessment of continuing such antiplatelet or NSAID therapy The paragraph dealing with aspirin should omitted or, it should be stressed that "*The recommendation for not interrupting ASA & NSAID should remain an investigator judgement and should be based on an individualized B/R assessment of continuing such antiplatelet or NSAID therapy"*.	Comment partly accepted. The text will read: "…Therefore, it is not necessary that aspirin be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding. Stopping aspirin in such patients immediately prior to surgery will not reduce peri-operative bleeding (because the antiplatelet effect of aspirin lasts a week). If necessary, aspirin might be interrupted in patients with very high bleeding risk. This remains at the discretion of the physician. It is important to ensure that aspirin be re-prescribed after surgery…"

2.3 2nd paragraph (3)	The statement "the use of aspirin should not be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding" should be clarified. We agree, as implied later in the same paragraph, the important point is that patients be re-prescribed aspirin after surgery. However, the guidance should not exclude the possibility of a temporary discontinuation of aspirin therapy shortly before surgery. We propose a modification of the text to advise accordingly and emphasize the need to continue therapy after surgery. "…Therefore, it is not necessary that aspirin be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding. Stopping aspirin in such patients immediately prior to surgery will not reduce peri-operative bleeding (because the antiplatelet effect of aspirin lasts a week). Regardless, it is important to ensure that aspirin be re-prescribed after surgery…"	Accepted. The text will read: "…Therefore, it is not necessary that aspirin be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding. Stopping aspirin in such patients immediately prior to surgery will not reduce peri-operative bleeding (because the antiplatelet effect of aspirin lasts a week). If necessary, aspirin might be interrupted in patients with very high bleeding risk. This remains at the discretion of the physician. It is important to ensure that aspirin be re-prescribed after surgery…"
2.3 3rd paragraph (1)	... It is recommended that patients with NSAID's be kept on this treatment as much as possible … ISTF Comment: … Good	No specific comment given

3.

Line no. + para no.	Comment and Rationale	Outcome
3.1 1st paragraph (1)	… venography or ultrasound assessment. If using ultrasound, a method with high specificity and sensitivity should be chosen. … Comment: Ultrasound method is not acceptable. It is not standardized and the sensitivity is too low and it gives too many false positive. In addition it is very painful for a newly operated patient with a swollen and tender limb. This is shown in the first prospective randomized and blinded multi-centre study with central adjudication (S. Schellong et al Abstract,	Performed at D10 or D35, ultrasound is not very painful. The given reference concerns the VENUS study which had some drawbacks: only CUS was performed and not Duplex or colour Duplex ultrasound, physicians were not trained for centralised reading. See related comments on ultrasound.

	ASH 2005, Submitted JTH)	
3.1 1st paragraph (2)	It is noted that there is no data from a global clinical trial, using centralized laboratory, to support the use of ultrasound as a replacement for ascending contrast venography for VTE ***detection*** in global trials. For example, the most commonly used ultrasound technique, compression ultrasound (CUS), has a pooled sensitivity of 93.8% (92.0 to 95.3%) and a specificity of 97.8% (97.0 to 98.4%) for ***confirmation*** of a symptomatic proximal DVT when compared to ascending contrast venography (CV) in very experienced hands in specialized centers.[i]. However, global validation studies have demonstrated that centrally adjudicated CUS is not a valid technique to replace CV for the screening and detection of DVT early after major orthopedic surgery in confirmatory trials of antithrombotic agents[ii]. There have been no other studies conducted in a similar population and manner that have demonstrated any other ultrasound technique, or combined ultrasound techniques to be valid replacement for CV in global trials. Therefore, Ultrasound (CUS) should not be put at the same level as venography which remains up to now the gold standard for diagnosing DVT. In addition, the clinical setting should be considered before using US as sensitivity/specificity depends not only on the method itself, but also and especially on the clinical setting. **CUS is still not a validated method and has a low sensitivity even for detection of proximal DVT** and should not be used in confirmatory trials in orthopaedic surgery. Indeed, Schellong & al[ii] have recently demonstrated that CUS was associated with high specificity but low sensitivity to detect proximal DVT in hip or knee surgery. Phlebography should remain the diagnostic method in surgical setting. In addition, CUS has a poor sensitivity and specificity for detection of asymptomatic DVT in post-operative patients (dependent legs cannot be obtained because of immobilisation, important oedema interfere with the interpretation of ultrasound imaging). The use of CUS is more possible and reliable in the medical patients setting. Also, Magnetic Resonance Angiography needs to be included. It is becoming more available worldwide and articles comparing it to CV are in the literature. It is suggested that the following sentences be included in the first	Duplex (CUS+Doppler) ultrasound and colour Duplex ultrasound are acceptable methods for the diagnosis of proximal DVT with a high specificity (98%) and sensitivity (96%). Compression ultrasound (CUS) has an excellent specificity for proximal DVT. As proximal DVT are an important part of the combined primary efficacy endpoint, it is acceptable to perform Duplex or colour Duplex ultrasound for their detection. It is true that these techniques are still incompletely standardised. However, recently published study compared sensitivity and specificity of colour Duplex ultrasound to venography. Only one case of distal DVT diagnosed by venography was missed by colour Duplex ultrasound. Venography is also an acceptable method of detection of total DVT, even if it is less and less performed both in daily practice and in clinical trials. In recently published trials, up to 30% of patients did not have venography and were lost for efficacy assessment. Statement not accepted. There is not enough data to specifically recommend Magnetic Resonance Angiography for the time being.

	paragraph in section 3.1 to clarify the in which circumstances ultrasound can be used: "***DVT may be diagnosed by bilateral ascending venography or ultrasound assessment or Magnetic Resonance Angiography. Venography remains the gold standard for diagnosing all DVT (symptomatic or asymptomatic). CUS is much more sensitive and specific for SYMPTOMATIC clot, but much less so for ASYMPTOMATIC clot, the type we are looking for in prophylaxis studies. Moreover, CUS is not sensitive and specific for clots below the knee, which make up about 90% of those asymptomatic clots found after TKR surgery. Therefore, CUS can be used only for diagnosing symptomatic clots, or for asymptomatic proximal leg clots. CUS is a permissible alternative to ascending contrast venography, but only if the technique that is used has been scientifically demonstrated to be a valid alternative to CV in global clinical trials that have used an independent, blinded centralised adjudication process"***	Not accepted. The text will read: Venography remains the gold standard for diagnosing all DVT (distal and proximal). Duplex ultrasound (compression ultrasound coupled with doppler) and colour Dupplex ultrasound have an excellent sensitivity and specificity for proximal DVT and symptomatic distal DVT, but less so for asymptomatic distal DVT. If Dupplex ultrasound is used, the technique should be standardized and the trial should use an independent, blinded centralized adjudication process. The choice of DVT diagnosing method will be partly influenced by the choice of the primary composite endpoint in therapeutic confirmatory trials (see section 3.5). Whichever diagnostic method is chosen, the same method should be used for the entire study to provide consistency. In case other diagnostic methods are considered, the relevance of such methods - especially their specificity - should be justified by the applicant
(5)	Proximal DVT, distal DVT and all DVT (as assessed by venography) are t only surrogate parameters for which a consistent correlation to clinical outcome has been demonstrated. It is incorrect to consider distal DVT of doubtful clinical significance given this clear correlation. There is a systematic non-fit between venography and ultrasound for asymptomatic DVT in patients one week after orthopedic surgery. This is true for proximal as well as for distal DVT. Hence, the present optimism of the value of ultrasound in the document is unfounded. Furthermore, there is no accepted documentation standard for central adjudication of venous ultrasound. This has been well established for venography. We therefore, strongly believe that contrast venography (with its inherent problems) remains the best method for evaluation efficacy and that distal DVT should remain a valid outcome component together with symptomatic VTE and asymptomatic proximal DVT.	Duplex (CUS+Doppler) ultrasound and colour Duplex ultrasound are acceptable methods for the diagnosis of proximal DVT with a high specificity (98%) and sensitivity (96%). Compression ultrasound (CUS) has an excellent specificity for proximal DVT. As proximal DVT are an important part of the combined primary efficacy endpoint, it is acceptable to perform Duplex or colour Duplex ultrasound for their detection. It is true that these techniques are still incompletely standardised. However, recently published study compared sensitivity and specificity of colour Duplex ultrasound to venography. Only one case of distal DVT diagnosed by venography was missed by colour Duplex ultrasound. Venography is also an acceptable method of detection of total DVT, even if it is less and less performed both in daily practice and in clinical trials. In recently published trials, up to 30% of patients did not have venography and were lost for efficacy assessment

		The text will read: Venography remains the gold standard for diagnosing all DVT (distal and proximal). Duplex ultrasound (compression ultrasound coupled with doppler) and colour Dupplex ultrasound have an excellent sensitivity and specificity for proximal DVT and symptomatic distal DVT, but less so for asymptomatic distal DVT. If Dupplex ultrasound is used, the technique should be standardized and the trial should use an independent, blinded centralized adjudication process. The choice of DVT diagnosing method will be partly influenced by the choice of the primary composite endpoint in therapeutic confirmatory trials (see section 3.5). Whichever diagnostic method is chosen, the same method should be used for the entire study to provide consistency. In case other diagnostic methods are considered, the relevance of such methods - especially their specificity - should be justified by the applicant
3.3 1st paragraph (1)	Appropriate dose response studies might need to be carried out, unless relevant information is already available … Comment: Good	No specific comment is given.
3.3 1st paragraph (2)	It is stated that the Laboratory test to support dose selection, should be a validated test: the term "validated test" as such is not so precise. References should be added or some explanation to help understand the requirements for such a validation: how to test correlation with efficacy and even with safety outcome? The suggested duration of post-operative thromboprophylaxis has an impact on the choice of the comparators in confirmatory trials: (i) There is no comparator labelled for such recommended long term prophylaxis in hip replacement (max approved length of therapy is up to one month) and (ii) there is no drug labelled for the major abdominal surgery due to cancer. Some guidance needs to be added in such case about the choice of comparator.	The term "validated test" will be kept. (i) Currently recommended duration of thromboprophylaxis for total hip replacement and hip fracture is up to 5 weeks; Enoxaparin and Dalteparin are acceptable comparators. (ii) There have been 2 published trials in major abdominal surgery setting, one with enoxaparin and one with dalteparin. MA has been granted to dalteparin (high risk and cancer surgery), and to fondaparinux (abdominal high risk surgery and abdominal surgery for cancer). Enoxaparin has a large indication (high risk surgery) and is frequently used in this setting.

3.3 3rd paragraph (1)	The following durations of thromboprophylaxis are suggested for: total hip replacement and hip fracture: 5 to 6 weeks Comment: We have only one study in HF patients that balance on the edge of safety and efficacy in super selected healthy patients (about 70 years). This study is probably not representative for the general HF population (about 80 years) and more studies are needed. A great mistake by the ACCP Committee that have been heavily criticized by North-Am surgeons (cfr letters Chest, J Arthroplasty, Clin Appl Orthop)	Accepted. The duration of thromboprophylaxis for total hip replacement and hip fracture will be up to 5 weeks
(5)	The recommendations about duration (i.e. cancer surgery 5 weeks) are at least in our view too strong. Much more data are necessary. As was done i the ACCP the word suggests was used, rather stronger language.	Accepted.
3.3 5th paragraph (1)	The level of benefit that is demonstrated should be clinically relevant for each clinical situation Comment: This is a very good suggestion but not possible with the above outlined suggestions. You need to add a study with pure clinical endpoints to the traditional phase II and II studies. In such a pure clinical study, we need to take into consideration all thrombin triggered vascular events in the whole circulation and all AE from the time of trauma or surgery until end of follow up and not only during drug exposure to look for rebound and catch-up phenomena. Concerning preop. Vs postop comparison: By introducing the investigation compound several hours after surgery and the comparator before surgery we do not have a face-to-face situation. Surgical bleeding will probably be a few ml lower in the postop arm than the preop arm. If all clinical thrombotic vascular events like MI, stroke and PE were counted, the postop arm would benefit from a lower number since intra- and perioperative thrombotic events would not be counted before the drug is on board several hours after surgery. Thus, from a clinical point of view, the postop start may be a disadvantage. The highest overall mortality (dominated by vascular death) is close to surgery that will not be prevented with post op start (Lie at al Acata Orthop Acnd 2002). However, in a human THR/TKR model with sole focuse on postoperative silent DVT to asses the benefit-	Not accepted. The reduction of total mortality by reducing overall vascular deaths is not an appropriate aim for thromboprophylactic agents. In addition, such aim would be impossible to demonstrate anyway in the pre-MA setting. Starting LMWH before (12h) or after surgery has no demonstrated effect on intra-and postoperative bleeding. Furthermore, the 7th ACCP states that “the decision should be based on the efficacy-to–bleeding tradeoffs for that particular agent (grade 1A). For LMWH, there are only small differences between starting pre-operatively and postoperatively and both options are acceptable (grade 1A)” In addition new compounds are now started post-operatively, and sometimes compared with a preoperative start of LMWH. Finally, as far as the risk of developing a spinal haematoma is concerned, when a neuraxial block is performed, it appears that there is no more room for any preoperative start.

	to-risk, a postop drug initiation will surely be beneficial. This shows how a postop initiation of a compound benefits on a study design that only focus on postoperative DVT and not take into account clinical events that occur at an earlier stage (e.g. after Hip fracture the patient may get a thrombotic event after the trauma and before the operation). Today these postoperative designs are commonly used in non-inferiority studies in order to show safety benefits vs the established comparator (mostly enoxaparin)	
3.3 5th paragraph (2)	This sentence referring to the level of benefit should be seen in the below comment regarding placebo-control. The sentence should be either deleted or further elaborated	The sentence will be deleted. Necessary information is already given in 3.3 (4th paragraph)
3.4 1st paragraph (1)	… the duration of which should cover the time period with an increased VTE risk. Comment: That is not 5-6 w in THR and 10d in TKR but longer according to epidemiological and pathophysiological studies … the incidence of patients with **total DVT …** Comment: Good … proximal DVT … Comment: Meaningless. There is no clinical correlation between symptoms and location i.e. distal vs proximal location in orthopaedic pts. (Dahl OE Acta Orthop Scand 20002,Bjørnaå B JBJS-B 2006, Haas JBJS-B 1992). This may be valid in medical patients but not in orthopaedic traumatized patients. This is of minor interest in proof-of-concept studies and gives no additive information of clinical interest for surgeons.	The necessary duration of thromboprophylaxis in TKR patients is currently under discussion; a longer treatment period might be considered necessary (or not) in the future. Therefore, current guidelines are applied.
3.5 2nd paragraph (1)	… VTE related death … Comment: Meaningless phrase with no clinical reality today and should be deleted from our scientific wording. Total mortality should be the final endpoint. The major cause of postop. Deaths are due to thrombotic vascular complications cfr earlier referred	Not accepted. VTE-related death for non-inferiority trials and total death for superiority trials will be kept.

	citations.	
3.5 2nd paragraph (3)	The recommended primary endpoint is a composite of well-documented proximal DVT (asymptomatic and symptomatic), symptomatic and well documented non-fatal PE and VTE related death or death due to any cause. We propose that distal DVT be included in this endpoint as well. We propose this since 1) All currently approved products for VTE propylaxis were approved on studies that included asymptomatic DVT as a component of the primary endpoint. In these studies, events categorised as distal DVTs were the dominant element of the primary endpoint. It is widely accepted that VTE prophylaxis significantly reduces morbidity among patients who are immobilised following surgery, or following hospital admission due to an acute illness. For most patient groups, sufficient numbers of randomised clinical trials are available to allow strong recommendations with regard to the benefit/risks of specific VTE prophylaxis as described in the 7th ACCP Conference. The authors of the ACCP guideline "Prevention of Venous Thromboembolism" include EU and US experts, reflecting the global nature of this guideline. 2) Venographically detected asymptomatic DVT, including distal DVT, is an established surrogate marker. While there is controversy over the clinical significance of asymptomatic distal DVT, it was extensively shown that asymptomatic distal DVTs would propagate to proximal DVT in 7-32% of these patients (Ohgi et al. 1998; Lohr et al. 1995 and 1991; Lagerstedt et al. 1985; Haas et al. 1992; Philbrick and Becker 1998), and to PE in up to 5% (Haas et al. 1992; Lohr et al. 1991). In addition, as summarised in the ACCP guideline, "there is strong concordnace between the surrogate outcome of asymptomatic DVT and clinically important VTE". In the vast majority of controlled clinical trials, treatments that reduce asymptomatic DVT also had a beneficial effect with a similar risk reduction ratio for symptomatic VTE. Therefore, while distal DVTs may not warrant specific treatment in clinical practice, these events have proven utility as a surrogate marker for assessing the overall treatment effect of new medicinal products for DVT prophylaxis. The supporting data for this position are well summarised by Seghers et al concluding that "the critical application of the predefined criteria for the validity of contrast venography as a	Not accepted. See related answers on distal DVT. The text will read: As the primary aim of thromboprophylaxis is to prevent PE (fatal and non fatal), which is usually resulting from proximal DVT, the most clinically relevant endpoint is considered to be a composite endpoint consisting of clinically relevant and objectively documented events: - proximal DVT (asymptomatic and symptomatic) - symptomatic non-fatal PE - VTE related death or death due to any cause In addition, as symptomatic distal DVT are clinically relevant (patients with symptomatic distal DVTs are treated) and can be easily objectively documented, they might be a part of the composite primary endpoint. In order to prevent bias, it is highly recommended that the occurrence and classification of all components of the composite endpoint is adjudicated by an independent and blind committee of experts. The same clinically relevant events are recommended for superiority and for non-inferiority trials, except for causes of death. In non-inferiority trials, it is generally recommended to choose an endpoint reflecting as much as possible the effect of a drug; therefore, a VTE related death (or a death considered to be due to VTE, such as fatal PE and sudden death, as autopsy findings may not be always available) is recommended as part of a composite endpoint. For superiority trials, a death form any cause is recommended as a part of a composite endpoint. All deaths must be reported. Deaths should be carefully characterized regarding their relationship to VTE through adjudication by the blinded clinical events committee. Autopsy should be performed whenever possible. Criteria for classifying deaths according to cause should be provided in the protocol and detailed in the adjudication manual of the clinical event committee. Special care should be taken to include in clinical trials patients with reasonable life expectancy. In both cases, a supportive analysis of the composite endpoint using the alternative group of deaths should be provided, i.e. VTE- related deaths for a superiority trial and all cause deaths for a non inferiority trial. The use of a clinically relevant composite primary endpoint (excluding

	surrogate outcome reveals that this test can be used with confidence in the evaluation of new thromboprophylactic regimens". 3) Excluding distal DVT primary endpoint would require a significantly larger patient populations (3-4x) for therapeutic confirmatory trials (i.e. Phase III). and therefore jeopardize the development of these medicinal products in general. We propose the following revision to the criteria for the proposed primary endpoint for therapeutic confirmatory trials: - well-documented proximal <u>and distal</u> DVT (asymptomatic and symptomatic) - symptomatic and well documented non-fatal PE - VTE related death or death due to any cause	distal DVTs) is mandatory for new medicinal products under development for thromboprophylaxis of patients undergoing high-risk surgery in at least one active comparative trial in the recommended patient population (see section 4 Strategy and design of clinical trials). In the Section 4 the added text will read: As previously stated (see section 3.5), it is recommended to perform at least one comparative trial with the most clinically relevant composite primary endpoint (excluding distal DVTs); the recommended study population are patients with hip surgery (hip fracture and hip replacement). Patients with hip fractures should be well represented in the trial as they are frequently elderly, frail, overweight or underweight patients, with renal insufficiency and high risk for bleeding. In addition, this population has the highest number of clinically relevant events. Once acceptable efficacy and safety of a new product (as compared to the adequately dosed reference treatment regimen) have been convincingly demonstrated in the recommended patient population and using the most clinically relevant primary endpoint, a less stringent primary endpoint, such as a composite of total DVTs (proximal and distal), PE and death, might be used in the subsequent product development in orthopedic surgery, e.g. in patients with knee surgery. A choice of less stringent endpoint is based on the existence of a large efficacy and safety database acquired form the study done with the most clinically relevant endpoint. All clinically relevant parts of the composite endpoint (especially proximal DVTs, PE and deaths) should support the efficacy of the product in the presence of an acceptable safety profile.
(5)	There are indeed considerable controversies related to both primary efficac outcomes and bleeding outcome as outlined in the document. It is however unlikely that they will be resolved soon. As discussed above it is our view that venography remains the best test and for bleeding, new data will revea better definitions for major and clinically relevant non-major bleeding. So of the recent trials have already incorporated these new definitions and the clinical relevance has been assessed. Again we should carefully look at the 2004 ACCP document which discusses all these controversies.	Partly accepted. Venography remains authorised for diagnosis of VTE.
3.5	… the composite endpoint is adjudicated by an independent and blind	Accepted.

3rd paragraph (1)	committee of experts … Comment: These Committees need an international standardized way of assessing the events	
3.5 5th paragraph (1)	…. a VTE related death (or a death considered to be due to VTE, such as fatal PE and sudden death, as autopsy findings may not be always available) is recommended. ISTF Comment: Autopsies are seldom done and difficult to request in a study. Consequently, all cause mortality should be the endpoint. We know from autopsy studies and epidemiological cohort studies that the waste majority of patients are dying from thrombotic vascular complications after MOS (Dahl OE Thromb Haemost 2005).	True. However, VTE-related death in non-inferiority trials and total death in superiority trials will be kept for consistency.
3.5 5th paragraph (2)	In paragraph 5, a recommendation is given for the endpoints in non-inferiority trials. It seems that the use of VTE related death alone is proposed as endpoint. This is in contradiction to the recommended primary endpoint in therapeutic confirmatory trials which should be a composite endpoint (2nd paragraph of this chapter). The composite endpoint including deaths seems to be reasonable whereas the use of VTE related death alone for a non-inferiority trial is difficult to understand: with the low frequency of deaths in these trials, the overall number of patients to be investigated will be extraordinary high making these clinical developments impossible For non-inferiority, a clear statement re. use of the composite endpoint as stipulated should be made. It should be clear from the text that the mentioning of VTE related death as part of the composite endpoint is meant. Sentence should read: "In non-inferiority trials, it is generally recommended to choose an endpoint reflecting as much as possible the effect of a drug; therefore, a VTE-related death (that is, a death considered to be due to VTE, such as fatal PE; unexplained death; or sudden death)) is recommended **as part of a composite endpoint**". Note that in the sentence that follows this one the word should be "from"	Accepted.

	not “form”.	
3.5 (2)	• The draft document notes the importance of distinguishing between the entities of THR, TKR, and Hip fracture. • The draft document also makes the distinction between the length of treatment (page 6) for THR/Hip fracture (5-6 weeks) vs TKR (10-14 days), and notes that “within the high-risk level of different types of surgery (e.g. knee surgery, as opposed to hip surgery; …) have different safety profiles (bleeding), which are inherent to each type of surgery” (page 7). • However, the document does not recognize in its discussion of the primary efficacy endpoint in therapeutic confirmatory trials (page 6) that the thrombi observed differ by location. The literature notes that in patients having THR there is a high incidence of proximal DVT (18-36%) (Freedman et al, 2000; Hull et al, 1990; Gallus et al, 1983; Turpie et al, 1986; Beisaw et al, 1988; Haake and Berkman, 1989; Lassen et al, 1991; Hoek et al, 1992). In contrast, patients having TKR have a preponderance of thrombosis distally, that is, below the knee (incidence of 41-85% if no prophylaxis given (Lotke et al, 1996; Westrich and Sculco, 1996; Stulberg et al, 1984; Lynch et al, 1988; Stringer et al, 1989). This is in keeping with the surgeon’s requirement for a tourniquet just above the knee to provide a bloodless field. • The draft document also notes on page 3 that “the formation of a thrombus in a deep vein predisposes patient to symptomatic DVT and PE (which may be the initial clinical manifestation of a DVT) and fatal PE.” While high-risk groups for VTE can be identified, it is not possible to predict which individual patients in a given risk group will develop a clinically important thromboembolic event. • VTE is a continuum ▪ Most thrombi start in the calf veins, and often asymptomatic ▪ 10-20% propagate to the proximal veins (Lohr JM J Vasc Surg 1991; Maynard MJ Clin Orthop 1991; Solis MM. J Vasc Surg 1992; Kearon C. Circulation 2003) ▪ *Propagation leads to PE in 5% (Haas JBJS 1992, Lohr J Vasc Surg 1991)* • Calf thrombi are not benign ▪ A high proportion of venous thrombi leave residual venous	Partly accepted. It is true that in TKR patients there are more asymptomatic distal DVT and less proximal DVT than in THR patients, where the situation is the opposite. However, this is not the principal reason for accepting distal DVTs as a part of the composite primary endpoint. The text in Section 4 will read: As previously stated (see section 3.5), it is recommended to perform at least one comparative trial with the most clinically relevant composite primary endpoint (excluding distal DVTs); the recommended study population are patients with hip surgery (hip fracture and hip replacement). Patients with hip fractures should be well represented in the trial as they are frequently elderly, frail, overweight or underweight patients, with renal insufficiency and high risk for bleeding. In addition, this population has the highest number of clinically relevant events. Once acceptable efficacy and safety of a new product (as compared to the adequately dosed reference treatment regimen) have been convincingly demonstrated in the recommended patient population and using the most clinically relevant primary endpoint, a less stringent primary endpoint, such as a composite of total DVTs (proximal and distal), PE and death, might be used in the subsequent product development in orthopaedic surgery, e.g. in patients with knee surgery. A choice of less stringent endpoint is based on the existence of a large efficacy and safety database acquired form the study done with the most clinically relevant endpoint. All clinically relevant parts of the composite endpoint (especially proximal DVTs, PE and deaths) should support the efficacy of the product in the presence of an acceptable safety profile.

	abnormalities including persistent occlusion and/or venous valvular incompetence. (Prandoni P et al. Ann Intern Med 1996; Lindner DJ et al. J Vasc Surg 1986.) ▪ Post Thrombotic Syndrome develops in 5% of patients after TKR/THR (Ginsberg JS Arch IM 2000) • Reliance on symptoms or signs of "early" DVT is an unreliable strategy to prevent clinically important thromboembolic events; the first manifestation of VTE may be fatal PE Interventions that reduce asymptomatic DVT also convey similar relative risk reductions in symptomatic VTE (Eikelboom JW Lancet 2001; Hull RD Ann Intern Med 2001; Mismetti Br J Surg 200; Eriksson BI Arch Intern Med 2003; Mismetti P Thromb Haemost 2000). Therefore, in TKR and THR, distal DVT, whether asymptomatic or symptomatic, deserve to be part of the composite primary efficacy endpoint	
3.6 2nd paragraph (1)	… The following secondary endpoints need to be considered: …… Comment The indicated secondary endpoint list is of minimal clinical interest. The secondary endpoint on this level i.e. phase II study should rather be, all cause mortality, vascular morbidity and Adverse Events (e.g. all AE and SEA that cause study drug stop). The cumulative events should be plotted (overall and separately), the overall rate in both arms and the difference i.e. net clinical effect should be calculated	Not accepted. Cardiovascular events are frequent in patients undergoing high risk surgery (myocardial infarction, arrhythmia, hypertension). However, arterial thrombosis is mainly due to platelet activation and antithrombotic agents, given for venous thromboprophylaxis, have no direct effect on platelets. Therefore, the reduction of total mortality by reducing overall vascular deaths is not an appropriate aim for thromboprophylactic agents. In addition, such aim would be impossible to demonstrate anyway in the pre-MA setting.
3.6 2nd paragraph (2)	It is recommended that the primary endpoint should not be restricted to proximal DVT. We believe that distal DVT (asymptomatic and symptomatic) should remain a component of the primary composite efficacy endpoint in therapeutic confirmatory trials for the following reasons: 1) Distal DVT remains a clinically relevant condition that requires anti-coagulant therapy. The British Committee for Standards in Haematology, in its recent update (June 2005)[iii], recommended that distal DVT (calf vein thrombus) be treated with oral anti-coagulation therapy at the same INR intensity as in proximal DVT (grade A,	The text will read: As the primary aim of thromboprophylaxis is to prevent PE (fatal and non fatal), which is usually resulting from proximal DVT, the most clinically relevant endpoint is considered to be a composite endpoint consisting of clinically relevant and objectively documented events: - proximal DVT (asymptomatic and symptomatic) - symptomatic non-fatal PE - VTE related death or death due to any cause In addition, as symptomatic distal DVT are clinically relevant (patients with symptomatic distal DVTs are treated) and can be easily objectively documented, they might be a part of the composite primary endpoint.

	level 1b). 2) Post-operative, asymptomatic, venographically confirmed DVT is known to propagate to proximal DVT in 7% to 32% of patients[iv,v,vi,vii,viii,ix], and to PE in up to 5% of patients [iii, vi] 3) Distal DVT is well established and recognized by Regulators worldwide as an acceptable part of the primary composite outcome in pivotal postoperative DVT prophylaxis studies. Lovenox/Clexane[x] and Arixtra[xi] were approved on the basis of a composite endpoint including the distal DVT. "The recommended primary endpoint in therapeutic confirmatory trials should be a composite endpoint consisting of clinically relevant and objectively documented events: - well-documented proximal ***and distal*** DVT (asymptomatic and symptomatic) - symptomatic and well documented non-fatal PE - ***VTE related death "***	In order to prevent bias, it is highly recommended that the occurrence and classification of all components of the composite endpoint is adjudicated by an independent and blind committee of experts. The same clinically relevant events are recommended for superiority and for non-inferiority trials, except for causes of death. In non-inferiority trials, it is generally recommended to choose an endpoint reflecting as much as possible the effect of a drug; therefore, a VTE related death (or a death considered to be due to VTE, such as fatal PE and sudden death, as autopsy findings may not be always available) is recommended as part of a composite endpoint. For superiority trials, a death form any cause is recommended as a part of a composite endpoint. All deaths must be reported. Deaths should be carefully characterized regarding their relationship to VTE through adjudication by the blinded clinical events committee. Autopsy should be performed whenever possible. Criteria for classifying deaths according to cause should be provided in the protocol and detailed in the adjudication manual of the clinical event committee. Special care should be taken to include in clinical trials patients with reasonable life expectancy. In both cases, a supportive analysis of the composite endpoint using the alternative group of deaths should be provided, i.e. VTE- related deaths for a superiority trial and all cause deaths for a non inferiority trial. The use of a clinically relevant composite primary endpoint (excluding distal DVTs) is mandatory for new medicinal products under development for thromboprophylaxis of patients undergoing high-risk surgery in at least one active comparative trial in the recommended patient population (see section 4 Strategy and design of clinical trials). In the Section 4 the added text will read: As previously stated (see section 3.5), it is recommended to perform at least one comparative trial with the most clinically relevant composite primary endpoint (excluding distal DVTs); the recommended study population are patients with hip surgery (hip fracture and hip replacement). Patients with hip fractures should be well represented in the trial as they are frequently elderly, frail, overweight or underweight patients, with renal insufficiency and high risk for bleeding. In addition, this population has the highest number of clinically relevant events. Once acceptable efficacy and safety of a new product (as compared to

		the adequately dosed reference treatment regimen) have been convincingly demonstrated in the recommended patient population and using the most clinically relevant primary endpoint, a less stringent primary endpoint, such as a composite of total DVTs (proximal and distal), PE and death, might be used in the subsequent product development in orthopedic surgery, e.g. in patients with knee surgery. A choice of less stringent endpoint is based on the existence of a large efficacy and safety database acquired form the study done with the most clinically relevant endpoint. All clinically relevant parts of the composite endpoint (especially proximal DVTs, PE and deaths) should support the efficacy of the product in the presence of an acceptable safety profile.
3.6 2nd paragraph (2)	"All DVT", component of the previous composite endpoint, is now replaced by "proximal DVT". This new composite endpoint is a major hurdle to perform confirmatory trials in the surgical setting and will dramatically increase (more than 5 fold increase) the sample size of such trials e.g. , the sample size of a knee trial will increase from 440 (if all DVT) to more than 3000 (if only proximal are considered, based on a VTE event rate in the comparator of 25%, RRR = 50%, power of 90% with an alpha of 0.05 and bilateral test). For a hip trial, the sample size would increase from 1200 to more than 6000 (for a 10% event rate in the comparator arm and based on 50% RRR). Distal DVT should remain part of the endpoint because a distal DVT carries the risk (1/5) of propagation to proximal DVT. The B/R should be assessed with the all DVT component otherwise the trial becomes unfeasible.	The comment is relevant. Comparative clinical trials using the currently recommended composite primary endpoint are considered feasible. There are currently ongoing clinical trials with 6000 patients to be included in total with the currently recommended composite primary endpoint (proximal DVT, PE and VTE-related death). In addition, symptomatic distal DVT are also included (this represents roughly 0,5% of patients).
3.6 2nd paragraph (2)	Adding all deaths in the composite end point would inevitably add background noise from competing risks e.g. in cancer mortality especially when dealing with patient with high mortality risk and in trials when there is a competing risk of death. Anyhow, number of all deaths in each group will be documented and looked at, independently of the type of design (non inferiority or superiority) as part of the proof that the investigational product is causing no adverse effect. It is strongly recommended to include VTE-related death (and not all cause deaths) as part of the primary composite endpoint in a trial	This is currently proposed in the guideline

	designed to demonstrate VTE prophylaxis. All other deaths should be reported as safety outcomes and should be included as part of a composite secondary efficacy endpoint.	
3.6 7th paragraph (2)	Deaths criteria should not be detailed in the protocol but are specified in the adjudication manual of the Clinical Event Committee since this latter will have an input into this definition. The paragraph pertaining to deaths (penultimate paragraph of page 6/11) should read as follows: "All deaths must be reported. Deaths should be carefully characterised regarding their relationship to VTE through adjudication by the blinded clinical events committee. Autopsy should be performed whenever possible. Criteria for classifying deaths according to cause should ***be briefly described in the protocol but detailed in the adjudication manual of the Clinical Event Committee***. . Special care should be taken to include in clinical trials patients with reasonable life Expectancy ».	Accepted.

4.

Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1 1st paragraph (1)	The majority of published trials have been performed in patients with high VTE risk Comment: Today: "high" means high risk of silent DVT not clinical – the clinical rate is low and fatal PE is rare even with a few days of prophylaxis – in Europe (Lie Sa Acta Ortop Scand 2002, Bjørnaråa B JBJS-B 2006)	Accepted. This will be specified.
4.1 4th paragraph (2)	For a trial stratified by surgery types, the additional request to power this trial for type of surgery is excessive: similar trend should be seen for each strata to corroborate the global results of the trial.	Not accepted. Full stratification for the type of surgery will be requested.
4.1 5th paragraph (1)	Therefore, this guideline will focus on clinical development of medicinal products aimed to provide appropriate thromboprophylaxis to patients undergoing surgery with **high VTE risk** Comment ISTF highly agree that we have to consider those patients that traditionally have been excluded from drug development studies. However, this information is best obtained in a final third-level study with solely clinical endpoints that comes in addition to the classical	No specific comment

	phase II and III studies	
4.1 5th paragraph (2)	This section about the different efficacy of prophylactic regimens is inconsistent with a previous statement under section 1, paragraph '**prevention by drugs'** where more than 60% reduction of VTE is claimed for all these drugs. Therefore, it is not appropriate to refer to a difference in efficacy because various surgeries carry different VTE risks but the RRR achieved is the same especially when referring to reference 7 & 8 with fondaparinux.	Not accepted. LMWH and fondaparinux are less effective in TKR patients than in THR patients.
4.1 6th paragraph (1)	… patients should be fully stratified and powered for type of surgery Comment Good. This should be a clinical study without surrogate endpoints.	No specific comment
4.1 7th paragraph (1)	… the same LMWH dose appears to be less potent in total knee replacement patients as compared with total hip replacement patients, as far as the venographic *and* symptomatic VTE are concerned Comment However, the DVT rate is higher than the PE rate in contrast to THR and the overall mortality is a bit lower than THR.	True.
4.1 7th paragraph (3)	The current draft of the guidance indicates that a larger claim, such as "prevention of VTE in patients (at high risk for developing VTE) undergoing major orthopaedic surgery", may be granted in case of positive results from 2 trials: - hip surgery (hip replacement and hip fracture together)(long prophylaxis trial) - knee surgery (short prophylaxis trial) We propose that a larger claim of prevention VTE should be granted following positive results from 2 trials, one each in hip replacement and knee surgery. Furthermore, we believe that patients undergoing surgery for hip replacement vs hip fracture represent significantly different populations with regard to potential risk profile and should not be considered in the same trial.	Not accepted. Patients with hip fracture should be the part of the development of a new thromboprophylactic agent (elderly, low body weight, high bleeding risk, decreased renal function, longer immobilisation).
4.1 8th paragraph (1)	A larger claim, such as "prevention of VTE in patients (at high risk for developing VTE) undergoing major orthopaedic surgery", may be granted in case of positive results from 2 trials: - hip surgery (hip replacement and hip fracture together)(long prophylaxis trial) - knee surgery (short prophylaxis trial) Comment:	Not accepted. Overall mortality trials are not feasible in the pre-MA setting. See related comments on cardiovascular events.

	Comment to THR and HF. These are two widely different populations. The first is a surgical selected, medical optimized and healthy group with a very low mortality, - at least below 70 years of age. In contrast, the HF patients are in average 10 years older (~80 years), non-selected, comorbide, gracile, vulnerable and with a high post-traumatic mortality. The HF group is not suited for early drug development studies with surrogate endpoints and a lot of blood sampling. These patients should be explored in pure clinical trials with simple clinical endpoints like overall mortality. This is based on experience from drug studies conducted in these patients. The studies conducted in the HF population up to now are mostly highly selected patients and the result of these studies can hardly be extrapolated to the general HF population at a much higher age.	
4.1 9th paragraph (2)	The global claim of VTE prophylaxis in major abdominal surgery based on a trial in long term prophylaxis in the same surgical setting in cancer patients is not without regulatory and legal difficulties: there is no comparator for the time being with a registered claim in this setting!	True. However, there have been 2 published trials in major abdominal surgery setting, one with enoxaparin and one with dalteparin. MA has been granted to dalteparin (high risk and cancer surgery), and to fondaparinux (abdominal high risk surgery and abdominal surgery for cancer). Enoxaparin has a large indication (high risk surgery) and is frequently used in this setting.
4.2 PK (2)	The recommendation is made to use some coagulation tests and not others. Ecarin clotting time is quoted whereas this test has been used to monitor some recent factor IIa inhibitors such as hirudin, but is not sensitive to heparins or other FXa inhibitors. Therefore, activated partial thromboplastin time (aPTT) used for decades to monitor UFH is missing and should be listed. Add activated partial thromboplastin time (aPTT) as a possible test to be used to monitor UFH	Accepted.
4.2 PK (2)	The recommendation is made to evaluate special populations including elderly (>70 y old). The 70 years cut-off used is different from the ones used in ICH-E7 which uses two different cut-off for geriatrics/ elderly: 65 years or older and 75 years or older. We suggest to use similar cut-off to ICH-E7.	Accepted. 75 years or older cut-off will be recommended.
4.3 1st paragraph (1)	These studies should allow to choose both the appropriate doses(s) of the medicinal product, and the appropriate timing of the initiation of treatment in relation with surgery (pre-op or post-op administration).	No specific comment

	Comment: Good, however, keep in mind that this is highly marked driven by the companies. To day they start postop. to avoid surgical bleeding. Since silent DVT is the efficacy outcome the study, clinical pre- (after e.g. hip fracture) and intra- operative events like the microembolism syndrome, (= fat embolism syndrome that may be fatal) or immediate postop events like stroke and MI will not captured. Recent large epidemiological studies (~180 000 pts, Norwegian and Australian Hip arthoplasty registers) have shown that the highest mortality is close to surgery. Thus, from a clinical point of view postop initiation should therefore be questioned. These periopeative cases will not be taken into account in early drug development trials since the endpoint is venographically proven DVT or, - the cases will be too few to give any meaning, due to the small sample size in such a study. However, in large population based studies, perioperative vascular mortality is the real health burden and not surgical increased bleeding that mostly cases no sequela.	
4.3 2nd paragraph (3)	Defines elderly as >70 years as one of the groups that might require specific evaluation. We propose >65 years as a definition of "elderly"	75 years or older cut-off will be recommended.
4.3 2nd paragraph (3)	Indicates "extremes of body weight" as one of the groups that might require specific evaluation. "Extremes of body weight" should be more clearly defined. We propose that BMI criteria be provided to define these populations	Not accepted. "Extremes of body weight" will be kept.
4.3 3rd paragraph (1)	The use of a placebo-control group, when ethical, is strongly recommended. Comment Very good. Highly appreciated.	No specific comment
4.3 5th paragraph (1)	If patients with more than one type of surgery are included (e.g. hip, knee), they should be stratified according to type of surgery. Comment: Good, elective groups should be in one study and not mixed with emergency patients like hip fracture patients (vide supra)	No specific comment
4.3	In this paragraph, it is strongly recommended to use a placebo-control group, when ethical. This guideline specifically deals with thrombosis prophylaxis in patients	No specific comment

	having a high-risk of thromboses. Therefore, it is hard to see how a placebo-control can be justified in this population. It would be highly appreciated to have more information under which circumstances placebo-control would be acceptable in these patients.	
4.6 6th paragraph (1)	Safety in special populations should be prospectively assessed for inclusion of the sub-groups in SPC. If monitoring is required, it is recommended that this be assessed in the main trials. Comment: The best way to implement "outliers" i.e. fat, thin, reduced clearance, thrombotic risk (previous MI, stoke, VTE) etc is to limit the exclusion criteria. This should be done in phase II studies. The exclusion criteria should be limited to contraindications to the comparator drug (if used) and the study procedure (e.g. hypersensitivity to radiological contrast media)	Agreed.
5.		
Line no. + para no.	**Comment and Rationale**	**Outcome**
1st paragraph (1)	If an anticoagulant is to be tested, bleeding is the most important safety issue that will need a thorough evaluation … Comment: From a clinical point of view, adverse events associated to the drug are as important as bleeding. Requested by surgeons for years	All adverse events, not only those related to bleeding, are systematically assessed in clinical trials.
3rd paragraph (2)	It is of interest that the definition of bleeding is outlined as follows "Bleeding should be classified as major or minor. Examples of major bleeding include: - fatal bleeding - clinically overt bleeding associated with a decrease in the haemoglobin level of more than 20 grams/l compared with the pre-randomisation level - clinically overt bleeding leading to transfusion of two or more units of whole blood or packed - cells - critical bleeding (intracerebral, intraocular, intraspinal, pericardial, or retroperitoneal) - bleeding warranting treatment cessation	

	- bleeding located at the surgical site and leading to re-operation Nevertheless, the definition of major and minor bleeding should be in accordance with the International Society on Thrombosis and Haemostasis (ISTH) Guidelines". <u>Should read:</u> "***While there are currently no internationally accepted guidelines on the*** *definition* ***of bleedings in surgical patients, bleeding should be classified as*** *major or minor* ***according to the international accepted standards, such as those formulated by the International Society*** *on Thrombosis and Haemostasis (ISTH) Guidelines* ***for medical patients".*** It is suggested that the definition of "bleeding should be classified by following as much as possible available clinical guidelines such as the ISTH, and this for the following reasons: 1. By making general reference to the International Society on Thrombosis and Haemostasis (ISTH) Guidelines for classification of major or minor bleeding it ensures that the Regulatory Guideline is always consistent with the Clinical guidelines and not out of date if the clinical guidelines are updated. 2. The definition in the draft CHMP/EWP/707/98 guideline is inconsistent with the International Society on Thrombosis and Haemostasis (ISTH) Guidelines and could lead to confusion and inconsistencies (the following examples are not included within the ISTH definition of major bleeding) - bleeding warranting treatment cessation - bleeding located at the surgical site and leading to re-operation	Accepted. This will be kept (specific for patients undergoing surgery)
3rd paragraph (2)	There is no ISTH guidelines on the definition of bleedings in surgical patients (ISTH definition applies only to medical patients). Therefore, the second example of MB cited *"- clinically overt bleeding associated with a decrease in the haemoglobin level of more than 20 grams/l compared with the pre-randomisation level"* is more appropriate in a medical setting and not really pertinent in a surgical	Accepted.

	setting because it would lead to classify all the patients as having had a MB (as indeed, it is rather normal for any patient undergoing orthopedic surgery to bleed and to have a decrease in Hb level). - The MB example *about "bleeding located at the surgical site and leading to re-operation"* should be better defined to add "any unusual medical intervention (e.g. ponction of an haematoma at the surgical site, transfer to an ICU or emergency room)". The sentence would read: - "*bleeding located at the surgical site and leading to re-operation or to* any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room)""	Accepted.
4th paragraph (1)	Nevertheless, the definition of major and minor bleeding should be in accordance with the International Society on Thrombosis and Haemostasis (ISTH) Guidelines Comment: This is a version that is under revision and this will be done by the surgeons in **ISTF.** We are currently working on a short version of the ISTF protocol previously presented to CHMP via Mia van Petegem. This paper has been approved by all global ISTF members and will be presented to the international scientific community. ISTH is a Society dominated by laboratory people and internist with no or limited experience with surgical patients. Bleeding is of major concern (together with other AE) to surgeons. This chapter should therefore be handled by surgeons and ISTF should be cited. The above referred definitions are originally derived from medical patients (although CPMP came with a note a few years back) and do not fit into surgical practice. Applying these definitions in surgical patients and even performing statistical calculations on those definitions can give strange results not seen in clinical practice. Almost 90% of bleedings in anticoagulant phase II and III trials are surgical wound bleeding. There is no need to name this something else. Among the other 10% as listed above, some are so unusual that they should be described separately e.g. CNS bleeding. The bleeding index has no meaning to surgeons and should be deleted. There is so much confusion among surgeons about these non-surgical terms that they should be thoroughly re-considered and revised. It is meaningless to use the same	The currently proposed definition of major and minor bleeding will be kept. Any new internationally accepted definition(s) in future will be discussed.

	wording e.-g major bleeding for e.g. a joint bleeding and a cerebral bleeding. In joint surgery, bleeding up to amore than 2 litres may be considered as normal in particular if non-cemented prostheses are implanted. While a few ml blood in a critical part of the brain stem will kill you. I suggest that the draft protocol by International Surgical Thrombosis Forum (ISTF) that has been circulated to you by Mia van Petegem should be considered. That is based on the experience of the most skilled scientists and surgeons in this area. Medical and surgical drug development should not be mixed. Your below suggestion to measure the real bleeding volume in suction drains and wound drains combined with measurement of Hgb and the number of transfused units PRBS, is in accordance with the clinical reality and should be used to quantify bleeding and not medical definitions and indexes. If special formulas should be used to get a more "correct" idea of bleeding, is more of academic interest. The most important is that all centres obtain bleeding information in the same way and in accordance with daily clinical practice.	
4th paragraph (2)	Concerning the bleeding related parameters, the instructions given (page 10, 3rd and 4th bullet) may not be feasible in every trial e.g., large trials and may give false sense of precision!	See text in the guideline for calculated blood loss
5th paragraph (1)	… (weight of swabs and operative drapes, volumes in the suction bottles after surgery, and drain collectors on admission to the post-anaesthesia care unit and thereafter for the two post-operative days), Comment: Very good … incidence of patients receiving transfusion of packed red cells and transfused quantities during the treatment period. (homologous and autologous transfusions need to be distinguished). Comment: Cell savers and retransfusion techniques should preferably be avoided in drug development studies. These methods carries a risk of retransfusion of activated Tissue Factor expressing cells, Tissue Factor containing microparticles and other procoagulant products. The prothrombotic risk of using these techniques in orthopaedic patients is not properly investigated.	No specific comment Cell savers are the part of the common clinical practice and can not be avoided.

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