20 July 2017
EMA/CHMP/33407/2017
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on clinical investigation of new medicinal products for the treatment of acute coronary syndrome' (EMA/CHMP/760125/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	AstraZeneca
2	EFPIA – Tiia Metiäinen (tiia.metiainen@efpia.eu)
3	The COMET Management Group* and Professor Philippe Gabriel Steg (Université Paris-Diderot) * The COMET Management Group: Professor Paula Williamson (University of Liverpool) Professor Jane Blazeby (University of Bristol) Professor Mike Clarke (Queen's University Belfast) Professor Doug Altman (University of Oxford) Dr Elizabeth Gargon (University of Liverpool) Dr Sean Tunis (Center for Medical Technology Policy)

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	EFPIA welcomes the opportunity to comment on the draft Guideline on clinical investigation of new medicinal products for the treatment of acute coronary syndrome. The proposed changes are suggested regarding the study endpoints, which may need to be tailored according to their relevance for specific patient types or therapies. Some comments are also proposed regarding the use of biomarkers, the patient population and overall treatment strategy.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 152 and Line 235	1	Comment: the requirement ("should" and "is mandatory") for central adjudications stated too strong. In large outcome studies, endpoints are usually centrally and externally adjudicated, a process intended to reduce bias and increase accuracy. Health authorities generally recommend adjudication of endpoints for these studies. However, depending on the study and the choice of endpoint, adjudication may have no material impact on the estimated effect of a treatment (Pogue et al 2009). A recent study suggests that treatment effect estimates in multi-site randomised studies assessed on-site (eg, by investigators) do not differ from those assessed by adjudication committees, and that adjudication by external adjudication committees may be most important in unblinded studies (Ndouga Diakou et al 2016). It has therefore been challenged whether the benefits of adjudication are great enough to justify the additional time and cost in all studies. The need for adjudication also depends on the nature of the endpoint in question, e.g. all-cause death does not need to be adjudicated, (Calvo et al 2014, Pogue et al 2009). For "softer endpoints" independent adjudication of these endpoints is necessary e.g., the need for urgent revascularization as this can reflect investigator preference or local practice, rather than the effect of a study drug (Bueno et al 2016).	Not accepted. Adjudication is still a relevant step to verify the robustness of the measured endpoints especially in global studies with different standards of care and definitions.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		References: Bueno H, de Graeff P, Richard-Lordereau I3 Emmerich J4 Fox KA5 Friedman CP et al. Report of the European Society of Cardiology Cardiovascular Round Table regulatory workshop update of the evaluation of new agents for the treatment of acute coronary syndrome: Executive summary. Eur Heart J Acute Cardiovasc Care. 2016 Jun 29. pii: 2048872616649859. [Epub ahead of print] Calvo G, McMurray JJ, Granger CB, Alonso-García Á, Armstrong P, Flather M, et al. Large streamlined trials in cardiovascular disease. Eur Heart J. 2014 Mar;35(9):544-8 Ndounga Diakou LA, Trinquart L, Hróbjartsson A, Barnes C, Yavchitz A, Ravaud P, et al. Comparison of central adjudication of outcomes and onsite outcome assessment on treatment effect estimates. Cochrane Database Syst Rev. 2016 Mar 10;3:MR000043. Pogue J, Walter SD, Yusuf S. Evaluating the benefit of event adjudication of cardiovascular outcomes in large simple RCTs. Clin Trials. 2009 Jun;6(3):239-51. Proposed change: Line 152: "Endpoints ~~should~~ may be centrally adjudicated by a blinded committee, but if justified investigator reported events may be considered. The need for central adjudication is also dependent on the	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		nature of the endpoint (e.g. all-cause death does not need to be adjudicated)." Line 235: It is mandatory to report ~~and centrally adjudicate~~ all mortality data where survival is an endpoint of the study. Central adjudication may be used, but is not mandatory.	
157-158	1	Comment: The statement "All cause mortality is the most important endpoint in clinical trials for the estimation of the benefit-risk balance of a drug." is partly contradictory, given that later on it is argued that CV mortality may be more specific and relevant. Proposed change: All-cause mortality is ~~the most~~ an important endpoint in clinical trials for the estimation of the benefit-risk balance of a drug, in particular when investigating newer medicinal products with possible safety issues.	Partially Accepted. The choice between investigating all cause vs cardiovascular mortality is updated throughout the document. This update takes into consideration the objective of the study and also the possible methodological issues encountered when cardiovascular deaths are investigated. Section now reads: As one of the goals of treatment of ACS is reduction of mortality, this is an important endpoint to measure. Assessment of mortality in confirmatory trials should include both all-cause mortality and cardiovascular mortality.
164 -165	1	Comment: It is suggested that when using CV mortality as a component in the primary endpoint, all cause mortality should be included as a key secondary endpoint. This should not mean that all cause mortality would be required as a part of the confirmatory testing strategy in this setting. Proposed change: As such, one of the two mortality endpoints should be included as a component of the primary endpoint, with	Partially accepted: Change: As one of the goals of treatment of ACS is reduction of mortality, this is an important endpoint to measure. Assessment of mortality in confirmatory trials should include both all-cause mortality and cardiovascular mortality

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the other investigated as a key secondary endpoint (note that the secondary endpoint does not need to part of the confirmatory testing strategy).	
Line 335	1	Comment: In the paragraph on enrichment strategies for achieving a higher event rate and thus reduce the time and number of patients needed to reach the target number of events, there is a wording opening up for not only the higher event rate, but also a "potentially larger treatment effect". However, a strategy resulting in such impact on the relative effect of the treatments should probably be discouraged, since this might also affect the outcome of a benefit-risk analysis compared to what might have been observed in an unenriched population. Proposed change: "Enrichment strategies are sometimes used in trials to obtain the required number of events with a reasonable time in specific subgroups who are likely to exhibit a higher event rate than the overall target population ~~and potentially larger treatment effect.~~ If such a strategy is to be used it is of importance that with the relative effect of the treatments stay unaffected; that the treatment investigated does not affect the enrichment factors per se; and that the results of this enriched study population can be extrapolated to the general population."	Partially accepted: The section is now re worded, removing reference to treatment effect: Enrichment strategies are sometimes used in trials to obtain the required number of events within a reasonable time frame by performing studies in specific subgroups which are likely to exhibit a higher event rate than the overall target population. If such a strategy is used, it should be discussed further within the context of the external validity for the claimed indication.
460-461	1	Comment: The recommendations for stratification seems too strong. Stratification may not be needed at all in large-scale outcome studies.	Partially accepted: There are similarities between the main qualifying conditions allowing investigating these patients in one study, if the

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: ~~At least,~~ It is recommended to consider stratification of the randomisation ~~should be stratified~~ for region (if applicable) and the qualifying condition (STEMI, NSTEMI and UA). Other risk factors (gender, age) may be considered for stratification of the randomisation, in addition.	intervention is comparable. Stratification for the qualifying condition is still mandatory to ensure proper representation of each subgroup, and thus enabling proper B-R assessment in each subgroup. The sequence of sentence is now changed, mentioning the stratification for the qualifying condition first, then the region (if applicable).
469	1	Comment: “all adverse events should be carefully documented” may need to be relaxed. In some outcome studies, for substances already approved, it may be sufficient to collect SAEs.	Partially accepted: In the context of a registration clinical trial, it is expected that all AE would be collected to assess causality. However, the emphasis is put on bleeding and mortality. This is currently addressed as: During the course of the clinical trials, all adverse events should be carefully documented; the most important being bleeding and all-cause death.
Line 496	1	Comment: Choice of appropriate bleeding scale has been debated. The GUSTO criteria has often been used, is clinically easily assessed, and could be an alternative for Large streamlined trials in cardiovascular disease. Proposed change: The GUSTO criteria is clinically easily assessed, and could be used for large streamlined trials in cardiovascular disease. Dual reporting of bleeding events using ~~both~~ either the GUSTO or TIMI and BARC definitions could be considered for future clinical trials and/or regulatory submissions to improve the comparative assessment of safety endpoints across	Partially accepted: Preference of one bleeding classification over the other is not supported by clinical data. The text is currently modified to include the choice between GUSTO, TIMI or BRAC definitions, as follows: line 531: Reporting of bleeding events using two acceptable definitions e.g, GUSTO, TIMI and BARC definitions [21] could be considered for future clinical trials and/or regulatory submissions to improve the comparative assessment of safety endpoints across medicinal products and trials.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medicinal products and trials.	
157-163	2	Comment: We agree that all-cause mortality is appropriate for the estimation of the benefit risk balance of a drug and that CV mortality is linked to the mode of action of the drug. However, when the primary endpoint is an efficacy endpoint, CV mortality is most appropriate. It should be further clarified what is meant by "the earliest part of the follow-up" as endpoints in ACS programs include both early (eg, 30 day) and later (6 month) time points. We agree that the endpoint will depend on the objective, but do not understand why CV mortality would be appropriate for non-inferiority trials and all-cause mortality is appropriate for a superiority design. Moreover, "net clinical benefit" which is implied by all-cause mortality is relegated to a secondary endpoint later in the document (lines 220-222) Proposed change: On the other hand, CV mortality is more specifically linked to the mode of action of CV medicinal products/intervention ~~and is especially relevant when the earliest part of the follow-up is assessed~~. The choice is also dependent on the objective of the study ~~i.e. in non-inferiority trials, CV mortality may be preferred while in superiority trials all cause mortality is usually used.~~ In fibrinolysis studies, all cause mortality is preferred (see section 4.9).	Partially accepted: The choice between investigating all cause vs cardiovascular mortality is updated throughout the document. This update takes into consideration the objective of the study and also the possible methodological issues encountered when cardiovascular deaths are investigated. Now lines 159-160: Assessment of mortality in confirmatory trials should include both all-cause mortality and cardiovascular mortality. (see section 5.1).
164-165	2	Comment: We agree with this statement and suggest that the intent is consistent with the discussion above.	No change is proposed.
204	2	Comment: We agree that occurrence of HF should be	No change is proposed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered as a clinical endpoint in Ph III studies and can be considered as part of a composite of the primary endpoint if the mechanism of action of the drug is to prevent HF.	
210-213	2	Comment: We agree that non-fatal stroke has had limited contribution to the MACE endpoint. However, non-fatal MI may also not be an appropriate component of the composite endpoint in all settings, for example when a drug's predominant effect is on preserving myocardial function. Proposed change: "Death and endpoints appropriate to the drug's mechanism of action; ~~As such, it is preferred to investigate the composite of death and non-fatal MI in confirmatory studies;~~ non-fatal ischaemic stroke could be included in the composite if justified."	Not accepted. Considering that the most frequently investigated medicinal group in ACS are antithrombotics, and the main objective of these studies is to prevent MI, it is justified to include non-fatal MI in the investigated composite .
218-219	2	Comment: We acknowledge that each component of the primary endpoint will be analysed separately. However the choice of secondary endpoints should depend on the study objectives. Proposed change: ~~Each component of the primary composite endpoint should be analysed as secondary endpoint.~~	Not accepted. The components of the composite endpoint should be analysed separately to adequately inform on the contribution of each component and eventually the B-R. However, it is agreed this analysis should not necessarily be part of the confirmatory testing strategy, unless there are specific claims.
Line 218-219:	2	Comment: The wording "analysed as secondary endpoint" can be interpreted as "analysed within an alpha-preserving multiple testing strategy". If this is the meaning it could be questioned then whether this is really necessary. It is clear that the components	Not accepted: See point before. This is an addition further clarified in section 7.3.5, where it is mentioned that "The components of a composite efficacy endpoint should be analysed individually in order to evaluate their contribution to the overall results."

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		need to be analysed separately, but this could be done in an exploratory manner, as the power to show an effect on the components is often low. The PtC on multiplicity also emphasize, that it is not necessary to test components as secondary endpoints, only if claims are to be based on subgroup of components. Usually, once statistical significance is shown for the composite EP, we should analyse the individual components just to assess the consistency of the treatment effect over the components rather than to demonstrate statistical significance. The sponsor is frequently discouraged (e.g. by FDA) to look at variations of the primary composite or the individual components “again” in an alpha-controlled testing strategy for the secondary endpoints. On the other hand (more unlikely case), given the test for the composite EP fails to show significance, the question is how to “save” the study if there is a clear benefit in individual component(s). To address this by secondary endpoints might not serve the purpose. Therefore, please clarify that each component of the primary composite endpoint should be analysed individually with no multiplicity adjustment necessary.	
293-294	2	Comment: Cardiac troponins play a central role in the diagnosis and risk stratification of MI. However, in global clinical trials, not all sites have access to troponin assays and rely on CK-MB for diagnosis. It may be useful to recognize this option.	Not Accepted. Use of troponin is the standard of care in EU, and centers recruited in global trials are expected to follow such standards.
Lines 308 -	2	Comment: The practical considerations of having	Not accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
312		separate clinical trials for NSTEMI and UA populations should be considered carefully as it may be difficult to categorize subjects at randomization. This would be dependent on the availability of highly sensitive troponin assays and for the results to be returned very quickly globally. Proposed change: In light of the above comment, another approach that could be considered and captured in the guideline would be to include both populations in one study and prospectively define subgroup analyses to investigate the outcome of interest in both groups.	The present wording is soft enough to allow the inclusion in the same study if justified.
338-339	2	Comment: Enrichment strategies are common in cardiovascular trials which are already very large and lengthy. In general, the enriched population represents one end of a pathophysiologic spectrum. Proposed change: " In that case, ~~it has to be shown that the results of this enriched study population can be extrapolated to the general population~~ consideration should be given to how the results are applicable to the general population."	Agreed, but wording is slightly different: Now line 374-375: If such a strategy is used, it should be discussed further within the context of the external validity for the claimed indication.
Lines 425 - 427	2	Comment: The guidance states that if the investigation drug has a different mechanism to that of standard therapy then it should be given in addition to standard therapy in the study. While this has been how drugs have been developed for this population of patients to date, looking at some recent failed ACS trials, one	Partially Accepted. It is acknowledged that the investigational drug should always be administered on top of all other products, but in some cases it can replace other products. The sentence is modified as follows: Whenever, plausible and adequate (i.e different mechanism of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		could question whether adjunctive therapy is always the right approach – one should also be testing approaches which involve the potential removal of older treatments to see if this would translate into better outcomes. New treatment strategies should be explored/compared and one should not always go down the route of adjunctive therapies as this a) raises the medicines burden for patients and b) does not represent the true benefit risk for the new medicinal compound. Proposed change: In light of the above comment, suggest additional wording at the end of sentence line 427: "Whenever plausible and adequate (i.e. different mechanism of action than that of standard therapy) the investigational drug or placebo should be given in addition to standard therapy. <u>However, different treatment strategies may need to compared to avoid increasing the burden of medicines in this patient population"</u>	action than that of standard therapy) the investigational drug or placebo should be given in addition to standard therapy, unless otherwise justified e.g investigating a different treatment strategy**.**
Lines 446-467	2	Comment: Consider referencing Wang et al. Statistics in medicine – Reporting of subgroup analysis in clinical trials. NEJM 2007; 357:2189-2194. Consider adding its key points relevant to the topic at hand. Proposed change: Add reference and incorporate relevant key points beyond those already stated.	Not accepted. Wang et al is an article about subgroups in general, and thus more suitable to be referenced in the general *Guideline on the investigation of subgroups in confirmatory clinical trials* rahter than a disease specific guideline. The relevant key points are general as well and relate mainly to reporting of subgroups in journal articles.
150-152	3	Comment: there is increasing recognition of the value	Partially accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of core outcome sets as a means of improving the efficiency of evaluations of the effects of interventions across health and social care. The COMET Initiative is facilitating this work, in part by the identification of core outcome sets that have already been developed (www.cometinitiative.org). Core outcome sets do not need to comprise an extensive list of all outcomes that might be measured in research. Rather, they identify the few particularly important outcomes that should be assessed in all studies as a minimum in that condition. These outcomes capture the ways in which patients, families, and clinicians assess whether a treatment regime is satisfactory, helping them to make well-informed shared decisions about whether to start, continue, stop or modify it. COMET has identified two articles relevant to the outcomes that should be used in the assessment of treatment of acute coronary syndrome: http://www.comet-initiative.org/studies/searchresults?guid=60d1185d-4710-486e-97c8-e67a17cec5f4 (1,2). A brief summary of these is provided below. Please note that no quality assessment has been carried out, and inclusion in the COMET database does not assure quality. **Steg et al (1):** This position paper summarises the research implications of bleeding, including measuring and reporting bleeding in trials and the importance of bleeding as an outcome measure. It made	Reference to the first article (Steg et al., 2011) related to bleeding is accepted. Reference to the second article is not accepted. The research is appreciated but it is too premature to include its reference in a regulatory document.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		recommendations on behalf of the Working Group on Thrombosis of the European Society of Cardiology. The report is unclear about whether, and how, the views of patients were incorporated. **CARDS (2):** The CARDS (Cardiology Audit and Registration Data Standards) project was developed by the Irish Department of Health and Children in partnership with the European Commission and the European Society of Cardiology to identify data to be collected in clinical cardiology practice for use in institutional, national and international registries; for quality insurance (audit) and for international comparisons of healthcare processes and outcomes. The focus of this paper is on ACS admissions. A Coordination Committee and three multidisciplinary Expert Committees developed the data standards. The process involved regular meetings of the Expert Committees, electronic communication between members, and consultation with specialist groups and cardiac societies represented by the European Society of Cardiology. The report is unclear about whether, and how, the views of patients were incorporated. **References:** (1) Steg PG, Huber K, et al. (2011) Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Cardiology. Eur Heart J 32(15): 1854-64. (2) The CARDS Expert Committee. (2014) Cardiology audit and registration data standards for coronary care unit/acute coronary syndrome admissions. https://www.escardio.org/static_file/Escardio/EU-affairs/CARDS-dataset-ACS-071004.pdf Date accessed: 12th August 2016.	
149-231	3	Comment: the two projects (outlined above) had different focuses; one on bleeding and one on ACS admissions, but both are relevant to the management of ACS. The two papers agree with the draft guideline on the inclusion of two efficacy outcomes: myocardial infarction and stroke. Furthermore, in agreement with the draft guideline, the CARDS paper recommends the inclusion of all-cause mortality and cardiovascular death as outcomes. The CARDS paper also recommends additional outcomes for assessment in ACS admissions, including resuscitated cardiac arrest, mechanical complications, Dyspnoea, discharge ECG rhythm and revascularisation. Proposed changes: a) The guideline should cite these two papers and note their common findings. b) There should be further discussion about the inclusion of additional outcomes (as suggested in the CARDS paper and listed above), in relation to ACS admissions.	See previous comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
468-531	3	Comment: the two projects (outlined above) agree with the draft guideline that bleeding should be included in addition to efficacy outcomes. Steg et al suggest two additional outcomes that should be assessed specifically for bleeding: modification of antithrombotic therapy (permanently or temporary discontinuation), and use of agents to mitigate bleeding or reverse the effect of antithrombotic agents (e.g. anti-fibrinolytic and general haemostatic agents such as recombinant factor VIIa, idarucizumab, andexanet alpha, etc.) Furthermore, in agreement with Steg et al, the draft guideline supports the use of the BARC classification/definition of bleeding but states that 'the proposed classification needs to be validated.' We are aware of at least four studies (3-6) that have validated this classification of bleeding. **References:** (3) Vranckx P, White HD, et al. (2016) Validation of BARC bleeding criteria in patients with acute coronary syndromes: the TRACER Trial. J Am Coll Cardiol 67(18): 2135-44. (4) Vranckx P, Leonardi S, et al. (2014) Prospective validation of the Bleeding Academic Research Consortium classification in the all-comer PRODIGY trial. Eur Heart J 35(37): 2524-9.	Accepted. Reference to the use of antidotes, and modification of co-administered therapies is included under bleeding, as follows: Transfusions of blood, red blood cells, coagulation factors, specific antidotes and/or modification of co-administered therapy are further indicators of bleeding severity and should thus be documented carefully….. Reference that BARC classification needs to be validated is deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		(5) Yoon YH, Kim YH, et al. (2015) Impact of in-hospital bleeding according to the Bleeding Academic Research Consortium classification on the long-termadverse outcomes in patients undergoing percutaneous coronary intervention. Catheter Cardiovasc Interv 85(1): 63-71. (6) Ndrepepa G, Schuster T, et al. (2012) Validation of the Bleeding Academic Research Consortium definition of bleeding in patients with coronary artery disease undergoing percutaneous coronary intervention. Circulation 125(11): 1424-31. Proposed changes: a) Additional outcomes in relation to bleeding (as listed above) should be considered for inclusion in the guideline. b) There should be consideration of the BARC validation studies (3-6) and the wording in the guideline should be revised accordingly.	