29 January 2021
EMA/548893/2020
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft Questions and answers on Data Monitoring Committees issues' (EMA/492010/2018)

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

Stakeholder no.	Name of organisation or individual
1	Association for Applied Human Pharmacology (AGAH), Hamburg, Germany
2	Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), Bonn, Germany
3	Clinical Trials Coordination Group (CTFG)
4	European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels, Belgium
5	University College London: Cancer Research UK & UCL Cancer Trials Centre, London, United Kingdom
6	European Association of Hospital Pharmacists (EAHP), Brussels, Belgium
7	Roche France Early Phase Board: • Dr Vincent Ribrag (Gustave Roussy, Villejuif) • Pr Christophe Le Tourneau (Institut Curie, Paris) • Pr Christophe Tournigand (Hôpital Henri Mondor, Creteil) • Dr Nora Ady-Vago (Roche, Boulogne-Billancourt) • Anne Raison (Roche, Boulogne-Billancourt) • Frederic Fleury (Roche, Boulogne-Billancourt)
8	Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V. (Association of Medical Ethics Committees in Germany) (AKEK), Berlin, Germany
9	Society of Quality Assurance (SQA), Charlottesville, (VA), USA
10	Rita Hattemer-Apostel, Verdandi AG, Zurich, Switzerland

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	The objective of the document is to clarify the role and necessity for a DMC in different phases of drug development and throughout the product lifecycle as well as with regards to the responsibilities for implementing DMC decisions. The document should better address common and differing aspects in setting up a DMC in early vs. late clinical development (e.g. focus on either blinded or unblinded data reviews, focus on assessing exploratory safety aspects (by a SRC) vs. confirmatory efficacy aspects (by a DMC), assessments during the conduct of early phase clinical trials. We recommend to differentiate different subtypes of DMCs - or even better to use different names - depending on the different tasks: 1) **DMC in early phase clinical trials (proposed name: Safety Monitoring Board):** as this is primarily a medical and pharmacological case assessment, adequate clinical and pharmacological expertise is needed; statistical expertise is less pertinent. Furthermore, the PI(s) need(s) to be consulted or should participate; Such safety assessments can well be realised internally with qualified persons unless there are complex safety issues e.g. in first-in-class FIH trials. In the latter case external expertise is meaningful to be considered in the DMC. Safety Monitoring Board monitors the safety data in the blinded manner. 2) **DMC in later phases where the safety of the trial participants is in the focus of the assessment (proposed name Safety Review Board)**: here adequate measures are needed to ensure that the DMC recommendation is not influenced by	The comment proposes to describe the role of DMCs in different stages in the life cycle and introduces and defines new terminology for this purpose. This comment would be better suited to an update of the existing Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) than the current Questions and Answers format. => No changes.

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	the sponsor. Adequate clinical expertise in the indication and adequate statistical knowhow needs to be present in the DMC. To make sure that the sponsor does not influence the DMC recommendation and to ensure that no conflict of interest occurs, adequate measures are to be defined in the DMC charter and financial disclosure forms are to be applied. The safety data review may require unblinding of the data. In such case adequate measures need to be installed to assure that the integrity of the trial is not affected by the unblinding of the data. 3) **DMC in pre-planned interim analysis (possible name: Data Monitoring Committee):** This DMC requires medical expertise, expertise in the methodology of interim analysis and clinical trials as well as statistical expertise. The statistical expertise may be of higher importance than in other DMCs as often sample size and complex statistical questions like interference with type-I-error are of relevance. In case such DMCs are unblinded (e.g. fully adaptive designs) it is of utmost importance to establish adequate measures which ensure - especially if a representative of the sponsor has to be involved in the final decision - that in no case any influence on further trial decisions may occur.	
2	Regarding especially question and answer 7 : A DMC should be independent and so should be its composition, which should be described in the DMC charter. . The main criteria of independence of the members should always be the condition for each DMC. If sufficient independency is not met the committee should be named different to avoid confusion e.g. advisory committee. Further, even if safety is obviously essential in early CTs, also efficacy is essential,	Agreed. => Different terms for non-independent committees are used. Of note, Question 7 has been combined with Question 6 in the new Question 9.

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	both need to determine, monitor and ensure positive benefit risk balance for the participants and clinical trials. Details see below.	
2, 3	Regarding especially question and answer 7 : a DMC should be independent and so should be its composition, which should be described in the DMC charter. . A DMC should always consist of independent members .If sufficient independency is not met the committee should be named different to avoid confusion e.g. advisory committee. Further, even if safety is obviously essential in early CTs, also efficacy is essential, both need to determine, monitor and ensure positive benefit risk balance for the participants and clinical trials. Details see below. There should be paid more attention on review of unblinded data by the DMC, DMC should have access to unblinded data: An additional question on the content of the charter should be added: 'The charter should clearly describe at which points in time the data will be reviewed, exactly what data are reviewed and whether the data are unblinded'	Use of different names for non-independent committees is agreed (see comment 2 above). It is now stated in Question 9 that monitoring safety or risk-benefit is important. The need for access to unblinded data is covered in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr). This is covered in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) section 5 on working procedures of the DMC. In conclusion: => No changes.
3	There should be paid more attention on review of unblinded data by the DMC, DMC should have access to unblinded data:	The need for access to unblinded data is covered in the Guideline. => No changes.

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3	An additional question on the content of the charter should be added: 'The charter should clearly describe at which points in time the data will be reviewed, exactly what data are reviewed and whether the data are unblinded'	See response to comment 3. => No changes.
4	It would be useful to briefly clarify some terminology in the introduction to the document (lines 12-15), perhaps referencing the prior CHMP DMC guideline, to avoid confusion, especially in the later questions involving early phase trials. For example, what's the distinction between a DMC and a safety review committee? The term "DMC" is in wide use in the field, but in some contexts refers to the *function*, not the *independence* (so that, for example, early phase groups could include sponsor members, as frequently occurs, and still be called a DMC). Thus, it would be better to clarify in advance the way the term is being used here.	Agreed. => Reference to the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) is made in the introduction to this Q&A, where it is highlighted that this Q&A should be read in conjunction with the guideline. The first use of the term 'safety review committee' contains clarifications that it is different from a DMC.
4	The draft Q&A document should clarify that the use of an external DMC (or DMC at all) in early development phases may not be needed in many circumstances (e.g. in some first in human trials, or phase 1 SAD/MAD trials). These trials typically do not meet the published requirements for a DMC and requiring a DMC for early dose escalation would be prohibitive logistically and also quickly exhaust the community of experts qualified to sit on DMCs with the hundreds of ongoing dose escalation trials around the world. Sponsors are responsible for safely making these decisions in partnership with clinical experts and study personal commonly deployed on dose-escalation committees to serve this purpose.	The Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) sets out principles for when a DMC is needed. The examples are acknowledged and are not considered controversial. Therefore, no changes are needed. => No changes.
4	We suggest having a section to clearly define the scope of the document or situations covered by the Q&As. For example, it seems that the document is focusing on blinded studies. In the case of	The view that most of the questions are dealing with blinded studies and are not applicable to open-label studies or studies without control is not supported. For instance,

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	open label studies or studies without a control the practice is different and most of the Q&As are not applicable.	the independence of a DMC, the advisory non-decision making role, the importance of preserving trial integrity as much as possible in the communication of unblinded results remains important, regardless of the design of the study. => No changes.
4	There is also a need to differentiate between Sponsor and study teams. They are different in many situations. In addition, a distinction should be made between the review committee that makes decisions about dose escalation, which typically includes study team members directly involved in study conduct and the Principal Investigator(s), and an independent SRC/Data Review Committee (which includes representatives from the Sponsor that are independent from the study team). The latter may also include an external expert who is independent from the Sponsor.	This distinction may be useful depending on the context. Nevertheless, a DMC should not include Sponsor personnel as their independence is, in practice, hard to justify. => No changes.
4	Reference is made in Questions 6 and 7 to early development studies. Clarification is requested regarding the scope of such studies, please define which studies are intended.	Which studies are intended is mentioned in the answer to these questions (now merged into one Question 9): studies where little is known about safety. => No changes.
4	There are 7 questions in this document, only the answer to the first question has "No". Suggest adding "Yes/No" to the other answers, if appropriate. This is particularly relevant for answers to Questions 6 and 7 which have some subtleties to them.	Given subtleties in addressing the questions, most of the answers are not a definite yes or no. => No changes.
4	There are many important issues regarding DMCs, and the rationale for the choice of issues addressed in the Q&A document is unclear.	The topics mentioned are included in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr).

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	Some examples of issues currently not addressed include: conflicts of interest; DMC membership; scope of DMC responsibilities; frequency/organization of DMC meetings; how DMC decisions are made; communication among DMCs, sponsors, and trial oversight bodies; DMC charters. Please consider addressing these issues.	Greater and updated guidance will be part of an updated guideline, not this Q&A. => No changes.
6	Overall EAHP agrees with the question and answer document.	This is gratefully acknowledged.
7	Internal monitoring committee in connection with investigators / experts from early phase capabilities may be an alternative option to an independent DMC in dose escalation part of adaptive design early phase. The internal monitoring committee expertise should cover patient population, indication and safety evaluation triggers. In fact, dose escalation part of adaptive design early phase is often conducted in few patients and require an ongoing / real–time supervision which is part of investigators/experts responsibilities. Formal communication of the discussion and the decision taken are prepared and available for both investigators and sponsor. This internal committee allows an immediate decision making process which is critical in such dose escalation part of trial. Expansion part of adaptive design early phase may require DMC for a larger population (eg. 100 – 200 patients….), as the decision-making process may require a preliminary data set analysis. We suggest that the DMC should be based on the Internal Monitoring Committee with external expertise as needed. The charter of IMC/DMC should promote an open discussion and guarantee the decision-making process.	The need to include internal members in safety oversight may be justifiable depending on the situation. However, this is not considered a DMC. As addressed in Question 9, it may still be in the interest of the Sponsor to have a DMC installed. => No changes.

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	With regards to accelerated development in oncology and frequent use of adaptive design methodology, the combined studies may require also to involve a combined approach in setting-up DMC without jeopardizing the risk benefit ratio for patients.	
8	The Association of Medical Ethics Committees in Germany represents all Ethics Committees in Germany that are involved in the assessment of clinical trials with medicinal products and medical devices. We appreciate that the EMA has initiated a public consultation on the draft ‚Questions and answers on Data Monitoring Committees Issues' . This offers the chance to contribute to the further improvement of this document. General comment: The Q&A paper should start with a clear definition of the term DMC so that everybody knows what it is. We suggest to use the definition as used in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr): **„Data Monitoring Committees** A Data Monitoring Committee is a group of independent experts external to a study assessing the progress, safety data and, if needed critical efficacy endpoints of a clinical study. In order to do so a DMC may review unblinded study information (on a patient level or treatment group level) during the conduct of the study. Based on its review the DMC provides the sponsor with recommendations regarding study modification, continuation or termination. Data Monitoring Committees also go under different names like Data Monitoring Board or Data Safety Monitoring Committee (Board)." We think that the terms ‚independent' and ‚external' are extremely important to characterize a DMC, and thus these characteristics	Because the Q&A should be read in conjunction with the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr), the definition of a DMC is not repeated. => No changes.

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	should always be stressed. The composition, the members of the DMC and their qualifications (incl. CoIs), the tasks, responsibilities and the organisation should be described in the DMC-Charter.	
9	This is not addressed in the draft document, but it would be beneficial to specify that evidence of the qualification of all DMC members (e.g., in form of a current signed and dated CV) should be requested and included in the respective TMF section. In the 'Guidance on Data Monitoring Committees' of 27-Jun-2005, it is only requested to document the qualification of the DMC members in the DMC working procedures.	The Q&A focuses on principles mostly, and therefore this suggestion is outside the scope of the Q&A. => No changes.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Question 1:			
20-26	1	**Proposed change:** To add: This does not refer to the situation when the activities of the DMC are pre-specified in the protocol that may be a case in the context of pre-planned interim analysis for early stopping or in case of complex study designs where a possible modification of the study design based on unblinded interim data is intended.	Also in that situation, the working procedure should preferably be such that the DMC can remain in its advisory role. => No changes.
21-26	10	**Comments:** The draft recommends that sponsors document in case they intend to **not** follow the DMC recommendations. This is a one-sided documentation requirement, mainly for the exceptions. A requirement to document the sponsor's decision based on the DMC recommendations in **every** case, as a norm, would increase the sponsor's awareness that it is ultimately the sponsor to make trial-related decisions and not the DMC who is in an advisory role. **Proposed change:** Consider including the requirement for the sponsor to document their decision following each DMC recommendation, regardless of the nature of the DMC recommendation.	From the current response, it is already clear that the Sponsor is responsible. Therefore, it is not considered necessary to require extra administration. => No changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
23	4	**Comments:** It is proposed that the guideline indicate where the documentation, justifying cases where DMC recommendations are not followed, should be sent or stored e.g. trial master file.	The Q&A focuses on principles mostly, and therefore this suggestion is outside the scope of the Q&A. => No changes.
23-26	4	**Comments:** If the recommendation of minor modification of the trial is not followed, ethics committees (EC)/regulatory authorities may not need to be notified. **Proposed change:** *However, in particular, if DMC recommendations to stop (in all cases) or **substantially** (as per the definition in Dir 2001/20/EC) modify the trial are not followed, the Sponsor is strongly advised to notify the Ethics Committees as well as the competent regulatory authority.*	Agreed. =>The wording has been modified: *"In particular, if DMC recommendations to stop (in all cases) or substantially (as per the definition 3.3. in Communication from the Commission 2010/C 82/01) modify the trial (e.g. in relation to safety considerations or the confirmatory nature of the trial) are not followed, the Sponsor is strongly advised to notify the Ethics Committee(s) as well as the competent regulatory authority(ies)."*
Question 2:			
27-29	1	**Comments:** The original guideline specifies the situation when the DMC monitoring activities are expected to have relevant impact on the conduct of the trial (e.g. stopping the trial) and these activities are pre-specified in the study protocol.	Also in that situation, the working procedure should preferably be such that the DMC can remain in its advisory role, see the response to Question 3. => No changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: To add: if DMC activities are not otherwise pre-specified in the protocol	
27-29	6	**Comments:** As for the question 2 in the same way as for question 1 it is important that the DMC can make recommendations to the sponsor to stop the study in case is needed. The sponsor can decide to follow or not the recommendation but should be justified and documented. **Proposed change:** Add clarifications, as outlined above, on the role of the DMC and the sponsor in relation to stopping a study.	The role of the DMC is primarily described in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr): *"Based on the results of the monitoring activities, a central responsibility of a DMC is to make recommendations on further study conduct. Such recommendations include continuing or terminating a trial or modifications to the trial."* => No changes.
28	4	**Proposed change:** In the answer to Q2, suggest adding the sentence "DMC can recommend, e.g., an early stop (generally due to efficacy according to pre-specified rule)" after "As mentioned above"	This is not considered within the scope of the question. The question is whether the DMC has the authority to stop the study, thus it makes little sense to reflect on that the DMC can *recommend* to stop. => No changes.
Question 3:			
30	4	**Comments:** It is appropriate to state that the DMC can propose unplanned changes to the study. However, in certain circumstances, it may be appropriate to manage an amendment as an "urgent safety measure", which is	This is agreed and clarified as follows: => Clarification added: *"Urgent safety measures are implemented immediately, e.g. if the DMC recommends terminating a particular treatment group due to safety*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		implemented immediately e.g. if the DMC recommends terminating a particular treatment group due to safety issues. However, a substantial amendment would need to be submitted subsequently (per "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial"). **Proposed change:** Amendments introducing changes to the confirmatory nature of the study are usually substantial and require approval from the competent regulatory authority and the Ethics Committee. **However, in certain circumstances, it may be appropriate to submit an amendment as an "urgent safety measure", which is implemented immediately e.g. if the DMC recommends terminating a particular treatment group due to safety issues. However, a substantial amendment would need to be submitted subsequently (per "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial").**	*issues; however, a substantial protocol amendment would need to be submitted subsequently (as outlined in Communication from the Commission 2010/C 82/01)".*
30-46	4	**Comments:**	Strictly speaking, and as discussed, the DMC cannot change the study design, but only make recommendations. The DMC may advise based on unblinded data, but should keep in

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		Changes to the study design for reasons other than safety should not be made by anyone with access to unblinded data, including DMCs. This might already be implied by the two statements about trial integrity in the existing text, but it should be stated explicitly.	mind that the trial integrity is maintained as outlined in the response *"In addition, while the DMC can propose unplanned changes to the Sponsor, the integrity of the trial must be protected."* Therefore, this is considered sufficiently clear. => No changes.
30-46	5	**Comments:** If sponsor is considering changes to study design aspects of the trial, they would be encouraged to discuss with/inform the DMC **Proposed change:** suggest additional sentence at line 44: "Sponsors are encouraged to consult the DMC where such a substantial amendment impacts on an aspect of study design".	It is considered a risk for trial integrity when the Sponsor tries to draw information on results in the ongoing trial by asking questions to the DMC. Moreover, if the questions can be addressed without knowledge of the trial results, then the Sponsor can seek advice from experts outside the DMC and those involved in the trial. => This has been included in the response.
32	4	**Comments:** It is proposed that the guideline clarifies the circumstances when the DMC can change an aspect of the study design. **Proposed change:** ~~Formally,~~ **With the exception of pre-specified design changes,** the DMC cannot change study aspects, because its role is to advise the Sponsor.	Also in that situation, the working procedure should preferably be such that the DMC can remain in its advisory role. Therefore, the DMC does not change the study - it is the Sponsor who adopts DMC advice. => No changes.

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33-40	4	**Comments:** It would seem useful to add to this paragraph that if a DMC were to recommend unplanned changes to a study, it would most appropriately be to address an unexpected safety issue that arises.	It is not considered that the DMC's advice on unplanned changes should necessarily be confined to unexpected safety issues. The critical point is that the DMC's advice would not affect trial integrity. => No changes.
39	4	**Comments:** This comment is in regard to Line 39, "In addition, the DMC can propose unplanned changes to the Sponsor but integrity of the trial must be protected". It would be helpful if this section of the question-and answer document included examples of unplanned design changes in this context for reference. For example, this may be more applicable to new diseases that are less understood or rare diseases that are difficult to study.	The usefulness of giving examples here for reference is not understood. It follows from the DMC's advisory role that a DMC can also give unplanned advice. => No changes.
41-42	4	**Comments:** Note that when changes are made according to pre-specified adaptation rules in adaptive design studies e.g. change in randomisation ratio according to response adaptive randomisation, changes do not always result in a protocol amendment. Suggest making the sentence more inclusive. **Proposed change:** …the Sponsor decides whether changes are implemented ~~and if so, this has to be done via~~	This is agreed and clarified as follows: => Clarification added: *"Changes not foreseen at the planning stage must be implemented via protocol amendments."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~protocol amendments~~. **Unplanned changes are required to be done via protocol** amendments.	
42	5	**Comments:** request clarification of meaning of underlined wording: 'Amendments introducing changes to the confirmatory nature of the study…'?	This is agreed and clarified as follows: => Clarification added: *"A protocol amendment introducing changes affecting the confirmatory nature of the study…".*
44-46	8	**Comments:** In Germany the respective law and ordinances provide explicitly the option for a scientific advice but for an explicitly ethical advice consultation too, provided by the competent EC. In some EU MS (e.g. The Netherlands) basically the ECs authorize clinical trial applications. Thus this Q&A document should mention this option too. **Proposed change:** Line 45: ….,the Sponsor may also wish to discuss the amendment with the competent regulatory authority **and/or ethics committee(EC)** during a scientific **and/or ethical advice** consultation before implementation.	This is agreed. => Change made as proposed.
Question 4:			
47-69	4	**Additional comments on this question:** The text refers to the Competent Health Authority and the DMC communicating directly in exceptional circumstances related to a public health concern.	

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		We are concerned about this suggestion because if there is a public health concern, it is the sponsor who can most efficiently provide additional analyses. Members of the sponsor's safety team or team members not working on the project could have access to unblinded data to assist in the assessment if needed. Finally, the sponsor should be involved in the discussion, planning and implementation of any subsequent actions in regard to the study or investigational medicinal product. If there is a public health concern, leaving the sponsor out may make the situation worse overall and not improve the outcome for patients.	It is acknowledged that the Sponsor is most aware how the relevant information can be retrieved from data files. Nevertheless, solutions that do not require unblinding of Sponsor personnel are conceivable (e.g. the dataset is provided by the Sponsor but the unblinding codes are provided by the DMC). => The involvement of the Sponsor is considered captured by the text: *"[…] as long as there is the option to continue the trial it is essential to maintain the integrity of the trial."*
48	8	**Comments:** The laws and regulations in many EU MS ask ECs to play a specified role while a trial is ongoing, e.g. re SUSARs, early stopping, risk/benefit monitoring. The Declaration of Helsinki states in 23. too: "The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events." Thus we propose a change in the text as proposed. **Proposed change:** …..between competent regulatory authorities, **ethics committees** and a DMC possible?	This is agreed. => For readability, this topic is addressed in a new question: *"Question 5: Is a direct communication between Ethics Committees and DMC possible?".*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
50	8	**Proposed change:** ….competent regulatory authorities **and ethics committees** on all matters…..	This is addressed as for the previous comment.
52	4	**Proposed change:** Add "**and, as needed, efficacy**" after "continuous safety", as described in the EMA DMC guideline.	This is agreed. => Change accepted.
53	4	**Comments:** A DMC works to preserve the continuing safety of trial subjects (and those yet to be recruited) as well as the continuing validity and scientific merit of the trial. This is better captured as "benefit:risk" rather than just "safety". **Proposed change:** "…in the interest of patient safety **(or, optionally, benefit-risk)** while the trial is ongoing"	Agreed. However, the revised version does not include the paragraph the comment refers to anymore. => No change.
53-55	4	**Comments:** Rather than say "Sponsor" generically, reference to "Sponsor personnel who serve as the DMC point of contact e.g. Sponsor Committee" is suggested since the DMC should not be speaking directly to the Sponsor Study Team. **Proposed change:** **Thus,** the DMC ~~**therefore**~~ has an advisory role for the Sponsor and therefore, as a general rule,	This is agreed. => The wording is changed to: *"The DMC has an advisory role for the Sponsor and therefore, as a general rule, communications primarily take place between the DMC and the Sponsor personnel who serve as the DMC point of contact (e.g. Sponsor Committee), without direct communication between the DMC and any third party."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		communications primarily take place between the DMC and the Sponsor **personnel who serve as the DMC point of contact (e.g. Sponsor Committee)**, without direct communication between the DMC and any third party.	
56-62	4	**Comments:** Any approach to a DMC to request additional data should occur via the trial sponsor in every case rather than 'preferably' as responsible party.	This is agreed. => "Preferably" has been removed.
57	8	**Proposed change:** ….. competent regulatory authorities **and ethics committees** may consider…….	Communication between Ethics Committees and a DMC are addressed in a separate question. => No changes.
58	2, 3	**Comments:** Exchange between NCA and DMC might be needed to ensure integrity of CT during supervision to ensure benefit risk, e.g. efficacy or safety update at specific points during conduct ,of a trial. Even if might be rare case it already happened where CTFG and DMC exchanged, e.g. facilitated via CRO to keep blinding. **Proposed change:** ….'before making decision about' **or during supervision of** 'the conduct of the trial.'	Notwithstanding that local law may require supervision of trials by competent regulatory authorities, it is understood that such action is needed because of strong concerns about safety. Therefore, it is considered captured by the wording: *"In exceptional circumstances related to a public health concern based on trial data or information from other sources than the trial at hand, competent regulatory authorities may consider it necessary to obtain more detailed information from the DMC before making decisions about the further conduct of the trial at hand or other trials."* => No changes.

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58	4	**Comments:** Clarification is requested regarding the circumstances when the regulatory authority would be making a "decision" about the conduct of the study as well as the rationale for this. It is suggested that reference be made to the relevant clinical trial legislation and guidance (under both Directive 2001/20/EC and EU Regulation No. 536/2014, as appropriate).	The clarifying wording is already given: "*In exceptional circumstances related to a public health concern based on trial data or information from other sources than the trial at hand…*". => No changes.
59	8	**Proposed change:** ….. competent regulatory authorities **or ethics committees** but not to the DMC….	Communication between Ethics Committees and a DMC are addressed in a separate question. => No changes.
59-62	4	**Comments:** The term "Vice versa" is not considered to be appropriate. Also, it is considered that it is always appropriate for the regulatory authority to contact the DMC through the Sponsor. **Proposed change:** ~~Vice versa, c~~**E**xternal data known to competent regulatory authorities but not to the DMC may be of importance to the DMC in respect to its roles and responsibilities. ~~Preferably, t~~**T**he Sponsor **must** ~~should~~ be involved in such justified requests and related communications to ensure that their respective roles and responsibilities are not undermined.	This is agreed. => "Vice versa," has been removed. "Preferably" (and "should" instead of "must") are handled as per comments above.

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62-64	4	"Considerations should be given to the fact that requests which may lead to unblinding of involved parties could potentially compromise the trial's integrity, the ability to proceed with the trial and with this the outcome of the trial." **Comments:** Maintaining trial integrity is important for all trials. The scope of the answer could refer to more complex designs such as master protocols, multi-phase studies etc, where the competent authorities may be asking to see interim reports of data which may require some level of unblinding. Maintaining trial integrity may be best addressed in a new question.	Maintaining trial integrity is considered a leading aspect in every communication of possibly unblinded results. Therefore, it is considered better not to remove this aspect from the answer. => No changes.
65-68	4	**Comments:** Modified the sentence as the DMC is not implementing the changes itself. Additional considerations which are not reflected in the proposed change: the needed communication between DMC and competent regulatory authorities and the modification of protocol/trial monitoring plan/statistical analysis plan are two different actions that can be carried out separately. It is also not clear why the recommendation comes from DMC to sponsors instead of directly from competent regulatory authorities to sponsors.	This is agreed and reflected in the revised response. It is agreed that these are two different actions that can be carried out separately. In the revised wording these have been separated: 1) when and how direct requests for information from the competent regulatory authorities to the DMC are possible; 2) information from the competent regulatory authorities to the DMC go via the Sponsor.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: *Where direct communication and information exchange between DMC and competent regulatory authorities is needed, this should preferably be without breaking the blind, e.g. with additional statistical analysis plans, intensified monitoring, or modified stopping rules which the DMC can* ***recommend to have*** *implement****ed*** *to address the public health concern.* ***The impact from this type of communication on the trial integrity should be kept minimal and the*** Sponsor should be fully involved in any such communication ***without unblinding the sponsor.***	
65-69	2, 3	**Comments:** This paragraph is not clear. If direct communication between DMC and competent authority takes place, unblinded information should not be a problem (the need for unblinded information is the reason for the direct contact isn´t it?). The last sentence should then be deleted.	Direct communication could also be in a blinded manner. For instance, the competent regulatory authority wants to check whether the DMC is aware of certain issues and takes appropriate monitoring measures. The sentence is relevant as *"the Sponsor should be involved in such justified requests and related communications to ensure that its respective roles and responsibilities are not undermined."* => The sentence is changed to: *"The Sponsor should be involved in such justified requests and related communications to ensure that its respective roles and responsibilities are not undermined."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
66	8	**Proposed change:** ….. competent regulatory authorities **or ethics committees** is needed…..	Communication between Ethics Committees and a DMC are addressed in a separate question. => No changes.
Question 5:			
72	1	**Comments:** "overall DMC recommendations" is somewhat too general. The investigator should know about "relevant safety findings and DMC recommendations"	This is further specified in the new answer. => The proposal is implemented using a revised wording.
72-73	4	**Comments:** This section of the question-and-answer document pertains to notifying Investigators of overall DMC meeting outcomes. We recommend that these notifications would be for outcomes where there are important new recommendations to share that are pertinent for patient care, and that this document provides more definition around this topic of notifications. For example, a DMC may comment on certain statistical considerations that may not need to go to the Investigators. At other times, the overall outcome is just to continue and there are no new recommendations to convey to the Investigators. We also recommend that this section add guidance as to when these notifications of overall outcomes may need to be submitted to regulatory authorities, as this	This is agreed and elaborated in the revised answer. => See the revised answer. This is agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		is not covered in the question-and-answer document or in the main guideline (EMEA/CHMP/EWP/5872/03).	=> See new Question 7.
72-73	4	**Comments:** It is considered that reference to "regarding safety" should include lack of efficacy. It is recommended that this be clarified. Also, there is no need to inform the Investigators when the recommendation is to "Continue the Study as Planned". **Proposed change:** **When a change in the study conduct due to safety or lack of efficacy is required** the Sponsor should ensure that the Investigators in a clinical trial with an appointed DMC ~~are~~ are informed about overall DMC recommendations~~, i.e. regarding safety~~ in a timely manner.	This is agreed and text in the new answer reads: *"Important DMC recommendations pertinent to patient care or patient recruitment regarding safety or negative benefit-risk should be immediately communicated."* No harm is considered in communicating this, but also no obligation. => The revised answer contains: *"Thus, no objections exist to informing the investigators that the DMC has met (e.g. after an interim analysis) and recommends the trial to continue as planned."* => The revised answer now contains: *"Thus, no objections exist to informing the investigators that the DMC has met (e.g. after an interim analysis) and recommends the trial to continue as planned. Similarly, no objections exist to communicating DMC recommendations to improve data quality. Important DMC recommendations pertinent to patient care or patient recruitment regarding safety or negative benefit-risk should be immediately communicated."*
72-73	4	**Comments:** The document should emphasize that DMC recommendations to investigators should be limited to	This is agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		information that does not compromise the integrity of the study.	=> In the answer it is added: *"In general, the recommendation of a DMC is either to continue the trial with no changes, to change aspects of the trial and then continue the trial, or to stop the trial. The underlying principle in communication of DMC recommendations to investigators, is to preserve the trial's integrity as much as possible."*
72-73	8	**Comments:** The investigators should be informed without undue delay only about whether the trial can go on, or not. If the sponsor disagrees with this recommendation of the DMC, his position and rationale should accompany the recommendation of the DMC for the investigators. The rest, e.g. recommended modifications of the trial protocol etc. are in the sole responsibility of the sponsor. Finally, any additional information to the investigators beyond the go on/stop recommendation may introduce bias and endangers the validity and integrity of the trial.	As the default situation is that the trial continues, it is of paramount importance that the DMC recommendation to stop a trial is communicated immediately. => The new answer reads: *"Important DMC recommendations pertinent to patient care or patient recruitment regarding safety or negative benefit-risk should be immediately communicated. The same holds when the Sponsor adopts the DMC's recommendation to stop the trial."* The leading principle is indeed that trial integrity should be preserved as much as possible. This gives possibility for other communications as reflected in the revised answer: *"Similarly, no objections exist to communicating DMC recommendations to improve data quality. Important DMC recommendations pertinent to patient care or patient recruitment regarding safety or negative benefit-risk should be immediately communicated."*
72-73	10	**Comments:**	It is acknowledged that a variety of approaches of communication is used. As there is not clear preference for

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It would be helpful to specify or include examples how the investigators are to be informed about DMC recommendations. In practice, there is a wide array of approaches, from providing the investigators with DMC meeting minutes (blinded) to just letting them know informally (verbally without any evidence left on site or in the TMF) that there are, for example, no changes to the trial. Also, it would be beneficial to specify 'timely' (e.g. before advancing to the next cohort)? **Proposed change:** Consider adding details on dissemination of DMC recommendation to investigators and the expected timeframe.	one over the other, it is not considered to specify them in the context of this question. The "timely" has now been replaced by "immediately" for important DMC recommendations regarding patient care.
Question 6:			
74	4	**(See the General Comments for a similar point)** **Comments:** Single dose and short term (<1 month) dosing in healthy volunteers or in a relatively healthy adult patient population may present logistical challenges for the timing of DMC reviews due to the short dosing intervals per cohort. Also, first in human studies typically have well defined protocol specified stop/pause criteria for individual subject dosing and dose escalation. In addition, for Phase 1 studies, treatment assignments may be unblinded to the sponsor if needed for safety decision making. Thus,	It is acknowledged that the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) mentions that a DMC is not always necessary and gives examples. Also, the Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1) provides examples of other committee types than DMC. The answer is expanded to reflect that internal/mixed committees may play a role as well. Even so, the case is made that it is still in the interest of the Sponsor to also have a DMC installed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		data integrity concerns do not necessarily require confining unblinded safety data reviews to a DMC. **Proposed change:** The above should be made clearer in the Q&A generally and in the question e.g. by addition text at the end such as: *First in human studies typically have well defined protocol specified stop/pause criteria for individual subject dosing and dose escalation. In addition, for Phase 1 studies, treatment assignments may be unblinded to the sponsor if needed for safety decision making. Thus, data integrity concerns may not necessarily require confining unblinded safety data reviews to a DMC.*	Of note, the answer to Question 6 is now combined with that to Question 7 as suggested in other stakeholder comments.
74-81	4	**Comments:** The question statement uses the term "DMC", but the response does not. The response introduces the term "safety review committee" which it does not define. This terminology is not used in the EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03), Is this SRC intended to be a committee distinct from the DMC, and if so, is a DMC relevant to the response to Question 6?	This is agreed. => The distinction between a safety review committee (SRC) and a DMC is clarified in the revised response to question 6 and 7 combined in Question 9: "*If safety review is implemented by a DMC in the definition considered in this Q&A, then by definition all members have to be independent from the Sponsor (see Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr)). Otherwise, the committee should be called differently, e.g., a safety review committee (see Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1)).”
74-81	7	**Comments:** Safety considerations related to indication, study population and knowledge of the treatment under consideration, may trigger the need for more intensive safety monitoring in early development phases, implemented via a safety review committee that monitors safety aspects. The need for such a safety review committee is usually higher in first in human clinical trials, and other early phase trials, as often there is only very limited information on the safety profile of a medicinal product. Such a committee often also has a role in assessing data before dose escalation in early phase trials, and to give recommendation to the Sponsor whether or not to proceed to the next higher dose.	=> No change.
74-81	4	**Comments:** The EMA guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03) covers the general concept that not all trials need a DMC and provides some general aspects that should be considered when it comes to the decision of whether or not a DMC should be set up. While the question-and-answers document continues this discussion of general aspects, we recommend that it be explicitly noted it is at the sponsors discretion to determine when a DMC or other safety review committee would be needed in	Depending on local law, it may be that Ethics Committees approve of the study design, including the commitment to install a DMC or not. Therefore, it is not automatically only at the Sponsor’s discretion whether a study has a DMC or not. => No changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		early development settings and the way in which these concepts might apply specifically in the early development setting.	
75-81	4	**Comments:** Question 6 refers to the need for a DMC. However, in the subsequent response, line 77 appears to indicate that the need for a 'safety review committee' is usually higher in first in human clinical trials and other early phase trials. If this is a correct assumption, then while it is accepted that rigorous safety monitoring is required for early trials, the juxtaposition of question and response implies that the safety committee referenced is a DMC. However, any implied recommendation for use of a DMC in early phase trials is not consistent with the EMA's Guideline on Data Monitoring Committees which does not make any specific reference to a need for DMCs for early phase studies and explicitly states that for clinical studies which can be performed in a short time frame, the use of a DMC might not be beneficial and may delay the conduct of the trial. In fact, in very early phase dose escalation trials, it is not usually the case that a bureaucracy is set up where a "committee" (especially an external one) makes recommendations that have to be reviewed and decided upon – rather, some trial personnel have that responsibility. In this exploratory stage, confidentiality is not critical in the same sense as in confirmatory studies, so the best available expertise	This is agreed. => The distinction between a DMC and a safety review committee is clarified in response to the new Question 9 that combines previous questions 6 and 7.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		would typically be utilized, and in the most time-efficient manner, in the best interests of the patients and the program, which could involve sponsor and / or external experts. It is proposed that the response is rewritten to more closely mirror the existing EMA guideline.	
75-81	8	**Comments:** The term safety review committee (SRC) is lacking a clear definition. Please specify the difference to a DMC. The headline uses the term DMC whereas the text uses the term safety review committee only. Please adjust accordingly.	This is agreed. => This is incorporated in revised response to question 6 and 7 combined in Question 9: *"If safety review is implemented by a DMC in the definition considered in this Q&A, then by definition all members have to be independent from the Sponsor (see Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr)). Otherwise, the committee should be called differently, e.g., a safety review committee (see Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1))."*
76	8	**Proposed change:** ….intensive safety **and risk/benefit** monitoring in….	This is agreed. => The revised answer uses *"Safety or risk/benefit monitoring…"*..

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
76-77	8	**Comments:** In our experience most often safety and efficacy aspects have to be considered at the same time by a DMC. In many, not only in oncology, early trials, pharmacodynamic outcomes are measured too. In addition many laws, regulations and conventions ask that the risk/benefit balance has be continuously monitored.	This is agreed. =>This is incorporated in revised response to questions 6 and 7 combined in Question 9: *"Safety or risk/benefit monitoring is of large importance in early drug development as much less knowledge of the medicinal product has been acquired than in later phases."*
77	8	**Proposed change:** …. monitors **safety and risk/benefit** aspects…..	This is agreed. => The revised answer uses *"Safety or risk/benefit monitoring…"*.
77-81	4	"The need for such a safety review committee is usually higher in first in human clinical trials, and other early phase trials, as often there is only very limited information on the safety profile of a medicinal product. Such a committee often also has a role in assessing data before dose escalation in early phase trials, and to give recommendation to the Sponsor whether or not to proceed to the next higher dose." **Comments:** Clarify the safety review committee is an internal one for early phase studies. But for multi-phase studies, there needs to be a clear distinction between an internal safety review used to support dose escalation	This is agreed. => Clarification has been added in the revised response to questions 6 and 7 combined in Question 9: *"Moreover, where the nature of such studies is not confirmatory but exploratory, the need for internal members may be greater."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		decisions versus an external DMC for monitoring safety in the confirmatory phase. Q6 and Q7 focus on early phase only studies but increasingly such studies are multi-phase which is not recognised so much and should be.	
78	8	**Proposed change:** ….is usually **high** in first in…..	It is agreed that *"The need for such a safety review committee is usually higher in first in human clinical trials"* can be replaced by *"The need for such a safety review committee is usually high ..."* => The revised answer uses "*Safety or risk/benefit monitoring is of large importance…*".
79-81	4	**Comments:** We recommend that this section on the early development phase includes the consideration that the sponsor, in consult with the investigators, can assess the data to make dose escalation decisions without the need for a DMC, and that this approach would be valid under various conditions.	Studies that are conducted in a short time frame are already mentioned in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) as situations where a DMC may not be needed. The current answer stresses that a DMC may also be in the Sponsor's interest. => No changes.
Question 7:			
82	4	**Comments:** Very often safety review committees in early development phases are internal within the Sponsor or include Sponsor personnel, especially in phase 1 studies. When there are qualified personnel within	This is agreed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the Sponsor who are independent from the development team, credibility of the committee usually is not a concern. Questions 6 and 7 are closely related so it is better to address together. The current format, e.g., without distinguishing between Sponsor and the study team is confusing.	=> Both questions 6 and 7 are combined in Question 9. Considerations are added to the composition of the oversight committee: *"Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product or the conduct of the trial which may impinge on objective decision making. However, in-depth knowledge of the medicinal product under evaluation might also be necessary. For early phase trials, such information might mostly be available within the Sponsor's organization, or the manufacturer's organisation for trials where the Sponsor is a non-commercial institution. Moreover, where the nature of such studies is not confirmatory but exploratory, the need for internal members may be greater."*
82	4	**Comments:** Two aspects of the response are confusing. (1) The first sentence states unequivocally that a DMC is external to the sponsor, but then the response discusses monitoring that includes the sponsor. This implies that the sponsor personnel are not part of the DMC. (2) Like the response to Q6, the response to Q7 mentions a safety review committee, which it does not define. Is the SRC distinct from the DMC? In the end, the response to Q7 doesn't answer the question.	This is agreed. => The distinction between a safety review committee and a DMC is clarified in the revised response to questions 6 and 7 combined in Question 9.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Clarify in this question or earlier in the Q&A document the difference between a DMC and a safety review committee, and ensure the response to question 7 is addressing the question.	
82-95	7	**Comments:** The term DMC always refers to a committee independent from the Sponsor. Safety monitoring is of even more importance in early drug development than in later phases when already more knowledge of the medicinal product has been acquired. Therefore, knowledge of relevant and possible safety issues related to the medicinal product should guide the selection of members of a safety review committee. The inclusion of members external to the Sponsor increases the credibility of such a safety review committee. Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product which may lead to subjective rather than objective decision making. However, it might also be necessary to have an in-depth knowledge of the medicinal product under evaluation. For early phase trials, such information might only be available within the Sponsor's organization. Moreover, where the nature of such studies is not confirmatory but exploratory, having also internal members may be more needed.	=> No change.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
82-95	7	**Comments:** The definitions of confirmatory / exploratory early phase, in case of adaptive phase I study, should be defined to avoid any misunderstanding	This distinction between confirmatory and exploratory seems self-evident. It is acknowledged that in an adaptive phase I study, safety oversight for the exploratory part and the confirmatory part should be differently organised, but this is implied by the revised answer. => No changes.
82-95	4	**Comments:** A safety review committee (if it is well understood that it is different from a data monitoring committee) might be used jointly externally and internally, comprising internal sponsor members and external study investigators – in this case it would be scarce to have truly independent members as part of the committee. A data monitoring committee should comprise independent members, and as such, it should be clarified that those 'external' members part of the DMC are not study investigators, who are not independent to the study. This distinction should be made clear in the text, since 'external' does not necessarily mean 'independent'.	This understanding is correct. This is agreed. => Therefore, it is added that members should be are external to the trial: *"Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product or the conduct of the trial which may impinge on objective decision making."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
82-95	8	**Comments:** **We are definitely in favour for having a DMC according to the definition mentioned above for all trial related advices and consultations. In case additional information that only the sponsor or a CRO knows, is needed, their representatives may report to the DMC, but all detailed deliberations and decisions by the DMC should be done only by the independent and external members of the DMC. We doubt that an internal SRC provides any added value re safety and wellbeing of the research subject compared to a true DMC. Therefore we suggest to delete lines 82-95 completely.** We are not convinced that it makes sense to prioritize the need for a SRC/DMC for early clinical trials vs. later ones. The risks of later trials regarding receiving an inferior treatment and to suffer from an irreversible endpoint does in our opinion not allow for any prioritisation due to being early or late.	There are cases indicated in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr) where DMC may not be needed, for example, trials executed in a short time frame and this may be the case for namely a dose-escalation trial in phase I or II for example. Therefore, a distinction between a safety review committee and a DMC is made. This being said, we do advocate in the revised answer to (also) have a DMC available. No prioritisation is intended. Sentence changed to: "*Safety or risk/benefit monitoring is of large importance in early drug development as much less knowledge of the medicinal product has been acquired than in later phases.*"
84, 75, 53	2, 3	**Comments:** Besides the main intention of enhancing safety during the conduction of clinical trials, the premature termination of clinical trials due to insufficient efficacy of the investigational medicinal product may be a result - especially in the early development phase. **Proposed change:**	This is agreed. => Safety monitoring changed to "*Safety monitoring or risk/benefit monitoring*".

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		84: Safety monitoring **as well as positive benefit risk balance, including efficacy,** is 75: Safety **as well as efficacy** consideration… 53:…continous safety monitoring **as well as efficacy monitoring** ….in interest of patient safety **and positive benefit risk balance** while the trial is ongoing.	
84	2, 3	**Comments:** Based on the European Guideline EMEA/CHMP/EWP/ 5872/03 Corr and on published literature, functional aspects for implementing these independent committee's should be described in the corresponding DMC charter. **Proposed change:** The term DMC ……from the Sponsor **and functional aspects for implementing these independent committee's should be described in the corresponding DMC charter.**	This does not seem to be related to the question. Moreover, the functional aspects are already covered in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr). => No changes.
84	4	**Comments:** The statement that a DMC always refers to a committee independent of a sponsor is not consistent with the definition of a DMC in the EMA guideline which refers to a group of experts independent of a trial. This distinction is important, as 'internal' experts who are independent of the conduct of a trial may provide a more immediate and accessible route for	It cannot be ruled out that Sponsor personnel, even if not involved in the study, have a conflict of interest in relation to the study. Therefore, practically, a DMC will not consist of Sponsor personnel. See for example the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr): *"Potential candidates for a DMC membership should have no financial interest in the outcome of the study. Thus, it is obvious that*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		decision-making to ensure patient safety. This is particularly important in the context of early phase trials where rapid decisions on dosing continuation may be required.	*e.g. employees of the sponsor who naturally have an interest in the trial outcome should not serve on a DMC."* However, the need for having 'internal' experts is acknowledged in some situations and to avoid confusion, such a committee is called differently, e.g., a safety review committee. => This is reflected in the revised answer.
84-86	4	**Comments:** Question 7 is addressing "Does safety monitoring in early phase studies need to be done by people independent from the Sponsor?" The first sentence of the response defines DMC as external to the Sponsor. **Proposed change:** Monitoring of an early phase study may be done by an external, internal, or blended (comprised of both internal and external members) committee. Safety monitoring is of even more importance in early drug development than in later phases when already more knowledge of the medicinal product has been acquired.	The different ways of monitoring are now present in the revised text, especially: *"The inclusion of members external to the Sponsor increases the credibility of such a committee. Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product or the conduct of the trial which may impinge on objective decision making. However, in-depth knowledge of*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			the medicinal product under evaluation might also be necessary. For early phase trials, such information might mostly be available within the Sponsor's organization, or the manufacturer's organisation for trials where the Sponsor is a non-commercial institution. Moreover, where the nature of such studies is not confirmatory but exploratory, the need for internal members may be greater."
84-95	1	**Comments:** The original guidelines indicates that completely independent DMC is desirable but not always possible. **Proposed change:** To add: The possible conflict of interests should be avoided.	It is agreed that conflict of interests should be avoided. This is already clear in the Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr). As this Q&A is supplemental to the guideline, it is not included here. => No changes.
85	4	**Comments:** In combination with Question 6, it seems strongly conveyed that safety monitoring has "more importance" in exploratory stages of development. This choice of wording seems ill-advised. While safety judgments and implications are different in the two stages as described, it does not seem appropriate to "order" them in importance, they're both critical, but different. It's certainly true as stated that there is more knowledge of the safety profile by the time of a confirmatory trial; however, a safety risk at that stage would affect more patients, and that will be a point at which crucial risk-benefit considerations can be better understood, and safety judgements can affect	The revised answer removes the suggestion that safety or risk/benefit monitoring per se would be more important in early than later phase trials. => The wording has been adapted in line with the suggestion: *"Safety or risk/benefit monitoring is of large importance in early drug development as much less knowledge of the medicinal product has been acquired than in later phases."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		whether the treatment may be approved and become available to a very large population of patients. **Proposed change:** "Safety monitoring is of even more importance in early drug development than in later phases when already more knowledge of the medicinal product has been acquired. ~~. Therefore k~~Knowledge of relevant …	"Therefore" has not been removed as the proposed change seems not in line with the argumentation provided. The 'therefore' signals that a large need for safety monitoring is important. => No changes.
88-91	4	**Comments:** For larger sponsors, there may be knowledgeable committee members who have not been involved in the development of the medicine. **Proposed change:** The inclusion of members external to the Sponsor may increase the credibility of such **a safety review** committee. Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product which may lead to subjective rather than objective decision making.	This would still be considered 'internal' members. => No changes are made as the statement is still correct: *"The inclusion of members external to the Sponsor increases the credibility of such a committee. "*
89-91	5	**Comments:**	This is agreed. => The proposed change is adopted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggested change to take into account non-commercial sponsors, where the manufacturer is not the sponsor. **Proposed change:** "Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been heavily involved in the development of the medicinal product or the conduct of the trial which may lead to subjective rather than objective decision making."	
89 and 93	2, 3	**Comments:** Concerning question 7, the optional point of internal members could be seen very critical in the assessment of early clinical trials from the regulatory point of view. Therefore, for the case that this committee shouldn't have sufficient independent members, the proposal could be to give this committee another name in the protocol of the clinical trial, e. g. advisory committee. Just to avoid misunderstanding, the main criteria of independence of the members should always be the condition for each Data Monitoring Committee; each DMC should consist of independent members. **Proposed change:** 89 add: The inclusion of …..safety review committee. **In case independency is not met the name of the committee should be different like 'advisory**	This is agreed, and is reflected in the current text as below: "*If safety review is implemented by a DMC in the definition considered in this Q&A, then by definition all members have to be independent from the Sponsor (see Guideline on Data Monitoring Committees (EMEA/CHMP/EWP/5872/03 Corr)). Otherwise, the committee should be called differently, e.g., a safety review committee (see Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07 Rev. 1)).*" => The proposed change is adopted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		committee' and not DMC, to avoid misunderstanding. Any case the committee should have sufficient…. 93: …such information might **mostly** ~~only~~ be available within……	
90	4	**Comments:** It is recommended that the phrase "heavily involved" be changed to "directly involved" and this would allow for internal members to serve who are not on the study team. **Proposed change:** Therefore, this committee should have sufficient independent members so that decisions are not made solely by members who have been ~~heavily involved~~ **directly involved** in the development of the medicinal product which may lead to subjective rather than objective decision making. However, it might also be necessary to have an in-depth knowledge of the medicinal product under evaluation. For early phase trials, such information might only be available within the Sponsor's organization. ~~Moreover, where the nature of such studies is not confirmatory but exploratory, having also internal members may be more needed.~~	This change is no longer needed, as internal members are allowed to sit in a safety review committee (but not in a DMC). => No changes.
92-93	5	**Comments:**	This is agreed. => The proposed change is adopted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggested change to take into account non-commercial sponsors, where the manufacturer is not the sponsor. **Proposed change:** "For early phase trials, such information might only be available within the Sponsor's organization or the manufacturer's organisation, for trials where the Sponsor is a non-commercial institution."	
94-95	5	**Comments:** Clarification proposed **Proposed change:** "Moreover, where the nature of such studies is not confirmatory but exploratory, including internal members may be important."	The distinction between the proposed sentence and the current text seems minor. => No changes.