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REVISION OF THE 'CLINICAL TRIALS DIRECTIVE' 2001/20/EC

SUMMARY OF THE REPLIES TO THE PUBLIC CONSULTATION ON THE 'CONCEPT PAPER'

1. INTRODUCTION

1. On 9 February 2011 the Commission launched a public consultation on a concept paper concerning the revision of the 'Clinical Trials Directive 2001/20/EC' ('CTD').[1] The concept paper put forward

   - a 'preliminary appraisal' of the options which appear to be the most suitable to address some of the key concerns of the CTD, on the basis of the current state of the impact assessment; and

   - the main numbers that are being used to evaluate the impacts of the various policy options.

2. This public consultation followed a public consultation on the revision of the CTD, which was held from 9 October 2009 to 8 January 2010 (the '2009/10 public consultation'). Its purpose was not to repeat the 2009/10 public consultation. Topics which had been explored extensively during that consultation are not being put forward again for discussion. Instead, the purpose of the public consultation was

   - to seek views on more concrete ideas regarding the issues that were presented in a rather general way during the 2009/10 public consultation. Consequently, some issues considered in this paper were of a more detailed and technical nature; and

   - to verify with stakeholders the core data which form the basis of the impact assessment.

3. The Commission received 143 responses. Fifty-two responses came from hospitals, investigators and 'non-commercial'/'academic' sponsors, 37 from the pharmaceutical industry and contract research organisations ('CROs'), 17 from national competent authorities ('NCAs'), ministries or agencies, including the European Medicines Agency ('EMA'), six from Ethics Committees ('ECs'), 14 from patient organisations, and 17 from other entities and individuals.

4. In accordance with the applicable guidelines, the responses have been published by the Commission.[2]

5. This paper summarises the responses to the public consultation document. In doing so, it not only reflects the majority views, but also tries to present a 'snapshot' of the range of responses.

6. This paper is in no way to be understood as an endorsement of any comment.

7. For the sake of brevity, the paper does not reproduce the consultation items. Therefore, this summary should be read in conjunction with the consultation items set out in the concept paper.

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1 http://ec.europa.eu/health/files/clinicaltrials/concept_paper_02-2011.pdf

2 http://ec.europa.eu/health/human-use/clinical-trials/developments/index_en.htm

8. The public consultation is part of the ongoing impact assessment exercise. The information and views gathered in this public consultation will be taken into consideration in the impact assessment process.

9. The adoption of the impact assessment report and the legislative proposal is planned for 2012.

2. GENERAL REMARKS

10. The public consultation was highly appreciated by stakeholders. It was noted that there is a significant consensus with regard to the impediments posed by EU-regulation and potential routes to address them. It was also appreciated that many suggestions from previous meetings, conferences and workshops have been taken into account.

11. It was also explicitly welcomed that the concept paper takes the concerns of the academic community into account. It was stated that the description of the issues and possible solution was "balanced", while the concept paper was overly optimistic on the issue of whether harmonisation is feasible.

12. In terms of substance, there was widespread approval of the majority of "preliminary appraisals" set out in the concept paper. The detailed comments summarised below have to be seen against a general approval by stakeholders of the key issues identified and the possible solutions.

13. Some respondents criticised the fact that there was not enough focus on ethics, and too much focus on costs and regulatory burden. It was argued that the "key problem", namely a dual 'approval' by NCAs and ECs, had not been addressed. The concept paper was also criticized for not having assessed how much regulation is actually necessary.

14. Some respondents argued in favour of the need for further consultation on details, such as on safety reporting, definitions and the 'single portal' (see below). It was also stated that the revision of the CTD should be taken forward as a matter of priority.

3. SINGLE EU-PORTAL (CONSULTATION ITEM NO. 1)

15. Practically all respondents welcomed the concept of a single EU-portal. They argued that this concept (also referred to as 'one-stop' or 'one-file concept') was a 'crucial prerequisite', independently of the assessment type, and the 'only way forward'.

16. A large number of respondents stressed that, for a single EU-portal to work, the documentation to be submitted has to be fully standardised. It was argued that this was a challenge because different ethics and health systems required different documentation. Other respondents stressed that, on the contrary, differences of ethical appraisal and local customs should not mean different documentation.

17. Some respondents highlighted the usefulness of a single EU-portal for cross-referring and sequential trials.

18. It was pointed out that the Investigator's brochure ('IB') and national-specific documentation is often submitted later. Examples of national-specific documentation were given, such as a power of attorney, labelling, sites, insurance and data protection. The idea to also include ECs in a single portal was described as a 'challenge'.

19. As regards documentation requirements, there were fears that a single EU-portal would lead to a comprehensive list of national requirements. Several respondents called for proportionate requirements, rather than a collection of national requirements. It was requested that the simplified investigational medicinal product dossier ('IMPD') should be codified.

20. There were also some critical voices arguing that a single portal was too complicated for non-commercial sponsors, and that - in the short term - the need for resources for small sponsors could increase. The question was asked as to whether the technical burdens were proportionate to the benefits. It was also pointed out that there might be a loss of flexibility in the approval process, as well as higher costs, i.e. fees.

21. Several respondents referred to existing national portals, in particular the Italian 'osservatorio' and the RIAS system in the UK. These references were made in different contexts: some argued that a single EU-portal should interface with these national entries, i.e. that these national systems should not be 'endangered'. Others argued that an EU system, in particular if it includes submissions to ECs, should replace national systems, in order to avoid parallel systems and so as not to confuse sponsors.

22. Several respondents raised the issue of languages, in particular in the context of labelling (the possibility of an 'English masterlabel' was raised). It was recalled that ECs often have lay members, who may only understand documents in their national language. The synopsis of the protocol should be translated. The issue of how languages would be dealt with in mono-national trials was also raised.

23. In the context of the single EU-portal concept, some respondents also raised the issue of whether it should apply to mono-national clinical trials. Most of the respondents who raised this issue were in favour.

24. Many respondents stressed that setting up a single EU-portal was challenging in terms of functionality, compatibility, performance and reliability. The following specific issues were raised: Confidentiality of certain information (e.g. related to the IMP), authentication of the applicant, validation (only technical or also as regards content?) which ensures a 'first time right', archiving rules, and personal data protection.

25. Several respondents recalled that there are possible follow-up submissions, such as those related to substantial amendments and the extension of a clinical trial to another Member State ('MS').

26. It was also stressed repeatedly that ECs should have access to the full dossier.

27. It was argued that clinical data should be based on eCTD modules.

28. Some respondents enquired who would administer the single EU-portal (the EMA or Heads of Medicines Agencies - 'HMA'?)

29. Some respondents asked about the impact on fees and, more generally, how a single EU-portal would be financed. It was stressed that there should be no increase in costs.

30. Several respondents asked how communication between the NCA/EC and the applicant would work in a single EU-portal model.

31. Some respondents asked how a single EU-portal would work in a study which falls partly outside the scope of the CTD, e.g. involving genetically modified organisms ('GMOs') or imaging techniques. It was suggested that a single EU-portal could eventually be extended to other areas of research.

32. Several respondents stressed the need for a pilot phase, training and additional consultation on the details of the single EU-portal.

4. SEPARATE ASSESSMENTS (CONSULTATION ITEM NO. 2)

33. Practically all respondents agreed with the preliminary assessment in the concept paper. It was argued that, in the case of a separate assessment, the burden of a single EU-portal would outweigh its benefits.

34. However, there were also some respondents who argued that the present system of separate assessment by individual MSs produces positive effects in terms of competition in the speed and efficiency of the approval. It was also argued that patients get a better hearing under the existing system, and that divergence and variability of assessment is not necessarily a negative thing.

35. It was argued that there should be a separate assessment in the case of multiple sponsorship (see below).

36. Apart from the concepts put forward in the concept paper, other ideas were floated, such as a recommendation by one MS to the other MSs concerned.

5. ASSESSMENT – GENERAL REMARKS (NO CONSULTATION ITEM)

37. Throughout their submissions, respondents made comments in various contexts which are valid for the approval process in general.

38. For example it was argued that, in any event, ECs should be addressed: It was argued that these were the most complicated, time consuming, bureaucratic and costly part of an application. Even within a MS, there is no harmonisation. A large number of suggestions were made, such as a 'European platform' of ECs.

39. The issue of where the (national) differences in approaches in MSs actually are was also raised: It was stressed that it is the content of the documents, rather than the documentation itself, where NCA expectations vary. It was also argued that the

differences of view relate mostly to quality (in terms of format of documents and data content).

40. Examples of divergent views on issues such as placebo and affordability of medication after trials were mentioned. On the other hand, it was argued that differences in ethics are not as substantial as sometimes argued.

41. It was recalled that some MSs have specific committees (first in human, viral safety, etc.). In other MSs, certain assessment tasks are delegated to local hospitals. How do they fit into the system?

42. It was stressed that any harmonisation should conform to the highest standard.

6. CENTRALISED ASSESSMENT (CONSULTATION ITEM NO. 3)

43. Practically all respondents agreed with the preliminary assessment in the concept paper.

44. It was argued that a 'centralised system', as it is known for the marketing authorisation for certain medicinal products, would be 'unworkable' in the case of clinical trials. The question was also raised as to whether this would be acceptable to the public. A national perspective was necessary for the acceptance of a trial by the public.

45. Respondents also agreed with the preliminary appraisal that a review of uninvolved parties should be avoided, and that resources of MSs who do not take part in the trial should not be tied up. It was argued that the only advantage of this system was that MSs could 'learn from each other' and that the best available expertise could be gathered.

46. However, some respondents also argued that the arguments put forward in the concept paper were not convincing: a 'central procedure' would save resources in Member States and avoid repetitive assessments. Clinical research programs for new medicines would be facilitated and the adding-on of centres in other MSs would be simplified.

47. Some respondents suggested establishing a 'centralised system' where only a small group of experts/MSs assess the clinical trial for the entire EU. Moreover, it was suggested that the experts should be permanently based with the EMA - either being physically present or working remotely.

48. Some responses suggested that a 'central procedure' should be optional, or only considered in the long run.

49. It was also suggested that a 'centralised procedure for the MSs concerned' should be set up.

7. 'COORDINATED ASSESSMENT PROCEDURE' ('CAP')

7.1. General comments

50. By far the majority of respondents welcomed the idea of a CAP, as set out in the concept paper. It was stressed that the experience with the 'Voluntary Harmonised Procedure' ('VHP') could be put to good use.

51. It was also argued that the CAP responds to the concerns of academic research, as it would allow a consistent application of a risk-based approach in all MSs concerned.

52. A few respondents, however, also criticised the concept of a CAP, arguing that it would lead to further bureaucracy.

53. Many respondents addressed the role of ECs in the CAP. They welcomed the fact that the scope of the CAP is based not on a concept of 'institution' (i.e. NCA vs. EC), but on a concept of 'substance' (i.e. which topics are assessed in a CAP, and which topics are assessed outside the CAP). This means that the CAP applies independently of whether a topic is being assessed by the NCA or by the EC in a given MS. Depending on how the tasks between NCA and EC are shared out in a MS this may mean an involvement of ECs in the CAP.

54. Many respondents indicated that risk-benefit considerations were difficult to separate from ethical evaluations and that ethical issues and methodology are linked. The idea of separating ECs and NCAs tasks was rejected: it was argued that it was 'not realistic' or even 'absurd' to make such a separation. For example, it was not possible to look at informed consent without knowing the protocol. It was also pointed out that the ECs have different responsibilities in different MSs – various examples were given. The organisational structure of a country should not be affected. Instead, in MSs where responsibilities of the NCA and the EC are overlapping, processes within a MS would need to be defined.

55. Some respondents criticised this concept, pointing out that depending on the extent of these 'overlaps' these processes may be very complicated. Moreover, ECs - even within a given MS - are not cooperating. Some respondents were also afraid that the CAP would infringe the independence of ECs.

56. As an alternative, several respondents put forward other ideas, such as a 'coordinated ethics procedure', where the respective roles of NCAs and ECs should be harmonised, while remaining 'clearly separated'. On the other hand, an 'overlap' of tasks between NCAs and ECs was welcomed. It was stressed that ECs - unlike NCAs - have active clinicians, and thus a special expertise.

57. It was asked how, in a CAP, interactions with sponsors would work.

58. Many respondents commented on the role of the 'reporting Member State': It was asked how that MS would be determined (choice, agreement, key system, rotation, etc.), referring to the risk of a 'booking system' as it is known in the area of authorisation of medicines. In this context, it was pointed out that the reporting MS potentially has an important role, but may be put under pressure by other Member States.

59. The question was asked concerning who would act as the secretariat of the CAP – the EMA or HMA – and whether the EMA could act as an 'advisory body'.

60. It was also pointed out that a CAP would have to involve follow-up measures such as assessment of suspected unexpected serious adverse reactions ('SUSARs'), development safety update report ('DSUR'), substantial amendments ('SAs'), etc.

61. Many respondents mentioned the practice of "staggered launches" of a clinical trial, where other trial centres are added later (also referred to as "2nd wave"). It was suggested that MSs other than the MS concerned should be able to participate already in the '1st wave'.

62. It was asked how it can be guaranteed that MSs do not go back on their decision taken with the CAP.

63. There was a fear that the CAP would lead to more opt-outs (see below) than agreements.

64. It was stressed that patient representatives should be involved.

65. The question of whether there would be an appeal mechanism for the sponsor was also raised. It was suggested that there should be an 'appeal mechanism' and a process of dialogue, into which patients and healthcare professionals should be able to provide input.

66. It was stressed that the possibility should remain to ask ECs for advice on research projects.

8. SCOPE OF THE CAP (CONSULTATION ITEMS NO. 4 AND 5)

8.1. Aspects to be considered in the CAP ('part a')

67. Several respondents asked for additional aspects to be included in the CAP, such as the informed consent form/process, remuneration of researchers, and local issues, such as suitability of the investigator.

68. By far the majority of respondents considered the catalogue to be complete. However, there were also respondents who pointed out that certain issues were missing, which needed to be assessed in the CAP: These issues included the following:

- Process of safety reporting;
- Auxiliary medicinal products (see below) and medical devices;
- Safety plan;
- Quality on the basis of pre-clinical and clinical data;
- Standard therapy;
- Supply of the IMP;

- Provisions for minimizing risk and monitoring safety, including follow- up monitoring.

69. It was suggested that the CAP should include assessment whether the product was an IMP or not, as well as questions on the completeness of the dossier.

70. Some respondents felt that the notion 'design of the trial' was not specific enough. Many respondents asked that the aspects of "statistics" and methodology, including sample size, randomization and unblinding, adequate comparator, etc should be added.

71. Other respondents discussed this aspect under 'relevance', raising more specifically the choice of the control group, primary and secondary variables, sample size and statistics, dosage and duration of the treatment.

72. It was argued that more emphasis should be put on the subject of safety, with particular emphasis on the vulnerable population.

73. It was argued that the CAP should be limited to labelling, manufacturing and importation. In particular, as far as the risk-benefit aspect is concerned, several respondents argued that this was an ethical issue and that the scientific and ethical aspects could not be separated.

74. It was recalled that the concept of risk/benefit includes the severity of indication and lack of alternative treatments, as well as ability to monitor safety, vulnerability, and risk-management measures. The 'risk of the disease' (also referred to as 'life-saving potential of the treatment being investigated') should be added as well.

75. In terms of drafting, it was recalled that the 'investigator's brochure' ('IB') might be replaced by the Summary of product characteristics ('SmPC') (the term "background information" was suggested).

76. It was also suggested that a reference be made to GCP. It was suggested that the Paediatrics investigation plan ('PIP') be taken into account.

77. Most comments referred to the aspect of normal clinical practice (it was suggested that the term 'standard clinical practice' should be used instead of 'normal clinical practice'). Several respondents stressed that there are differences throughout the EU which are based on authorisation status and reimbursement decisions. The example of infectious diseases and antibiotic use was given.

78. However, it was also mentioned that this was an opportunity to increase understanding of products and care in general. Moreover, it was pointed out that standards of care might be local.

8.2. Ethical aspects ('Part b')

79. It was argued that data protection should be under 'part b'. There were some questions relating to the term 'reward' ('rewarding recruitments' or 'rewarding referring patient to a CT'?).

80. In line with what had been said under 'part a', some respondents argued that issues of 'design and relevance of the trial' should fall under 'part b'.

8.3. Local aspects ('Part c')

81. It was argued that issues of importation were local issues, and therefore fell under 'part c'.

82. It was also argued that points under 'part c' should not be assessed at all, but should remain under the responsibility of the sponsor.

9. DISAGREEMENT BETWEEN MEMBER STATES IN THE CAP (CONSULTATION ITEM NO. 6)

9.1. General remarks

83. Several respondents recalled that, in practice, the response to an application for a clinical trial approval is not a simple 'yes/no', but rather a request for modifications, or additional questions.

84. In this respect, some respondents asked how many contradictory decisions there would actually be in a CAP. It was argued that, on the quality issue, there should be no disagreement in practice. It was noted, however, that different MSs have different 'focuses', such as contraception, viral safety, batch identity analysis, stability data, etc.

85. It was argued that, in any event, divergences should be communicated to the sponsor.

86. It was asked how the withdrawal of an application would work and how a disagreement between MSs would affect the start of a trial.

87. As regards 'opt out', it was asked whether an 'opt in' (without additional assessment) should be considered.

88. Overall, there was broad agreement that, where possible, an effort should be made to achieve consensus, and that any kind of vote/opt out should remain the exception.

9.2. Opt-out on the basis of 'serious risk to public health'

89. Many respondents favoured an 'opt out' mechanism. Moreover, many respondents agreed that an 'opt out' should be subject to conditions in order not to lead to a proliferation of 'opt outs'.

90. However, many respondents found the condition 'serious risk to public health' to be 'illogical'. It was suggested that reference should be made instead to aspects of normal clinical practice in a MS, ethical issues, or to 'major issues with national specificities'.

91. Several respondents stressed that, in order for an 'opt out' to work, there has to be first a group decision from which one can 'opt out'. Therefore, an 'opt-out' only works in combination with a vote.

92. Several respondents stressed that an 'opt out' should not veto a whole trial, i.e. one MS should not prevent the other MSs from approving the trial.

93. It was asked how a sponsor can address the concerns of the MS who opts out. The possibility of re-applying was mentioned.

94. Some respondents suggested that the reason for an 'opt out' should be made public and transparent – e.g. through publication by the Commission or the EMA.

95. The risk of sponsors possibly moving into countries which usually do not opt out was mentioned.

9.3. Vote

96. Several respondents saw difficulties arising if a majority of MSs is able to overrule a minority as regards acceptance of the aspects covered by the CAP. Various issues were raised, such as the situation if the vote is evenly split, and how to deal with MSs of different sizes.

9.4. Referral to a European authority

97. Many respondents pointed to the potential delays involved in a 'referral' to a European body. The question was also asked concerning the basis on which a referral decision would be taken. Regarding the EMA, it was argued that this task would have to be separate from marketing authorisation activities.

98. Only a few respondents favoured this approach, arguing that this was the only way to achieve a common decision.

10. MANDATORY/OPTIONAL USE OF CAP (CONSULTATION ITEM NO. 7)

99. This consultation item was one of the few topics where responses diverged strongly. Some respondents also addressed the question of whether the single EU-portal (see above) should be obligatory for mono-national trials. Some respondents had misunderstood the notion of 'optional' as being 'optional for MSs'.

100. Many respondents argued in favour of a 'phase-in' ('pilot phase', 'learning curve', 'transition period'), i.e. the CAP would become obligatory only a few years after it had come into operation.

101. Several respondents argued in favour of a mandatory CAP for multinational trials as opposed to an optional system. They argued that an optional approach would entail the risk of a two-tier system. They also pointed out that clinical trials might have additional trial sites later during the study. A mandatory CAP might facilitate this 'second wave'. Moreover, the overview of an IMP gets lost if there are different routes of application.

102. Moreover, a mandatory system would 'keep things simple', and remove the issue of different forms and documentation between the CAP and national procedures.

103. On the other hand, some respondents argued that academics might prefer authorisation routes which they know and understand. Many academic trials are mono-national (example: patch testing for skin allergy). The need for flexibility was mentioned. Also, it was pointed out that a few MSs have a good record in terms of the speed of phase-I approvals. This must not get lost with a CAP. A CAP should not become more cumbersome than it currently is for mono-national trials.

11. TIMELINES, TACIT APPROVAL AND 'TYPE-A TRIALS' (CONSULTATION ITEM NO. 8)

11.1. Tacit approval

104. Several respondents disagreed with the concept paper on the issue of the 'tacit approval'. It was stressed that the concept of 'tacit approval' has been helpful, as it penalizes delays and ensures a clear timeline.

105. However, it was also stressed that inspectors expect an authorisation document and that tacit approvals do not work in practice.

106. Opinions differed as to whether a tacit agreement would work with a CAP.

11.2. Length of timelines

107. As regards timelines, there was broad agreement that a CAP should not lead to longer timelines than at present. Several suggestions were made, e.g. that timelines should take into consideration whether there is a Paediatrics Investigation Plan ('PIP') or scientific advice by the EMA, or that there is no other treatment option.

108. Some respondents argued that, in the case of mono-national trials which would not require coordination under CAP, timelines should be shorter.

109. It was argued that timelines for pharmacokinetic studies in healthy volunteers should be shorter, and that clinical trials with 'advanced therapy IMPs' should have a longer timeline.

11.3. Validation, additional information request, clock-stops

110. Some respondents drew attention to the need for clear rules on validation, including information of the sponsor when the dossier is validated.

111. Several respondents stressed that clear rules for clock-stops are needed in order to have predictable timelines.

11.4. Substantial amendments (SAs)

112. It was stressed that a clear deadline for approval of SAs was needed. 35 days was an absolute maximum, while it was also said that 20 days was too short for NCAs to assess a SA.

11.5. Other issues

113. Some respondents raised other issues or made general comments. For example, it was argued that a simple 'notification process' did not necessarily save resources.

114. It was also pointed out that a simple submission process was more important than timelines.

11.6. Type-A trials

11.6.1. Idea as such

115. The majority of respondents welcomed the concept of type-A trials in principle – also with a view to the workload of the approving body. Many respondents drew attention to the ongoing work in the UK in this respect, as well as to the US system (21 CFR 312.2(b)) and the Canadian system.

116. Examples were given for medical disciplines where type-A trials are very relevant, such as off-label uses for contrast enhanced magnetic resonance imaging and ultrasound.

117. However, there were also critical voices who stressed that the time gains were minimal, and may be offset by complicated assessments of the risk, and possible discussions in the event of disagreement.

118. Some respondents criticised the concept of a 'category' as a whole, arguing that risk-assessment was about method, not categories. It was also argued that risks cannot be predefined in a clinical trial, which is by definition characterised by a lack of certainty.

119. It was also argued that the limit to non-interventional studies would be blurred if the concept of a type-A trial was introduced.

11.6.2. Pre-assessment

120. Virtually all respondents requested further clarification concerning the pre-assessment. This included the following aspects:

- Who carries out the pre-assessment? (the sponsor, the NCA, in the case of CAP: all NCAs?)
- In the case of the CAP, what if there is disagreement in the pre-assessment?
- Would the patient's view be incorporated in the pre-assessment?
- How is the EC involved in the pre-assessment?
- Would the pre-assessment be part of the validation?

121. It was stressed that the workability of a pre-assessment would depend on the NCA, not the sponsor. It was also suggested that there should be a 'letter of intent system' to provide the sponsor with a degree of certainty.

11.6.3. Definition

122. Practically all respondents had follow-up questions concerning the definition put forward in the concept paper.

123. Generally, there were concerns that the definition provides a degree of flexibility which raises predictability issues. Respondents were apprehensive about the many new, complex guidelines that would be necessary for making the definition operational in practice. On the other hand, it was acknowledged that a 'rigid system', for example based on the authorisation status of the IMP (the authorisation status would be the surrogate for knowledge of the compound), might also lead to distortions.

124. It was argued that various other factors should be taken into account, such as the trial phase, the type of products (such as herbal medicinal products and vitamins) or whether the IMP is modified.

125. Several respondents made specific comments on the definition set out in the concept paper:

- 'Significant': it was argued that this term is used in statistics and should not be used here. The term should be "clinically relevant".

- 'Used within the authorised indication': it was asked how this works for cancer indications. 'Indication' should be replaced by 'condition', as the term 'authorised indication' was too narrow. Other terms discussed were 'authorised or similar indication'. Generally, it was pointed out that indications are becoming increasingly narrow.

- 'Intervention': It was asked how 'intervention' is defined. The example of an additional blood test was given.

- 'IMP is authorised': It was suggested that authorisation in ICH regions should also be considered. It was pointed out that there are clinical trials with products that are routinely used off-licence. It was suggested that reference should be made to "the" Member State, rather than "a" Member State. It was pointed out that marketing authorisations might be withdrawn.

- 'Standard treatment' Some respondents pointed out that a given therapy may be an undertreatment in one MS and an overtreatment in another MS.

- It was argued that the words 'part of' should be replaced by 'used as' when referring to a standard treatment.

126. It was also stressed that the definition should take into account the risk to the robustness of data, thus including issues such as complexity of endpoints, complexity of trial design, and degree of deviation of the protocol treatment and examination from standard clinical practice.

127. It was argued that clinical trials in children should be specifically included in type-A trials.

11.6.4. Timelines

128. As regards the timelines for the pre-assessment, it was stressed that these should not be longer than a week. The idea of a 'tacit agreement with a pre-assessment by the sponsor' after one week was put forward.

129. It was asked whether shorter timelines mean lower review standards.

11.6.5. Other issues

130. Other points raised by the respondents included the following:

- Could the classification as type-A trials also be used for aspects other than rules for approval (e.g. rules on monitoring, insurance, labelling, safety reporting)?
- What is the interface with SAs?

131. It was suggested that it should be optional for the sponsor to undergo a pre-assessment. A pilot-phase was suggested.

12. INTERVENTIONAL/NON-INTERVENTIONAL TRIAL (CONSULTATION ITEM NO. 9)

12.1. General remarks

132. Several respondents recalled the difficulties caused by the narrow definition of "non-interventional trial" (some respondents stressed that the term "non-interventional *study*" would be more correct).

133. In this context, examples of low-risk additional interventions were given. It was noted that the issue of whether an intervention is 'additional' depends on the (local) normal clinical practice.

134. The different types of additional intervention were listed (e.g. randomisation, additional diagnostic measures).

135. It was pointed out that the definition makes it difficult to conduct studies in normal clinical settings, which may be useful in order to test real-life situations.

12.2. A wider definition

136. By far the majority of respondents agreed with the concept paper in that the definition of 'non-interventional trial' should not be widened. However, many respondents stressed that this would make the risk-based approach (including a category of 'Type-A trial') even more important.

137. However, there were also voices calling for a widening of the definition, thereby limiting the scope of the Clinical Trials Directive – these respondents did not want to see this idea dismissed completely. It was suggested that the 'WHO definition' should be used (*'Any research project that prospectively assigns human participants or groups to one or more health-related interventions to evaluate the effects on health outcomes.').*

138. It was argued that cohort studies, retrospective data analysis, etc. should be clearly excluded.

139. Fears were expressed that a broader definition could facilitate drug promotion.

140. The terms 'epidemiological methods' were discussed, as well as the explicit reference to a 'protocol' (the question was asked as to why epidemiological studies would not have a protocol).

141. It was stressed that the existing rules for clinical trials do not take into account retrospective trials, as well as long-term studies which may be limited to secondary endpoints.

12.3. Other comments

142. Some respondents called for a separate regime for non interventional trials.

143. Some respondents had misunderstood the concept paper and discussed whether non-interventional trials should be included in the scope of the CTD – an option which was not put forward in the paper.

144. It was suggested that a definition of an 'interventional trial' should be drawn up, and not a definition of a 'non-interventional trial'.

145. It was also stressed that, because of national regulations, it has become more difficult in some MSs to obtain approval for a non-interventional trial, than for a clinical trial.

146. The concept of a 'non-interventional phase in an interventional trial' was raised.

13. EXCLUDING CLINICAL TRIALS BY "ACADEMICS/NON-COMMERCIAL" SPONSORS

147. All of the 143 respondents (with one nuanced response) agreed that clinical trials conducted by 'academic/non-commercial' sponsors should not be excluded from the scope of the CTD. The arguments put forward in the 2009/10 public consultation were repeated. The main argument throughout the responses was that the rules on safety, rights, and robustness of data should apply independently of whether or not the sponsor is 'academic'/'non-commercial'.

148. Some asked why this distinction/discussion should even be raised. On the other hand, it was also argued that this definition may be relevant for issues of fees and electronic submissions schemes, which require an expensive infrastructure for the sponsor.

149. It was suggested to explicitly refer to "Clinical research cooperative groups".

14. RISK-ADAPTED RULES (CONSULTATION ITEMS NO. 11 AND 12)

150. Respondents used this consultation item to stress various points as regards risk-adapted regulation.

151. Various examples for other risk-categorisations were given, such as the area of medical devices. Reference was made to the definition used by the US regulation.

152. It was stressed that risk in clinical trials refers to two separate issues: data reliability and subject safety.

153. It was also stressed that the concept of risk was challenging, because it is perceived differently by patients (also according to the disease) and because it depends on future developments. Moreover, any clinical trial is a singular event, which calls for a case-by-case assessment. Legislation or guidelines cannot cover all scenarios.

154. Regarding the idea of 'more' risk-adapted rules, some respondents feared that this could reduce flexibility. Lack of flexibility may lead to risks for the patient.

155. Respondents highlighted the following areas where more detailed, risk-adapted rules should be considered in the revised legislation:

- Import/export, distribution and 'pharmacy procedures';
- Follow-up treatments;
- Monitoring;
- Unblinding;
- Content of dossier;
- Requirements for GCP training;
- Traceability system for IMP.

156. However, the area most frequently mentioned was safety reporting. It was stressed that the rules for periodic reporting must be clear, and that at present the information is too much based on quantity, rather than quality.

157. In this respect, however, other respondents suggested that the volume of reported events should be increased by including serious adverse reactions ('SARs').

158. It was argued that informing the investigator through the IB was sufficient. It was argued that there was no need for a DSUR for marketed medicines, if they are used in their approved indication.

Other issues

159. With a view to the existing guidance to be taken into account, it was pointed out that certain ICH guidelines were not appropriate in the context of clinical trials, as they concern commercialised products only. Various other existing guidelines were highlighted.

160. Several responses highlighted the need to involve MSs when setting up delegated acts.

15. INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS) AND AUXILIARY MEDICINAL PRODUCTS (AMPS) (CONSULTATION ITEM NO. 13)

15.1. The issue

161. Many respondents highlighted the difficulties they face with the rules on IMPs. It was argued that the complexity of the rules 'discourages' research into comparative effectiveness.

162. The question was raised as to whether medicines used as standard base therapies are IMPs.

163. It was stressed that most problems relate to costs (national insurance administrations do not cover IMPs) and GMP-compliance (allergen patch testing was mentioned as an example).

15.2. IMPs

164. It was argued that reference products should not be IMPs. It was also stressed that placebos and modified medicines should remain IMPs.

165. As regards Directive 2001/83/EC, it was asked whether 'intended for research…' was meant to refer to the point in time of 'placing on the market'.

15.3. AMPs

166. While a large majority of respondents welcomed the concept of AMPs (provided that this term replaces the non-IMP, which is the case), there were also critical voices: It was feared that regulation might become overly complex and that this regulation would replace common sense and scientific judgement.

167. It was argued that background treatment, rescue and escape medication, comparators and concomitant treatment medicine which is used in line with the standard of care should, in principle, be considered as an AMP. Also, non-modified post-marketing drugs should be AMP, as well as PET tracers and other diagnostic agents.

168. The term 'AMP' should also include 'ancillary material'.

169. As an additional element in the definition, it was suggested to state that the medicine is mentioned in the protocol.

170. It was suggested to abandon completely the differences between IMP and AMP, but simply refer to the criterion of whether the medicine is modified.

171. The question of how to deal with unrelated medication (referred to as 'concomitant medication') was asked.

172. Several respondents stressed that they agreed to the concept of AMP, while rejecting any new regulation. Instead, AMPs should be unregulated in order not to stifle research ('hands-off approach'). In particular, there should be no rules on labelling, accountability records or destruction logs.

173. Others argued that there should be no rules for AMPs if they are used within the MA. With regard to costs for AMPs it was stressed that AMPs should be paid by social health insurance.

15.4. Other issues

174. The possibility of a list of pre-approved AMPs ('list of validated AMPs') was raised. It was also asked whether a trial could consist solely of AMPs.

16. INSURANCE REQUIREMENT (CONSULTATION ITEM NO. 14)

16.1. The issue

175. Several respondents made general comments on the issue of insurance in which they argued that insurance is not the decisive factor for companies, and that the costs of finding out about coverage are not so high.

176. On the other hand, it was stressed that insurance for multinational trials is inordinately expensive.

177. It was stressed that the real problem lies in the different liability rules.

16.2. Removing insurance

178. On this point there were very mixed reactions amongst respondents. Some agreed, recalling that, at least for type-A trials, the existing insurance schemes of the investigator, the manufacturer of the IMP and the hospital are sufficient.

179. On the other hand, many respondents had doubts about this approach: They pointed out that the risks are not always predictable and that the risk might evolve. 'Low risk' still means that there is a risk. Also, the sponsors would no longer have an incentive to look into risks.

180. It was also pointed out that removing insurance does not remove the liability for sponsors.

16.3. National clinical trial indemnisation fund

181. Several respondents acknowledged that this concept could be a solution for sponsors who have difficulties obtaining insurance. It was pointed out that little cash flow, but a strong capital stock was needed for this option.

182. It was also argued that the costs to governments would be much less than what is currently spent by public funding on insurance costs.

183. However, there were also critical voices on the issue of feasibility. The question was also asked as to whether this might lead to more bureaucracy, highlighting the fact that the insurance industry has knowledge and expertise which is missing elsewhere. It was also asked whether this might lead to a different approach to the authorisation of clinical trials by MSs.

184. Some respondents misunderstood the notion of 'optional' as meaning optional for the MS, rather than for the sponsor.

185. It was suggested that such a fund should only be introduced for Type-A trials, or only for non-commercial sponsors, or only where national governments have an interest in the research.

186. It was suggested that the fund be sourced through the pharmaceutical industry, or by means of fees.

187. The question was asked as to whether the state-funded compensation could turn against the sponsor/investigator to recover the damages paid.

16.4. Other issues

188. Several other comments were made regarding insurance, for example related to insurance for travelling to the clinic. Several respondents called for Europe-wide harmonisation of the liability rules in the context of a clinical trial.

189. It was argued that a classification as low-risk might help to reduce insurance premiums, so that they better reflected risk in general.

190. It was stressed that 'self-insurance' by pharmaceutical companies should be avoided.

17. SINGLE SPONSOR (CONSULTATION ITEM NO. 15)

191. While there was broad agreement with the appraisal in the concept paper, several respondents disagreed and called for a concept of "multiple sponsorship".

17.1. Single sponsor

192. Several respondents argued that single sponsorship is the better concept. It was recalled that otherwise there might be 'gaps' in the responsibility. A network of several contracts was an undesirable scenario. It was argued that a concept of 'multiple sponsorship' might lead to 'collective blame'.

193. Several respondents stressed that the issue of 'single sponsor' was not as critical as it seems, provided that:

- The possibility to delegate tasks was clearly set out;
- The issue of insurance is dealt with (see above); and
- The difference between 'liability' and 'responsibility' was clarified.

17.2. Multiple sponsorship

194. Some respondents called for a concept of 'multiple sponsorship', arguing that it facilitates fundraising and cooperation with third countries. Several models were put forward, such as a system of 'sub-sponsors', where the 'main sponsor' should not be required to verify compliance in other MSs.

195. As a compromise, it was suggested to provide flexibility in the interim, and to resort to a system of single sponsorship once rules for the conduct of clinical trials are properly harmonised in the EU.

196. The point was raised that large multinational companies, who conduct multinational trials through their national branches, are acting *de facto* on the basis of a co-sponsor model.

17.3. Other comments

197. This point of the concept paper was used as an opportunity to raise a related point – namely the function of the legal representative of the sponsor. Several respondents highlighted the legal uncertainty as to the role, function and responsibility of this legal representative. It was argued that, ideally, the legal representative has the same function as the sponsor.

18. EMERGENCY RESEARCH (CONSULTATION ITEM NO. 16)

198. All respondents welcomed the fact that this point had been addressed.

199. Several respondents explicitly welcomed the suggestion made in the concept paper.

200. It was asked critically what the patient would consent to if he survives. This was also discussed as 'deferral of consent', not 'waiver of consent'. It was suggested that a distinction should be made between 'consent to continue' and 'consent after the trial'.

201. On a similar point, the difficult situation was highlighted where informed consent is obtained by a legal representative where the subject had died.

202. It was also asked how, in practice, investigators can verify if there is an 'expressed objection'.

203. Several respondents made suggestions for additional criteria. In particular, the addition of the words 'prospect of direct benefit' was suggested ('to all possibility, it will serve the interest of the patient'/'likelihood of individual benefit needed') or 'potential benefit to the participant or the group' ('no inclusions if there is no likelihood of benefit for them, unless it is intended to promote the health of the population represented by the potential subject').

204. As regards direct benefit, it was pointed out that this may lead to an inconsistency with the concept of equipoise.

205. Other criteria discussed by respondents included:

- Emergency clinical trials should be the 'rare exception';
- ECs have specifically (re-)assessed this aspect of a clinical trial;
- Oversight by the independent data monitoring committee (IDMC);
- Prospective candidates cannot be identified;

- There must be no risk 'at all';
- The inability to consent is based on the condition that is treated;
- Impossibility to perform research on patients who can consent;
- Only minimal risk and burden.

206. It was recalled that the provision should be addressed in the context of Articles 4 and 5 of the CTD.

207. It was also suggested to signify consent by issuing a card that expresses consent, which would be registered in central database.

208. Reference was made to the US-rules on this matter (US 21 CFR §50-24).

Data

209. Several respondents raised the issue of data generated in an emergency clinical trial. This relates to the obtaining of consent, the prior withdrawal of consent, and the case of a diseased subject.

210. There should be clarity as to which data rules apply in these circumstances.

19. 3RD COUNTRY CLINICAL TRIALS (CONSULTATION ITEM NO. 17)

211. Practically all respondents stressed that it should be acceptable to have a clinical trial registered in other public databases than the 'ClinicalTrialsRegister'. Clarification was needed with respect to the timing of entering this information, in view of retrospective registration.

212. It was argued that bioavailability studies and bioequivalence studies should be excluded from transparency requirements.

213. Some respondents stressed that self-statements have little value and registration does not mean GCP compliance.

214. Other additional ideas were put forward:

- An international system of certification;
- Parts of marketing authorisation studies should always be performed in the EU;
- Public posting of violators and violations.

215. It was stressed that, in terms of substantial requirements, the Community should also benefit.

216. It was argued that it was not easy to find out about relevant texts in the EU.

20. FIGURES

217. Very little additional data and quantifiable information was submitted. Some comments were made on the figures of costs for insurance.

21. OTHER ISSUES

218. The public consultation was used as an opportunity to raise a large number of other issues. Some are listed below:

- Patient participation and representation should be strengthened. Patient representation in ECs should be mandatory;
- Patients should have access to the results of the clinical trials and to post-trial treatment (for free or reasonable costs). However, this should not discourage investment in research;
- The reference to a specific version of the Declaration of Helsinki should be omitted;
- Traceability tools other than labelling should be accepted;
- A EU database on healthy volunteers should be established;
- Sponsors, as well as sites and investigators should be 'accredited' on a global level (i.e. not for a specific trial), and for a specified period of time;
- Written information to subjects should be brief, but more relevant;
- Rules should be adopted for data safety monitoring boards;
- Rules on the consequences of breaches to the GCP, including communication between NCAs and ECs, should be adopted;
- Minimum and maximum insurance fees should be published by the Commission;
- Subgroups of medicines (radiopharmaceuticals, homeopathics, etc.) should be specifically addressed.

219. Some comments related to medicinal product marketing authorisations and the respective data requirements. These were, for example, related to calls for specific designs, or the inclusion of specific subpopulations in a trial submitted for marketing authorisation purposes.

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