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On 11 April 2013, CPME issued the "CPME Statement on the European Commission proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM/2012/369)"
(CPME 2013/019 FINAL)[1]

CPME Statement
on the report of Glenis Willmott 2012/0192(COD) and the subsequent amendments tabled to the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

The Standing Committee of European Doctors (CPME)[2] represents national medical associations across Europe. We are committed to contributing the medical profession's point of view to EU and European policy-making through pro-active cooperation on a wide range of health and healthcare related issues.

[1] This statement follows the previous CPME statement on the Commission Proposal (CPME 2012/132 FINAL) adopted by the CPME Board on 24 November 2012.
[2] CPME is registered in the Transparency Register with the ID number 9276943405-41.
More information about CPME's activities can be found under www.cpme.eu

1/ Ethics Committees

The Standing Committee of European Doctors (CPME) warmly welcomes the introduction by the rapporteur of a definition of ethics committee inspired by the definition contained in Directive 2001/20/EC (Amendment 19 ENVI). This is indeed a clear step towards guaranteeing a high level of patient safety in the conduct of clinical trials in Europe, while the European Commission had excluded this guarantee from its proposal.

However, the provision by which *"the view of an ethics committee shall be taken into account"* is clearly insufficient (Amendment 33 ENVI). First, because the current wording does not provide with a formal obligation to follow the decision of the ethics committee. The decision of an ethics committee should be decisive in the final approval of a clinical trial, ie. a negative assessment by the ethics committee should result in the refusal for granting the authorisation of a clinical trial. Second, because the Article in which the role of the ethics committee is mentioned is not the most suitable one. CPME would suggest an article specifically dedicated to the definition of the role of ethics committees be included in the regulation. In this regard CPME welcomes the approach of Amendments 17 and 73 of Michèle Rivasi and António Fernando Correia de Campos (ITRE opinion) and Amendments 88 and 89 of Bernadette Vergnaud and Heide Rühle (IMCO opinion). CPME would however suggest Amendments 252 and 253 tabled in the ENVI committee by Peter Liese and 16 other MEPs be the preferred ones. These amendments are comprehensive enough to precisely define the role and competences of ethics committees in line with the Helsinki Declaration and the ICH-GCP guidelines, while respecting at the same time the principle of subsidiarity.

CPME therefore invites the rapporteur and the shadow rapporteurs to take Amendments 252 and 253 (ENVI) as a basis for compromise.

CPME acknowledges the proposal in Amendments 3, 6, 8 and 66 (ENVI) by which the European Commission would need to facilitate cooperation of ethics committees and the sharing of best practices. However, in practice this might be rather difficult to implement. The procedures and principles of ethical review are of intrinsic national nature. Therefore creating a process of cooperation should not entail the risk of harmonising these rules and procedures in a way that could weaken national specificities.

CPME therefore invites the rapporteur to carefully consider the risks presented above.

2/ Approval time limits

The rapporteur did not introduce any modifications on the time limits for approval, the argument being that the concept of tacit approval will incentivize the persons taking the authorisation decisions to do so on time. The actual problem with the deadlines proposed by the European Commission lies in the fact that because they are so short, they do not provide with sufficient time for the ethical assessment to duly take place. Should the wish of the policy makers be to guarantee quality ethical reviews through robust legal safeguards in this regulation, then the allocation of time should allow this quality review to effectively happen. The time frames proposed by the European Commission are counterproductive in the sense that the sponsors of a clinical trial in Europe, whether industry or academics, risk being impeded to develop new therapeutic treatments. This is in the end counterproductive and harmful to European research.
Additionally, CPME disagrees with the approach consisting of leaving this debate to the Council. The European Parliament, directly representing European citizens, should take a strong stand on this key issue.

CPME therefore welcomes Amendments 269, 276, 280, 310, 313, 317, 341, 411 and invites the rapporteur and the shadow rapporteurs to take them as a basis for compromise.

3/ Protection of the subject

- **Well-being, freedom to participate in a trial, quality of life**

CPME welcomes the introduction throughout the regulation and by many MEPs, among which the rapporteur, of the notion of “well-being”. This is consistent with point 6 of the WMA Helsinki Declaration. Amendment 44 introducing that “the rights, safety and well-being of the subjects shall prevail over all other interests” is also supported.

CPME welcomes the introduction of the notion of freedom in the definition of “informed consent” (Amendment 20 ENVI, Glenis Willmott) and of “subject” (Amendment 230 ENVI, Richard Seeber), as well as in the general provisions for consent in Article 28 (Amendment 452 ENVI, Richard Seeber).

CPME also welcomes the introduction of Quality of life as a benefit criterion, together with the therapeutic and public health benefits (Amendments 23, 26, 42 ENVI, Glenis Willmott)

CPME welcomes all the amendments introduced in this regard and invites the rapporteur and the shadow rapporteurs to take them as a basis for compromise.

- **Other vulnerable population groups**

CPME welcomes the introduction by the rapporteur of additional protection measures for other vulnerable population groups. These groups include for instance people suffering from a multitude of health conditions, elderly and frail people (Amendments 12, 34, 49 ENVI, Glenis Willmott)
Complementing the rapporteur's approach, specific amendments were tabled by other MEPs:

- Incapacitated subjects

While we understand the logic behind Amendment 482 (ENVI) tabled by Richard Seeber, we would recommend it to be slightly rephrased. The WMA Declaration of Helsinki sets in its Article 27 as a precondition that a clinical trial can only be performed on an incapacitated subject if it cannot instead be performed on a capacitated subject. Article 27 does not state that *"clinical trials should exclusively be performed on capacitated subjects. Only if those subjects are not available, clinical trials can be performed on incapacitated subjects",* as cited in the justification for Amendment 482. Conducting a clinical trial on an incapacitated subject should indeed be possible if there is a scientific need to do so because it is expected that the results will benefit the population or community concerned. It is therefore not a question of "availability" of the subject as suggested in Amendment 482, but rather of "benefit" to the patient and the vulnerable group concerned.
CPME would recommend the following wording:

Article 30.1. – Clinical trials on incapacitated subjects

Proposal of the Commission	Amendment
	(a)(new). The clinical trial cannot instead be performed on a capacitated subject;

- Emergency Trials

CPME supports Amendment 513 (ENVI) tabled by 17 MEPs and setting as a precondition that in the case of an emergency trial, the ethics committee should positively assess the direct benefit to the patient;

- Minors

CPME supports Amendment 491 tabled by 17 MEPs.

CPME rejects Amendment 231 (ENVI) tabled by Roberta Angelilli which aligns the definition of minor on the definition of "paediatric population" contained in Regulation (EC) 1901/2006 on medicinal products for paediatric use. According to Regulation (EC) 1901/2006 *"'paediatric population' means that part of the population aged between birth and 18 years"*. Situations vary between Member

States: in some Member States, the legal age for giving consent is 16, while others limit it to 18. CPME would therefore advise to leave the definition of minor to the discretion of the Member States as stipulated in Recital 22 of the regulation, and suggests the following amendment:

Article 2 - Definitions

(16) 'Minor': a subject who is, according to the laws of the Member State concerned, ~~***under the age of legal competence to give informed consent;***~~	(16) 'Minor': a subject who is, according to the laws of the Member State concerned, ***considered a minor;***

CPME invites the rapporteur and the shadow rapporteurs to reach a compromise where these high standards are specifically addressed in Articles 30, 31 and 32 of the regulation.

- **Information given to the subject**

CPME welcomes amendments 47 (ENVI) of the rapporteur on Commission guidelines on the information to be given to the subjects and on informed consent. CPME also welcomes amendment 48 (ENVI) whereby the subject shall be informed about the results of the clinical trials he participated in once it has ended.

Many amendments (45, 128, 461, 462 ENVI) were tabled on the format and way the information should be given to the subjects. Amendment 45 (ENVI) by the rapporteur foresees the information should be given orally "where possible"; "otherwise" it may be given in writing. CPME is of the opinion that information should not be given either orally or in writing, but rather both orally and in writing. Also it should be made compulsory that the subject is provided information by a medical doctor during the prior interview and that he receives it in writing before giving consent. CPME therefore welcomes amendments 454 and 463 (ENVI) tabled by Peter Liese and 16 other MEPs.

CPME recommends that the compromise reached by the rapporteur and the shadows on the issue of information provision should foresee that subjects receive both oral -by a medical doctor- and written information -before the subject consents to take part in the trial as proposed in Amendments 454 and 463.

- **Trials conducted outside the Union**

CPME highly welcomes amendment 39 (ENVI) by the rapporteur and amendment 25 (ITRE) by Michèle Rivasi which makes it compulsory for the clinical trials conducted outside the Union to comply with the Regulation and not *"with principles equivalent to those of the regulation"* as

stipulated in the Commission's proposal. It goes even further since they should also respect the Helsinki and CIOM's guidelines.

CPME welcomes Amendment 648 (ENVI) whereby these compliance principles shall be controlled by the Commission.

Rapporteurs and shadow rapporteurs should consider both that the clinical trials conducted outside the Union should fully comply with the principles of the regulation and should be subject to controls by the Commission as proposed in Amendments 39 and 648 (ENVI).

- **Damage compensation**

CPME welcomes amendments 624 and 625 by Theodoros Skylakakis and Margrete Auken introducing that all clinical trials should be guaranteed compensation safeguards in case of damages to the subject. Low-intervention trials should indeed not be excluded from this mechanism, since it will result in a two-speed protection mechanism. In the end, patients might be reluctant to participate in low-intervention trials, which would be counterproductive for research.

CPME invites the MEPs to support amendments 624 and 625.

4/ Role of medical doctors

CPME welcomes the reinforcement of the provisions introduced in Article 9 on the persons assessing the application. This article should indeed concern both Parts of the assessment as suggested by Amendments 30 and 367 (ENVI). The provisions introduced in Amendments 31, 369 and 371 (ENVI) with regard to transparency and declaration of conflict of interest should also be supported.

Additionally, Art 9.2. would need to clearly specify that the assessing team shall be composed of medical doctors, as suggested in Amendment 375 (ENVI).

While recognising the good intention behind Amendment 373 (ENVI) of Philippe Juvin, CPME expresses reservations since it restricts the qualification requirements only to the team assessing Part II, whereas both Parts should be covered. Also, the reference made in this Amendment to Article 46 does not entail sufficient guarantees as per what qualifications are needed. The current wording of Article 46 foresees the possibility of having either a "medical doctor as an investigator" or "a qualified professional recognised in the MS to be an investigator" or another "individual qualified to conduct a clinical trial". Referring to article 46 would lead to a very wide interpretation and could result in having no physicians in the assessing team.

CPME would suggest MEPs to reject amendment 373 and support amendment 375.

With regard to Article 46, CPME would suggest the following amendment:

Article 46 – Suitability of individuals involved in conducting the clinical trial

Proposal of the Commission	Amendment
The investigator shall be a medical doctor as defined in national law, ***or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.***	The investigator shall be a medical doctor as defined in national law. ~~***or a person following a profession which is recognised in the Member State concerned as qualifying for an investigator because of the necessary scientific knowledge and experience in patient care.***~~
Other individuals involved in conducting a clinical trial shall be ***suitably qualified by education, training and experience to perform their tasks.***	Other individuals involved in conducting a clinical trial shall be ***professionals recognised in the Member State concerned as qualifying for being member of the investigating team because of the necessary scientific knowledge and experience in patient care.***

The investigator should be a qualified medical doctor as he has the necessary scientific knowledge and experience to conduct the trial and is aware of the risks and inconveniences for the subjects.
Clinical trials should only be conducted by professionals recognized in their Member States. It is of utmost importance that patients while undergoing a clinical trial are handled by healthcare professionals, as they are qualified and experienced in patient care.

CPME invites the rapporteur and shadow rapporteurs to reach a compromise where this proposal is addressed.

5/ Transparency and Publication of the data

All Clinical trials should be registered in the EU database prior to their start. CPME therefore would advise to reject Amendment 443 (ENVI) by Christofer Fjellner. Allowing Clinical trials to be registered after they started, entails a risk of legal uncertainty since trials could be running while not being officially registered.

CPME highly welcomes the proposal of Glenis Willmott of a clinical study report containing a full description of the trial and its results (Amendments 21, 51 and 59, ENVI). This will clearly help the purpose of transparency.

Sharing the results and making them available to the public is a matter of trust in medical research. While CPME shares the view that commercially confidential information is critical to pharmaceutical companies, CPME insists that all results, whether they are positive, negative or inconclusive, should be made publicly available. This includes Phase I trials data which are currently not made public. CPME therefore welcomes Amendment 528 (ENVI) tabled by Alda Sousa which specifies that "positive, as well as negative and inconclusive" results should be published.

CPME welcomes amendment 532 (ENVI) specifying that the results should be also published on the Eudrapharm website.

CPME rejects amendment 535 (ENVI) by Philippe Juvin since it intends to extend to two years the deadline for the publication of results after the end of the trial. One year was proposed by the Commission. It is expected that this timeline is sufficient for all results to be gathered and compiled in a clinical study report.

CPME supports amendment 537 (ENVI) by Philippe Juvin intending to facilitate access of lay persons to comprehensible and "easy-to-read" description of the results.

CPME supports the amendment 52 (ENVI) by the rapporteur introducing penalties for the sponsor who does not respect the deadlines of publication of the results.