CONSULTATION ON THE EUROPEAN COMMISSION'S PROPOSAL FOR A CLINICAL TRIALS REGULATION

Response sheet

Instructions

Please send your responses electronically to clinical.trials@mhra.gsi.gov.uk using the table below. If you reply in writing, please also use this table. Responses should be sent by 31 December 2012.

Respondent details

Please provide your details as requested below.

- Please provide your name and (if relevant) the organisation or body you represent:

Oliver Watson on behalf of the **Medical Schools Council** and **Association of UK University Hospitals**.

- Please tick this box if you want the information that you provide to remain confidential: ☐
- Please tick this box if you or the body you represent are in the NHS or public sector: ☒
- If you represent a private sector company, please indicate the number of employees in the company by ticking the relevant box below:

9 or less ☐ 10-49 ☐ 50-249 ☐ 250 or more ☐

Nr.	Question	Response
1	**Do you have views on the scope of the Regulation?**	We are content with the scope of the Regulation and believe that it will lead to reduced burden on the institutions driving forward clinical research.
2	**Do you agree with the introduction of low-interventional studies?**	The move to a more risk-based approach and the introduction of the low-interventional studies concept is particularly welcome.
3	**Do you have views on any of the proposed definitions in Chapter 1 (Article 2) of the proposal?**	**Standard treatment** Within the definition of low-interventional trials, we are concerned that there is a lack of clarity on what is meant by 'standard treatment' (Article 2, para 3 [page 26]). It may be challenging, particularly for non-commercial sponsors, to identify what is standard treatment across all member states. Indeed there will also be 'within country' variability in what is considered 'standard'. We are aware that the Commission intends for 'standard treatment' to be softly defined. However, we are concerned that inconsistent interpretation could lead to increased numbers of member states opting out of trials as treatments may more easily be considered inferior without clarity on how they are defined as 'standard'. In addition, few clinical trials use an investigational medicinal product purely "in accordance with the terms of the marketing authorization", except as a comparator against another agent without a marketing authorisation. Many more trials use a product which already has marketing authorization for patients with a different condition (or severity of condition) e.g. a glucose-lowering antidiabetic agent vs placebo to prevent cardiovascular disease in people without diabetes; OR spironolactone vs placebo to prevent diabetic renal disease. It will be important to have clarity on whether this will be considered 'standard treatment'. We recognise that a restrictive definition of standard treatment could be counter-productive, but we feel that more guidance in this area would be welcome. **Clinical Study/Trial** We feel the definitions are confusing. We understand that the intention of the Commission was to clarify the distinction between interventional and non-interventional drug trials; however, the nested definition means that it is hard to understand. We believe that a clinical study should be defined in its widest sense as an investigation of any healthcare intervention in man that follows a protocol. A clinical trial should be defined much as the Clinical Trial of an Investigational Medical Product is defined in the current legislation:

Nr.	Question	Response
		Chapter I; Article 2: p 25 *The following definitions shall also apply:* *(1) 'Clinical Study': any biomedical or health related investigation in human subjects that follows a protocol.* *(2) 'Clinical Trial': a clinical study of one or more investigational medicinal products intended:* *a. to discover or verify their clinical, pharmacological or other pharmacodynamic effects;* *b. to identify any adverse reactions;* *c. to study their absorption, distribution, metabolism and excretion;* *with the objective of ascertaining their safety or efficacy, and which fulfil any of the following criteria:* *a. any of the investigational medicinal products are not authorised;* *b. according to the protocol of the clinical study, any authorised investigational medicinal products is not used in accordance with the terms of the Member State concerned;* *c. the assignment of the subject to a particular.....* *d. the decision to prescribe....* *e. diagnostic or monitoring procedures....* **Investigational medicinal products** We feel that it would be helpful to have reference to trials involving placebos. The implication of Article 2(3)(a) "the investigational medicinal products are authorised" is that they are not included, but an explicit reference would be helpful. For example the following text could be added to Clause (3) after point (c): *"Low intervention clinical trials may include the administration of placebo where the use of placebo does not pose more than minimal additional risk to the safety or wellbeing of the subjects."*
4	**Do you agree that a single authorisation and a single decision (for both regulatory and ethics approval) through an EU portal will be of benefit to researchers? If so, how will this benefit you?**	We believe that this should simplify and speed up the process for researchers. However, it is important that the EU portal is effective and user friendly in order to deliver these benefits.

Nr.	Question	Response
5	**Do you agree that the proposed multi-state application and authorisation process reduces the burden on researchers? If so, how and would you be able to quantify this reduction?**	The MHRA proposal on how member states will work together in the application and authorisation process is welcome and an improvement on that suggested by the Commission. We feel that the proposed process will reduce burden on researchers.
6	**Keeping in mind that the proposal introduces a single decision (including regulatory and ethics approval) - would an extension of the timelines beyond the Commission's proposal (maximum 65 days) impact significantly on the conduct of clinical trials? And what timeline would be acceptable for this single decision?**	65 days would be acceptable as a maximum. Currently permissions are usually obtained significantly faster than the stated maximum for the majority of trials. It would be hoped that this would be the case with the single decision too.
7	**What opportunities do you see to introduce more risk-adapted elements?**	We believe that the current proposal is sufficiently risk-adapted. It will be important for the UK to maintain its current risk-adapted approach to complement this.
8	**Have you ever experienced difficulties obtaining insurance for a clinical trial?**	While obtaining insurance in the UK has not presented difficulties, member organisations have reported difficulties in obtaining insurance in a number of EU member states (e.g. France). This has largely arisen in multi-state trials whereby a participating member state does not accept existing insurance and demands that local insurance is secured. In some instances the barriers of cost and resource in obtaining this have led to the termination of clinical trials.
9	**Do you recognise the Commission's suggested rise in costs of insurance?**	While we do not have direct evidence of rising insurance costs, as outlined above we do recognise difficulties in obtaining adequate insurance. Additional costs arise when local insurance is required in member states. The logistical challenge of finding appropriate insurance further contributes to rising costs. We would anticipate that a system of national indemnification would create economies of scale and thus reduce costs.
10	**Do you see benefits in a Government run scheme? If so, please explain what you think the benefits would be?**	We believe that the following benefits arise from a Government run scheme: • Reduced cost • Reduced duplication of effort • Fast assurance that adequate cover is obtained

Nr.	Question	Response
11	**Do you think that there are opportunities to include more specific requirements for GCP, or is the regulation specific enough?**	The Regulation is adequately detailed.
12	**Have you identified any potential risks or improvements to the quality of clinical trials based on the proposed Regulation?**	Assuming the portal is robust and user friendly, we expect the analysis of safety reporting and signal detection would be improved, allowing in trial decision making to speed up modifications to protocols and/or Investigator Brochures/Summaries of Product Characteristics.
13	**Are there any features that you think should be included in the proposal that would make the EU a more attractive place for the conduct of clinical trials?**	We feel that (with the suggested amendments we have outlined) the Regulation will make the EU a more attractive place to conduct clinical trials. The most significant factor in achieving this is the move to a more risk-based approach.
14	**Are there any other elements of the proposal that you would like to comment on?**	**Article 28(1)(d)** Suggested amendment*: "the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, ~~in a~~ **through** prior ~~interview~~ **contact** with the investigator or a member of the investigating team..." or "the subject or, where the subject is not able to give informed consent, his or her legal representative has had the opportunity, ~~in~~ to have a prior interview with the investigator or a member of the investigating team..."* Both this section and Article 32 (1) would benefit from the suggested amendment above and/or clarification of 'emergency' and 'interview'. In the context of studies such as those in an intensive care setting, participants need to be recruited in a narrow timeframe. In many such instances the patient will have travelled a very great distance for treatment and it may not be possible for a suitable legal representative to travel to the site in order to be interviewed in person in the time allowed for inclusion by the study. Frequently in these scenarios, the strategy of seeking consent by telephone, fully documenting this in the notes, and ensuring that it is witnessed by another member of staff is employed. As soon as is reasonably practicable, this consent will be replaced by written consent. If solutions such as these are not permissible under the new legislation then a valuable cohort of patients will be lost and as a result, an important strand of research will become unfeasible.

Nr.	Question	Response
		Article 30 (h) Suggested amendment: *"there are grounds for expecting that participation in the clinical trial will produce a benefit to the incapacitated subject outweighing the risks ~~or will~~ ~~produce no risk at all~~"* As all clinical trials inherently involve risk, it would be more accurate to remove the final part of this statement. **Articles 33 and 34** Reporting timelines have been added and/or tightened up. Some will be onerous and add little benefit to the process. **Article 37(2)** There should be reference to Annex III regarding immediate reporting of serious adverse events. **Article 39 (2)** For non-commercial sponsors, trials are often conducted on products that are neither owned nor controlled by the Sponsor. As a result, the number of trials conducted with any particular Investigational Medical Product (IMP) is not driven by Sponsor strategy so there is no way to know when a trial finishes if it is the last trial with that IMP. In principle, that means Annual Safety Reports will need to be submitted in perpetuity... **Article 41** Annual reporting of Suspected Serious Adverse Reactions to Marketing Authorisation holders will be onerous for generic and/or combination products. **Article 55** Suggested amendment*: "The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be ~~restricted to~~ controlled by those individuals."*