

Response of the Faculty of Pharmaceutical Medicine to the EMA reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted in third countries and submitted in MAAs to the EMA

On the whole this is a very good paper and brings together many aspects of existing guidelines.

Specific comments:

Although clearly defined as non-EEA countries in the introduction, the term 'third country' seems odd and the first and second countries are undefined? Suggests that the term was originally third-world countries. On this aspect of definition, the committee cannot see a strong rationale as to why large well developed countries with influential agencies such as US and Japan are effectively grouped with less developed countries (these appear to be the real area EMA wishes to address).

Comment in relation to lines 543 onwards.

The committee recognise that the definitions are based on existing ethical guidelines; however, a key area of concern is the breadth of those patients and groups of patients described as "vulnerable". There is an implication that anyone falling into these categories would need to be specifically mentioned in the protocol and/or require separate approval from the ethics committee before inclusion.

Describing groups such as the poor, the unemployed, the elderly, those on benefits, employees of pharmaceutical companies and those from racial or ethnic minority groups as vulnerable is very wide ranging. Such groups may be vulnerable, but equally they may not be. One needs to consider the benefit to the patient of taking part in the study and the ethics of potentially turning them away, simply because they fit one of these "vulnerable categories". Although this is not the intention, on face value, the document does appear to categorise them as requiring particular ethics consideration and possibly approval. Researchers may simply avoid such groups rather than face the burden of having to justify why they are included and seek additional approval. One needs to be careful that the pendulum is not seen to swing too far and minority groups feel they are being discriminated against. Section 3.5 (especially lines 551 to 559) could be more carefully framed so there are groups that are always considered vulnerable – those imprisoned, children, the unconscious etc and those who may be, depending upon the local social and cultural circumstances e.g. the unemployed, ethnic minorities etc. Guidance on dealing with these latter groups would seem best dealt with general documents and guidance on conducting and managing clinical trials rather than requiring in depth review and justification in every clinical protocol. In reality, given that trial entry requirements are focused on medical criteria, the latter categories are only likely to be picked up after consent when data collection starts so it would be a case of turning them away when they thought they could take part, as well as excluding that group from representation in the data.

Comment in relation to line 1000.

Companies should be informed of the action to be taken and given a chance to comment before a decision becomes final – especially as there is discretion in the sanctions taken (this is likely to be the case but best to be agreed as part of the process).

Comment in relation to lines 1129-1132.

Should be made explicit that provided a study is conducted ethically and the data from the ethical sites is sufficient to give a robust outcome to the study, the study data should still be admissible if a single site, or small number of sites, did not act in accordance with GCP was discovered and appropriately dealt with before study reporting.

Comment in relation to line 307 onwards

Regarding the need for international organisations to get approval in an ethics committee of their own country, presumably even if study not run in the 'home' country. This could be difficult to implement, as what is home country for a large organisation with multiple R&D sites and local affiliates may not be readily defined. Also it seems over burdensome to recommend that a large organisation seeks protocol approval in an EU territory for a study to be run solely in the US which already has solid institutional review board and FDA review processes. It would be helpful to be more explicit in areas that we are talking about less developed territories countries not just all non EEA territories.

Comment in relation to line 654 onwards

Regarding providing comparators and background therapies of same or similar standard of care and comparable treatment options to those available to trial participants within EEA. It is intuitively sensible on both ethical and scientific levels to require the same direct comparators to be used in all participants. However, implying that lack of national approval should not be a barrier is unrealistic; lack of approval of a comparator may lead to inability to conduct the study in certain countries. While appropriate for comparators to be the same for all pts, background therapy is more difficult to mandate as national clinical practices and preference for therapies vary based on custom and beliefs, and are not necessarily dependant on what treatments are available. So for practical purposes the language in the document should be centred around encouraging not mandating sponsors to seek patients in third countries receiving similar background therapies as EEA countries.