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Faculty of Pharmaceutical Medicine submission to the House of Commons Science and Technology Committee Inquiry into Clinical Trials

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1 The Faculty of Pharmaceutical Medicine is a professional membership organisation and standard-setting body, with 1,450 members, who are practising pharmaceutical physicians or those with a professional interest in the speciality. It was founded in 1989, and is a Faculty of the Royal Colleges of Physicians of the UK.

2 Pharmaceutical medicine is a medical specialty concerned with the discovery, development, evaluation, licensing and monitoring of medicines and the medical aspects of their marketing. The Faculty's members work in diverse environments; from front line clinical trials, to pharmaceutical marketing and medicines regulation.

3 Our mission is to advance the science and practice of pharmaceutical medicine by working to develop and maintain competence, ethics and integrity and the highest professional standards in the specialty for the benefit of the public. The Faculty seeks, through its activities, to bring about an improvement in the health of the public.

4 The Faculty welcomes the opportunity to submit evidence to this important inquiry and we would be happy to supplement this written evidence with oral evidence to explore these issues in more detail.

Question 1: Do the European Commission's proposed revisions to the Clinical Trials Directive address the main barriers to conducting clinical trials in the UK and EU?

5 The Faculty has recently responded to the MHRA "Consultation on the European Commission's proposal for a clinical trials regulation." The following comprises an abridged version of that response which we feel relevant to the specific questions posed here.

6 We believe that the general scope and aims of streamlining and harmonization are to be welcomed. However, while it is stated that Directive 2001/20 is to be repealed, the Faculty is concerned that in practice national laws, customs and practices will be slow to change. There is a danger that for a significant time period additional requirements and complexity are being created rather than replacement ones.

7 The proposal is very unclear as to precisely which functions remain with the 45 national competent authorities (NCAs), the ethics committees which are currently affiliated with research sites (and not, by design, the NCAs), both when an NCA may opt in, or after it uses a qualified opt out.

8 The Faculty can see some merit in having a central body review the overall ethical aspects of a study. Such a body can include relevant scientific experts and professional ethicists and give a degree of

consistency. However, the Faculty has major concerns over a single body making ethical determination for the whole of the EU. This is not the process in the United States of America where the FDA approves clinical studies but independent institutional review boards making ethical determinations. The delegation of ethics approval to NCAs, or even a single referring NCA, if that is what is meant by Article 6, para 1, is itself unethical. A referring NCA assessor in, say, London is highly unlikely to understand the cultural and medical position of a patient in, say, Valetta. If NCAs intend to retain local arrangements for Ethics Committees, then a layer of review has been added, not removed, by the Regulation; furthermore, there is the risk of mutually exclusive conditions for a clinical trial being imposed by the two reviews. We believe that there will be a risk to quality if the NCA ethics reviews supplant the local ones. If both are required, and the results conflict, then some compromise will be needed or the trial will not take place at all.

9 The Faculty believes that in practice there will remain a process of national and local review in many territories. The regional MREC is working well in the UK and a case could be made to adopt the same model Europe-wide with the same focus on ethics. This would deal with the regional differences and allow responsiveness to local populations. The clinical trials authorisation (CTA) submission of a multi-national trial within the EU appears optimized by the implementation of Voluntary Harmonization Procedure (VHP), though not all EU countries participate in VHP because of various national regulatory (and probably cultural) differences.

10 From the point of academic research, this regulation provides no reduction in paperwork. It threatens an additional layer of ethical review. From the point of view of industry-sponsored clinical trials, the imposition of the timelines, taken together with the various extensions available to the regulators, would seem to be a slower, rather than faster, process compared to what has hitherto been the case in the United Kingdom, Sweden, and The Netherlands (and possibly also elsewhere).

11 We believe that the EMA may lack the manpower and expertise for these clinical trial applications, which will be in large volume.

12 Hence the Faculty considers that these proposed revisions will need refining if they are to enhance the speed and effectiveness of clinical trials in the UK and EU. Indeed there should be more focus on the needs of all researchers, both academic and in industry, if we are to make the EU more attractive for conducting clinical trials.

Question 2: What is the role of the Health Research Authority (HRA) in relation to clinical trials and how effective has it been to date?

13 The National Research Ethics Service has transferred to the HRA. One such service has been the in-line submission of studies. This Integrated Research Application System (IRAS) was launched in January 2008, and has since become a successful system with an excellent record of system availability. To date, IRAS has been available 24 hours a day, 7 days a week with less that 0.1% 'downtime' for system upgrades and maintenance. The HRA will enable research ethics committee (REC) and MHRA electronic submissions through IRAS. This service has greatly simplified submission and will greatly enhance efficiency and should serve to improve the attractiveness of the UK as a country to conduct clinical trials in.

Question 3: What evidence is there that pharmaceutical companies withhold clinical trial data and what impact does this have on public health?

14 To provide clear direction to all pharmaceutical physicians the Faculty published its "Guiding Principles for Pharmaceutical Physicians" in 2006 and revised in 2010. This forms the basis for the ethical and professional standards of its members.

15 This document contains a section entitled 'Sharing Findings' which states:

16 "*All studies should be performed to increase knowledge in some useful way, and there should be openness and honesty in the sharing of this knowledge with the wider world. Trial findings need to be communicated, whatever the outcome, for the benefit of the community at large. The sponsor should have a clear policy regarding trial publication which should be agreed with the clinical researcher prior to trial initiation, and neither the sponsor nor the researcher should seek to prevent publication or the admission of trial results within the public domain. Communications on clinical studies must be a correct objective representation of all the findings, allowing others, in their turn, to give well-balanced risk-to-benefit advice to patients and their families. It is especially important that negative results or adverse safety data are communicated to regulators and clinicians in a timely manner where this information may affect prescribing practices and the protection of patients*."

17 This is a clear direction to pharmaceutical physicians to ensure open access to study trials.

18 However, even though there is a requirement that all clinical trial data are submitted to regulatory agencies, there is clear evidence that not all clinical trial results have been made publicly available in medical or scientific journals. Research by Ross et al.[i] has demonstrated that most studies registered on the US-based ClinicalTrial.gov clinical trial registry and website had not lead to publication of study results; though nearly all had included all the data elements mandated by ClinicalTrials.gov, such as intervention and sponsorship. Looking at a sample of trials registered, less than half (311 of 677, 46%) of trials were published. Trials primarily sponsored by industry (40%, 144 of 357) were less likely to be published when compared with non-industry/non-government sponsored trials (56%, 110 of 198; $p<0.001$), but there was no significant difference when compared with government sponsored trials (47%, 57 of 122; $p = 0.22$). Evidently there is a long way to go before the publication of all clinical trial data is achieved. However, it is obvious that the issue is not confined to the pharmaceutical industry and similar patterns of non-publication are found amongst non-industry and government sponsored trials.

19 Well known examples of clinical research where a lack of public dissemination of clinical trial data has been linked to an avoidable and detrimental health impact for patients treated with those drugs include vioxx and paroxetine. Over the last couple of years the ability and requirements to make results public has increased markedly especially with ClinicalTrials.gov. The ClinicalTrials.gov registration requirements were expanded after the Food and Drug Administration Amendments Act of 2007; more types of trials fell within scope for registration and there was a requirement for the submission of results for certain trials. This led to the development of the ClinicalTrials.gov results database, which contains information on study participants and a summary of study outcomes, including adverse events. The results database was made available to the public in September 2008. There are penalties for failing to register or submit the results of trials. However, it is often the case that not until meta-analyses of all clinical trials with a drug are conducted that some important safety signals emerge. These meta-analyses are often conducted by academics outside of industry and regulatory agencies; and they require full and complete access to the data on a drug to be reliable.

Question 4: How could the occurrence and results of clinical trials be made more open to scrutiny?

20 The amended Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) requires prospective trial registration with a statement that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject". In addition, many medical journals make it a pre-condition of acceptance for publication that a trial was registered. Relatively recent moves within the United States also make the provision of results from "applicable clinical trials" to ClinicalTrials.gov a requirement once the study has completed. The US FDA normally holds open public meetings with experts to discuss clinical trial data submitted as part of a

new drug application though in other regions these types of meeting are normally closed sessions. Therefore there is public access to the occurrence of clinical trials and their key features are already well served via the requirements to enter clinical trial data into the US ClinicalTrials.gov clinical trial registry/website and, more recently, via the EMA supported EU Clinical Trials Register.

21 However the key question is how to enable the full set of raw clinical trial data to be made available to third parties to assess, review and analyse and not be restricted to just the trial sponsors and regulatory agencies. The Faculty has, for a long time, been supportive of greater transparency in clinical research and has promoted allowing third party access to clinical trial data. However this needs to be conducted in a fair and responsible manner. We believe that there is enormous potential for benefits to the broader research effort and public health if data could be more openly scrutinised by third parties. Under the current system, researchers are able to make their own assertions about the 'significance' of their research and data. However, it may be that other researchers can spot potential in the data that was not originally recognised, or can combine historical data with new information to highlight unforeseen benefits. Collaboration and transparency between researchers will also lead to less duplication of efforts and wasting of resources.

22 Overall, the Faculty favours a policy of both prospective and retrospective disclosure of data, but with a system that ensures adequate safeguards for both the anonymity of trial subjects and maintains safety for potential patients. Whilst open access should be enshrined in any new process of searching the data sets, there would need to be an orderly and scientifically sound process to facilitate access. We recommend the establishment of a 'gate keeper'; an independent body reviewing requests for data. Third parties would be required to submit a statistical analysis plan or at the very least clear questions that they wish to address. The identities of those third parties requesting data should not be anonymous to the 'gate-keeping' body, but not necessarily made public. The cost of such a system could be shared by government, the sponsoring company and perhaps also the requesting party.

23 The Faculty would recommend that the following requirements should also be upheld for all clinical research:

24 Sponsors and clinical investigators should make available the methods and results of their trial within one year of study completion.

25 The task of policing this policy could fall on the Health Research Authority as an extension of the IRAS. The HRA is best placed to take account of local needs, but would need to integrate seamlessly with EMA, FDA and other national regulatory agencies, given the global nature of pharmaceutical product development.

Question 5: Can lessons about transparency and disclosure of clinical data be learned from other countries?

26 Of note, the US FDA organises open advisory committee hearings for many new drugs, particularly where there is potential for significant public health impact, where FDA staff, external advisors and company representatives debate issues around the clinical trial results and implications for public health. The general public is also able to contribute to these meetings. The FDA assessment reports on the drugs reviewed become publically available on its website. The US ClinicalTrials.gov website and data registry now requires posting of the results of "applicable" clinical trials, this includes key clinical trials supporting marketing approval for new drugs and subsequent clinical trials with them. We believe that this system works well and would be appropriate and applicable in the UK/EU.

27 The EMA does now support the EU Clinical Trials Register and provides a publically accessible

(commercially confidential material having been redacted) version of its assessment report for new drugs on its website. The EMA could look to mirror FDA in holding open public meetings when issues pertaining to new drug applications are debated with the medical and scientific experts. Given the ease of accessing information via the internet, international nature of major pharmaceutical companies and the fact that results from all relevant trials are available in the EMA assessment report for a drug.

Reference

[i] Ross JS, Mulvey GK, Hines EM, Nissen SE, Krumholz HM (2009) Trial Publication after Registration in ClinicalTrials.Gov: A Cross-Sectional Analysis. PLoS Med 6(9): e1000144. doi:10.1371/journal.pmed.1000144