SCIENCE AND TECHNOLOGY COMMITTEE (COMMONS)

Inquiry into clinical trials and disclosure of data

Medical Schools Council and Association of UK University Hospitals response

22 February 2013

1. Introduction

1.1. The Medical Schools Council (MSC) represents the interests and ambitions of UK medical schools as they relate to the generation of national health, wealth and knowledge through biomedical research and the profession of medicine. The membership of the Medical Schools Council is made up of the Heads or Deans of the 32 UK undergraduate medical schools, plus the postgraduate London School of Hygiene and Tropical Medicine.

1.2. The Association of UK University Hospitals (AUKUH) is the key leadership body across the UK promoting the unique interests of University Hospitals. Its purpose is to represent the unique role and interests of UK University Hospital Trusts in the tripartite mission of service, teaching and research in partnership with other national bodies. There are currently 44 member Trusts.

1.3. We welcome the opportunity to submit evidence to the Science and Technology Committee inquiry into clinical trials and the disclosure of data. Clinical trials are core business for both MSC and AUKUH; therefore members have a keen interest in ensuring they are conducted to the highest standard with public support and engagement.

2. 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?

2.1. The EU Clinical Trials Directive has been a significant barrier to the conduct of clinical trials in the UK and EU. Proposals to create new regulation that will replace the Directive are welcome. In particular, we support the move to a more risk-based approach and the introduction of the 'low-interventional studies' concept.

2.2. While we are supportive of the revisions, we feel that there are a number of opportunities to improve the proposal. A summary of these considerations can be found in our response to the MHRA consultation on the proposed regulation (Annex 1). In addition to these points, we would note that to ensure revisions truly reduce burden on those driving forward clinical research, the IT system / portal to be created by the Commission must be robust and user-friendly.

2.3. In addition, care must be taken to ensure that existing processes are compatible with the proposals (and vice versa) to avoid duplication (e.g. ensuring that the portal compliments the Integrated Research Application System [IRAS]). There is a risk that a dichotomy between Clinical Trials of Investigational Medical Products (CTIMPs) and non-CTIMPs will emerge if proposals are not carefully aligned with current processes. In doing this, a unification of terms and language used will be necessary.

2.4. We feel that there is an opportunity for the EU to consider 'phase zero' trials. Very often materials made and used for early trials in the USA are not admissible for use in the EU. This is anticompetitive and gives the UK a major scientific disadvantage. For example, in gene therapy for cancer, therapeutic viruses made and used for early phase trials in the US cannot be used in Europe. This places a heavy burden for translational science in Europe, particularly university-led science, and should be changed.

2.5. Internal barriers for the conduct of research in the UK have greatly reduced in recent years. Efforts to develop a more streamlined and proportionate approach to regulation have been particularly helpful in achieving this. It is heartening to see commitments to the importance of biomedical research in key Government and DH publications including, but not limited to, the Life Sciences Strategy, the NHS Constitution revision, Innovation, Health and Wealth and the NHS Mandate. We support the National Institute for Health Research and the Health Research Authority's continuing work to ensure barriers to conducting and attracting trials are removed. One key aspect of this work is efforts to improve access to patient data records for the benefit of research and ultimately patient care.

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

3.1. While the HRA is a newly formed organisation, we believe that the early signs are encouraging. For example, we feel that changes to IRAS that have been proposed and/or carried out are beneficial.

3.2. It is important that the HRA ethics review programme is integrated into existing Research Ethics Committee processes, to avoid duplication of effort. The HRA appears to be aware of this risk and we are optimistic that, through careful piloting, unnecessary burden can be avoided.

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

4.1. Publication bias in all its guises is a real issue of concern. The preference for the publication of 'statistically significant' findings is hugely damaging to the corpus of published research and is unfair to participants of unpublished trials. The more obviously dishonest practice of prohibiting/hiding research which disfavours a product causes more direct harm.

4.2. While evidence of this has not consistently been identified by members at a local level, there is a considerable body of evidence at a larger scale of withheld data.

4.3. Lack of clinical trial data can have both direct and indirect effects on public health and the health of individual patients. Poor treatment choices based on incomplete information will have a direct effect on patients. Care costs from the use of insufficiently evidenced treatments can lead to the waste of limited resources.

5. How could the occurrence and results of clinical trials be made more open to scrutiny? Who should be responsible?

5.1. We feel that the publication of all trial data would be welcome to improve scrutiny. To make this truly effective, there are a number of key considerations:

5.1.1. **Anonymity:** transparency of data must not have the counter-productive effect of losing patient and public trust in clinical trials through the release of identifiable information. The publication of Clinical Study Reports rather than individual patient level data may therefore be preferable.

5.1.2. **Commercialisation and publication:** it is important that the timeline for publication of trial data does not harm prospects for commercialisation or publication for the researcher(s) through the premature release of sensitive information. Mutually agreed, appropriate timescales will be required.

5.1.3. **Meaningful data:** data would need to be released at an appropriate stage to be meaningful (i.e. once analysed, verified and peer reviewed).

5.1.4. **Which trials?:** CTIMPs, Devices trials and other interventional trials (e.g. of a surgical intervention) would all need to be considered.

5.1.5. **Scrutiny by whom?:** The public, health professionals, regulators, manufacturers, researchers and sponsors all have a role in scrutinising clinical trial data. With this in mind, the format of data on trial outcomes will need to differ dependent on the intended audience.

5.1.6. **The global nature of trials:** Installing a system for opening all trial data to scrutiny would require concerted global effort.

5.1.7. **Avoiding duplication of effort:** Existing processes need to be harnessed rather than duplicated.

5.2. Regulators are the only bodies with the power to require the publication of all trial data and this would need their full support to be effective. A mandatory commitment to share the clinical study report of a trial could be a condition of its approval. R&D authorities could follow up on studies at regular intervals from a pre-agreed date after a study has closed to ensure this happens. After an appropriate time period of checking, a study which has not reported could be flagged as “not published within *x* years”. This statement (if not accompanied by a valid explanation) would then be viewed as a ‘black mark’ by the research community. This should have the effect of discouraging the suppression of clinical trials data. Any trials where one would not expect to see results published (e.g. withdrawal of a medication from approved use) should be accompanied on the database by as informative a summary as possible.

All studies on such a database would need clear links to other places the data are available (e.g. link to a peer-reviewed publication).

5.3. As a long-term option for the UK, the involvement of NICE could be beneficial. We believe that NICE has the competency to interpret, synthesise and communicate these data. The enlargement of the National Research Ethics Service (NRES) database may assist with this work. The Medicines and Healthcare products Regulatory Agency is another organisation that could host a publically accessible database.

5.4. Compelling sponsors to deposit (anonymised) trial data into an EU repository is another option to explore. This would require commitment from the EU and a sophisticated and secure database, in addition to the considerations above. There is a risk that while this would make trials more open, effective scrutiny of these data would require clear presentation and effective indexing of huge volumes of information. Systems for the registration of clinical trials already exist, on international databases such as www.clinicaltrials.gov – this could be extended to include protocols and Clinical Study Reports with better regulation and audit of their reporting.

5.5. Existing data could be used more efficiently as a short-term solution. NRES publishes a synopsis of all trials which go to Research Ethics Committee on its website and requires a synopsis of results when a trial is concluded. Were the synopses of results rigorously collected, of a high standard and published in an easily searchable format, it would assist in the dissemination of appropriate data. Committee members would need to interrogate results to ensure they are fit for purpose under this option.

5.6. An alternative proposal would be for all data to be issued on reasonable request, with the possibility that release may be subject to a time restriction. This would avoid some of the problems with release of all trial data, but the mechanism for doing this would need to be clear. Requests for access to detailed trial data would need to be accompanied with a clear rationale for their use and description of the intended analyses. Peer review of these requests by the original researchers and the competent authorities would ensure that data are not used inappropriately.

5.7. Another potential lever would be academic journals signing up to a code of practice that ensures that publications are only accepted from companies who make all of their trial data available. This would build on the model adopted by the *British Medical Journal*[1]. Journals should be encouraged to review trial protocols before results are analysed, and accept them for publication in principle, unless there are overwhelming academic reasons not to do so. This may help reduce publication bias.

5.8. In Ben Goldacre's *Bad Pharma*, referenced by this inquiry, medical schools are tasked with the following: "teach medical students about how to spot bad evidence from the pharmaceutical industry, and in particular how its marketing techniques work". Our publication: *Consensus Statement on Relationship between UK Medical Schools and the Pharmaceutical and Medical Devices Industries* makes it clear that:

[1] http://www.bmj.com/about-bmj/resources-authors/article-types/research

"Students should be aware of the potential for the challenges to professionalism and clinical judgement that may be presented by certain interactions with the pharmaceutical industry. Students should be exposed to balanced information that describes both potential benefits of the relationship between the pharmaceutical industry and the healthcare sector, as well as the potential risks that inevitably derive from the commercial imperative of the industry"

Therefore, medical schools acknowledge the need to ensure students are fully informed and sensitive to the functioning of the pharmaceutical industry. This is important in ensuring the future medical workforce is equipped to scrutinise these data.

5.9. We agree that withholding appropriate data can do a disservice to the patients who participate in clinical trials and the broader population. Along with many other organisations, we are supporters of *The concordat to support research integrity*[2] and its requirement for rigour, transparency and open communication when reporting research data, including the sharing of negative results.

6. Can lessons about transparency and disclosure of clinical data be learned from other countries?

6.1. We are not aware of other countries achieving greater success in this area.

[2] http://www.universitiesuk.ac.uk/Publications/Documents/TheConcordatToSupportResearchIntegrity.pdf