Research integrity and clinical trials transparency

Thank you for inviting me to give evidence to the research integrity inquiry on 30th January. During the evidence session, I promised to follow up with further information about final reports, registration of phase I trials and conflicts of interest. I also wanted to take the opportunity to clarify our role and our planned next steps to enhance research transparency.

At the session on 30th January, you asked me about how we are ensuring compliance with a 2014 requirement to report the outcomes of research. I now realise you were referring to the European Commission rule¹ that sponsors post summary results of clinical trials of investigational medicinal products in the European Clinical Trials Database (EudraCT) managed by the European Medicines Agency. The public-facing end of EudraCT is the EU Clinical Trials Register (www.clinicaltrialsregister.eu), which identifies completed drug trials with and without posted results. The Medicines and Healthcare products Regulatory Agency is responsible for ensuring that sponsors provide results for all drug trials registered in EudraCT. We will seek to work with the MHRA to understand better the situation regarding the trials they regulate.

Final reports

You asked me to see what could be disclosed in relation to final reports. Following research ethics approval of a study, researchers should inform the research ethics committee (REC) within 12 months of the end of the study whether the study achieved its objectives, what were the main findings and what are the arrangements for publishing or otherwise disseminating the research, including feeding back to participants. There is not currently a set format for these reports so the contents vary. They tend not to include summary results but the few that do are marked commercially sensitive.

Phase I drug trials

I undertook to supply a copy of the report² of our latest audit of clinical trials registration and to provide further information about the four phase I drug trials which the audit did not identify as registered. Those four represented 5% of the 84 phase I trials in the audit period and 0.5% of all clinical trials in question. We have followed up further and I can confirm that all four are registered on EudraCT (which is not a public register). One is already on the US public register, clinicaltrials.gov, two are taking action to register publicly, prompted by our follow-up, and the other trial did not start so it does not need public registration.

Conflicts of interest

I also undertook to provide details about the processes for asking researchers about conflicts of interests and eliciting declarations in the course of applying for REC approval. The Integrated Research Application System contains the questions, supported by guidance, and declarations, that I have appended to this letter (Annex A). I also enclose the guidance regarding conflicts of interest from our National Research and Ethics Advisors’ Panel³. The Academy of Medical Sciences has also done some recent work on this topic which is now being followed up by Sense about Science, and we will ensure that our approach learns from these developments.

Next steps for the HRA

Through the Transparency Forum, which we chair, we are working with registries, publishers and funders to work collaboratively on our respective parts of the research process to enhance research transparency. We also see a mechanism, working with Dr Goldacre and others, to explore publication and dissemination. We want to focus our efforts on the parts of the process over which we have the most influence and can therefore bring about the most change.

In 2013, we committed to audit trial registration and our recent follow-up audit confirms that although transparency appears to have improved in drug trials, particularly commercial drug trials, there are still shortcomings in registrations. Our immediate priority is awareness. Our activity so far shows that engaging with the research community increases the registration rate, so we will be working to set out our expectations more clearly and introduce automated measures to prompt registration at the appropriate point. We anticipate that this will then enable us to explore making approvals contingent on researchers’ or sponsors’ track record of registering clinical trials.

We will also review our requirements around final reports. This will include standardising the contents of these reports and exploring what we can extract from them to be published on our website alongside the research summary (https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/), aligning with the transparency information that will be in the new EU Clinical Trials Database under the forthcoming EU Clinical Trials Regulation. Achieving this will be partially dependent on our new information systems, which we hope will be substantively complete by April 2019. I attach a summary (Annex B) of the transparency information on drug trials that will be publicly available in the EU database, or in the national equivalent we are planning if the UK does not have access to the EU systems after Brexit.

February 2018
Annex A: Integrated Research Application System content regarding conflicts of interests

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research? If Yes, please indicate how much and on what basis this has been decided

Guidance: Question A47 – Payment to researchers

- This question is concerned with "in pocket" financial payments or additional benefits to be provided direct to researchers personally, over and above the costs of conducting the research. Such payments could include, for example, contributions to a library, additional equipment not actually required for the research, social events etc. The question is not concerned with payments agreed between the sponsor and NHS care organisations or other sites to reimburse the costs of hosting the research.

- Personal payments or benefits to researchers should not be set at a level to cause undue influence.

- You should record the fact that researchers are receiving personal payments or benefits in the participant information sheet. See the guidance on informed consent on the Health Research Authority (HRA) website at: http://www.hra.nhs.uk/resources/before-you-apply/consent-and-participation/consent-and-participant-information/

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest? If yes, please give details including the amount of any monetary payment or the basis on which this will be calculated

Guidance: Question A48 – Conflicts of interest

- Information should be given about any potential conflict of interest for the Chief Investigator or any other investigator or key collaborator in undertaking the proposed research.

Chief Investigator’s declaration

3. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

[Note:

- Article 22 (Scientific Requirements and Research Protocols) of the Declaration of Helsinki states: “The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.”

- Article 26 (Informed Consent) states: “In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study.”

- Article 36 (Research Registration and Publication and Dissemination of Results) states: “Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication.”]
Annex B: EU Clinical Trials Regulation: summary of impact on transparency

The clinical trial regulation (EU) No 536/2014 places emphasis on increasing transparency and availability of information on clinical trials and results. The clinical trial database (linked with the portal) will be the source of public information on clinical trial applications assessed, and clinical trials conducted in the EU, from the time of the decision to authorise the trial to the finalisation of those trials and inclusion of their results on the database.

The Regulation states that the EU database “shall be publicly available unless one or more exceptions apply”:

• to protect personal data;
• to protect commercially confidential information, in particular taking into account the marketing authorisation status of the medicinal product, unless there is an overriding public interest;
• to protect confidential communication between Member States in preparing their assessment;
• to protect the supervision of clinical trials by Member States.

The information that will be made public for all clinical trials registered in the system will include:

• the main characteristics of the trial comprising design, scientific and, where applicable, therapeutic intent, title, identification of the investigational medicinal products (IMPs), treatment arms, treatment population and number of subjects, inclusion and exclusion criteria and main objectives and endpoints;
• conclusion of the assessment and decision on the trial;
• information updated during the trial to indicate the start and end dates of recruitment;
• substantial modifications to the trial;
• the end date of the trial and 12 months later the summary of results and a summary in lay language;
• clinical study reports for medicines for which a marketing authorisation has been granted, the procedure completed or the marketing authorisation application withdrawn.

The Regulation sets out a detailed account of what should be included in the summary of results and the lay summary.

ANNEX IV

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL

The summary of the results of the clinical trial shall contain information on the following elements:

A. CLINICAL TRIAL INFORMATION:

1. Clinical trial identification (including title of the trial and protocol number);
2. Identifiers (including EU trial number, other identifiers);
3. Sponsor details (including scientific and public contact points);
4. Paediatric regulatory details (including information whether the clinical trial is a part of a Paediatric Investigation Plan);
5. Result analysis stage (including information about intermediate data analysis date, interim or final analysis stage, date of global end of the clinical trial). For clinical trials replicating studies on already authorised investigational medicinal products and used in accordance with the terms of the marketing authorisation, the summary of the results should also indicate identified concerns in the overall results of the clinical trial relating to relevant aspects of the efficacy of the related medicinal product;

6. General information about the clinical trial (including information about main objectives of the trial, trial design, scientific background and explanation of rationale for the trial; date of the start of the trial, measures of protection of subjects taken, background therapy; and statistical methods used);

7. Population of subjects (including information with actual number of subjects included in the clinical trial in the Member State concerned, in the Union and in third countries; age group breakdown, gender breakdown).

B. SUBJECT DISPOSITION:
1. Recruitment (including information on the number of subjects screened, recruited and withdrawn; inclusion and exclusion criteria; randomisation and blinding details; investigational medicinal products used);
2. Pre-assignment Period;
3. Post Assignment Periods.

C. BASELINE CHARACTERISTICS:
1. Baseline Characteristics (Required) Age;
2. Baseline Characteristics (Required) Gender;
3. Baseline Characteristics (Optional) Study Specific Characteristic.

D. END POINTS:
1. End point definitions (*)
2. End Point #1 Statistical Analyses
3. End Point #2 Statistical Analyses 27.5.2014 L 158/69 Official Journal of the European Union EN (*)Information shall be provided for as many end points as defined in the protocol.

E. ADVERSE EVENTS:
1. Adverse events information;
2. Adverse event reporting group;
3. Serious adverse event;
4. Non-serious adverse event.
Written evidence submitted by Professor Jonathan Montgomery, Chair, Health Research Authority (RES0047)

F. ADDITIONAL INFORMATION:
1. Global Substantial Modifications;
2. Global Interruptions and re-starts;
3. Limitations, addressing sources of potential bias and imprecisions and Caveats;
4. A declaration by the submitting party on the accuracy of the submitted information.

ANNEX V

CONTENT OF THE SUMMARY OF THE RESULTS OF THE CLINICAL TRIAL FOR LAYPERSONS

The summary of the results of the clinical trial for laypersons shall contain information on the following elements:

1. Clinical trial identification (including title of the trial, protocol number, EU trial number and other identifiers);
2. Name and contact details of the sponsor;
3. General information about the clinical trial (including where and when the trial was conducted, the main objectives of the trial and an explanation of the reasons for conducting it);
4. Population of subjects (including information on the number of subjects included in the trial in the Member State concerned, in the Union and in third countries; age group breakdown and gender breakdown; inclusion and exclusion criteria);
5. Investigational medicinal products used;
6. Description of adverse reactions and their frequency;
7. Overall results of the clinical trial;
8. Comments on the outcome of the clinical trial;
9. Indication if follow up clinical trials are foreseen;
10. Indication where additional information could be found.

[Attached: