Health Research Authority

HRA and Research Transparency

Clinical trial registration

The HRA has reviewed this text to ensure greater consistency in the use of language in conveying standards that should be followed (ethical obligations or best practice) or must be followed (legal requirements) although readers are advised that the HRA holds both in high regard.

The HRA website material is a statement of the HRA understanding. Whilst the reader is encouraged to seek further clarification from the HRA in respect of any queries via the queries line, it will be for the reader to take their own legal advice as to what their legal duties are.

Key messages and Q&A

Please note this document supersedes previous versions. The HRA is a listening organisation and this latest Q&A may not be fully consistent with previous consultation documents but does represent an accurate position when written.

18 August 2015

The August 2015 version has been updated to provide consistent and transparent reference to where the HRA is fulfilling its statutory duties to promote research transparency through itself stating an expectation that researchers, research sponsors and others should meet best practice standards and where it is of the view[1] that they are required to meet legal responsibilities. Researchers, research sponsors and others should be aware that the HRA regards both as being important and will enquire against the expectations to meet best practice standards as well as monitoring compliance with requirements.

Any queries on the HRA expectations or requirements can be directed to the HRA queries line.

[1] While the HRA is making clear its own view, researchers and others are advised to take their own advice as to their legal obligations.

Context

The HRA has a duty to promote transparency and researchers, sponsors and funders correspondingly have duties (that may be legal requirements or ethical and moral expectations within an accepted governance framework of best practice and standards) to participants in research, patients and the wider public and research communities.

The simple default is that all clinical trials should be registered and the HRA expects all researchers, research sponsors and others to meet this fundamental best practice standard.

The effect of EU legislation is that medicinal clinical trials are entered in a public register (with a limited exemption for healthy volunteer studies). The HRA introduced requirements for all clinical trials (i.e. not just those falling under the EU legislation) by way of a condition contained within a favourable REC opinion in September 2013. These requirements include a simple deferral option for trials that are not entered in a public register as a result of EU legislation.

In order to fulfil its statutory responsibilities to promote transparency, the HRA has extended its audit activities on clinical trial registration from a compliance check on the requirements introduced in September 2013, to add an enquiry for all research in active recruitment in the UK, whether registration is legally required or expected as best practice . The sponsor declaration on IRAS and the HRA website are used to highlight this and to support sponsors and others in meeting expected best practice standards and legal responsibilities. Sponsors may contact the HRA to arrange deferral of registration for trials that are not entered in a public register as a result of current EU legislation. The first report on these audit activities is scheduled to go to the HRA Board later in 2015.

The HRA introduced the specific REC condition to register clinical trials in September 2013, to set out the requirement to register for all clinical trials as a requirement of the REC favourable condition from that point. The purpose of creating this 'line in the sand' is to sharpen focus and awareness of the ethical obligation to ensure all trials are registered and so that, when we do look later at measures and sanctions and subject to consultation, we may apply them from that point to all clinical trials (not just those trials of medicines falling under current or new EU legislation).

1. Key messages

1.1. Transparency is fundamental to the role of the HRA to promote and protect the interests of patients and the public in health research. The HRA has a duty to promote transparent research and research registration.

1.2. Subject to possible deferral the HRA expects registration of all clinical trials before the first participant is recruited in line with researcher and sponsor duties as set out by the WHO, current Declaration of Helsinki and in the Research Governance Framework.

1.3. Many journals insist on registration before the first participant is recruited. Failure to do so may prevent publication in key journals, such as the BMJ, which actively implement that requirement.

1.4. Since 30 September 2013 the HRA has identified trial registration as a specific ethical expectation within the existing duties of the sponsor, and it has been a condition of the Research Ethics Committee (REC) opinion, and hence a requirement, to ensure clinical trials are registered. Failure to do so within 6 weeks of the recruitment of the first UK participant is therefore a breach of the favourable ethical opinion unless

a request to defer registration has been granted by the HRA and is still valid. This action was to enable the duties of sponsors to be captured as a legal requirement from that point for all clinical trials.

1.5. The HRA offers a deferral option for trials that are not entered in a public register as a result of current EU legislation, noting the commercial sensitivities of some areas of research, notably within early phase trials. The HRA deferral policy and procedure is on the HRA website.

1.6. The HRA uses the sponsor declaration on IRAS, IRAS guidance and linked text on the HRA website to inform and support sponsors and others to meet best practice expectations and legal responsibilities. The HRA audits against both, as a compliance check against legal responsibilities and simple enquiry against established and expected best practice standards.

1.7. The HRA has a duty to ensure the decisions made by its research ethics committees are in the public domain, and so the HRA publishes the REC opinion and a short research summary on the HRA website. This is not trial registration as it does not include the World Health Organisation (WHO) data fields, that are required for publicly accessible research registries. However, it does provide a record of the ethics committee decisions, the publication of the opinion cannot be deferred although it is possible to request deferral of the research summary.

2. Q and A

2.1. Q: *How are clinical trials being defined by the HRA?*

A: All clinical trials of medicines, devices or other clinical interventions. These are the first four options in the project category filter question in IRAS (Integrated Research Application System; filter question 2), so no further judgment is required from the applicant, sponsor, REC or HRA.

2.2. Q: *Shouldn't other studies be registered as well? Why limit to clinical trials only?*

A: Yes, they should be registered and the HRA expects that they will be. However, the HRA approves a wide range of other studies and a judgment is needed on whether these studies are suitable for registration on the current public registers. The HRA will bring this judgement into HRA Approval process as it is adopted during 2015 / 2016.

2.3. Q: *Surely all studies should be registered if they involve human participants?*

A: Yes, however the studies the HRA approves include some with minimal intervention (e.g. postal questionnaires) and studies that may be of largely educational benefit which would not be suitable for the public registers. A short summary of research reviewed by RECs in the UK is placed on the HRA website so there is that level of transparency for all studies in the UK.

2.4. Q: *Do clinical trials include all phases of clinical trials / Does it include clinical trials in healthy volunteers as well as patients / Does it include commercial and non-commercial trials?*

A: Yes, although the HRA recognises the need to maintain UK competitiveness and so we have put in place a simple mechanism to request deferral of registration where there are, for example, concerns of commercial confidentiality and where the trial is not entered in a public register as a result of current EU legislation. Deferral is therefore available for phase 1 healthy volunteer trials and clinical trials that do not fall under EU legislation.

2.5. Q: *Has the HRA introduced an option for exemption or deferral of registration?*

A: The HRA has introduced a simple mechanism to request deferral based on a justification of the need for delay in registration and assurances that the studies will be registered later. The HRA may consider requests for exemption from registration, but has set out that it does not expect to grant exemption although it does recognise the need for deferral to maintain UK competitiveness.

2.6. Q: *Will HRA audit activities delay REC applications*

A: No, the audit is a separate quality assurance activity

2.7. Q: *What happens if a Sponsor does not comply with registration requirements?*

A: Where registration is a specific condition of the REC favourable opinion for that trial, a sponsor will be in "serious breach". Breaches are managed in accordance with REC standard operating procedures. These do not include legal sanctions.

2.8. Q: *What sanctions are there for non-compliance with a registration requirement imposed as a condition of a REC favourable opinion?*

A: There are currently no specific sanctions operated by the HRA. The HRA is working with REC members, other stakeholders and with legal advice on a set of administrative measures for further consultation later in 2015. These would only apply where registration is a legal requirement. The new EU Clinical Trials Regulation will require Member States to have legal sanctions for non-compliance with transparency provisions of the Regulation.

2.9. Q: *If a clinical trial is published on HRA's research summaries list does this fulfil sponsor duties for registration?*

A: No. The HRA research summaries list does not contain the information fields to meet the World Health Organisation (WHO) requirements for a trial registry.

2.10. Q: *How do sponsors confirm to HRA that their clinical trial is registered?*

A: If the trial has been registered before the application for ethical review is submitted then the details of registration must be included in the application form. Where registration occurs after submission of the initial application the registration must be confirmed and details provided at the first opportunity (i.e. submission of substantial amendment or progress report, whichever is earlier).

2.11 Q: *What is the legal basis for registration in EU legislation?*

A: Information on interventional clinical trials on medicines conducted in Europe which started after May 2004 is publicly accessible (with some specific exceptions) through the EU Clinical Trials Register. The EU Clinical Trials Register is a primary registry in the World Health Organization (WHO's) Registry Network. Information about this Register and its legal basis is provided at https://www.clinicaltrialsregister.eu/about.html.