Health Research Authority

Clinical Trial Registration Report

April 2016

1. Background

Since October 2013, it has been a condition of the favourable ethical opinion for clinical trials (as defined by the first 4 categories on the IRAS form) to be registered on a publicly accessible database, no later than 6 weeks after recruitment of the first participant into the trial. The HRA recognises that ethical and moral obligations of researchers and researcher sponsors set out a best practice standard for all health research to be registered. In addition to this, Clinical Trials of Medicinal Products (CTIMPs) are legally required to be registered under the current European Clinical Trials regulations, and UK Clinical Trial legislation. Although this legislation has specific exemption for Phase 1 trials involving healthy volunteers.

The HRA recognises that in certain circumstances, such as where details of the clinical trials could be considered commercially confidential, deferral of registration would be acceptable. A simple deferral mechanism was therefore put in place. This allows sponsors to request, on a trial by trial basis, for an agreed deferral to registration, with the expectation that assurance is given that the trial will be registered when no longer commercially confidential or immediately should the trial be terminated early for safety reasons.

2. Method

CTIMPs, with the exception of Phase 1 trials involving healthy volunteers, are always registered on the EU clinical trials register via EudraCT and it can therefore be assumed that all CTIMPs have been registered and the monitoring therefore covers other clinical trials and Phase 1 trials involving healthy volunteers.

For the first phase of the monitoring, publicly accessible databases (primarily clinicaltrials.gov and ISRCTN) were searched via google using the full study title and, if the trial could not be located using the title, the REC reference was searched. The clinical trials monitored were all those listed as a clinical trial on the IRAS form which received a favourable opinion between 1 January 2015 - 30 June 2015 for medical device and 'other' clinical trials and from 30 September 2013 - 30 June 2015 for Phase 1 clinical trials. The search was undertaken at the end of August which allowed 7 weeks from the end of the reporting period to the date of the monitoring. However, it was accepted that it was unlikely studies would have commenced and recruited immediately after the favourable opinion had been issued and therefore it was accepted that not identifying a clinical trial did not necessarily mean that the sponsor was in breach of the condition of the favourable opinion. Additionally, in some cases, not finding the trial may have been due to the search method rather than the trial not having been registered.

The second phase which was undertaken December 2015 - January 2016 involved searching databases to see whether the trial could now be located and if not, writing to sponsors and Chief Investigators (for Phase 1 trials the CRO was contacted and not the sponsor) to request confirmation

of whether the trial has been registered and if not, what the reason for this was and what the expectation of the sponsor was in terms of registering the trial.

The e-mail informed the CI about the monitoring and asked:

A) Has the clinical trial been registered and if so, to please provide the registration number.
or
B) If the clinical trial has not been registered then please provide an explanation of why it was not registered and to confirm when the trial would be registered.

Where no response was received after the first e-mail, a second e-mail was sent. Where a second e-mail was sent and a response was still not received, a 'no response' was recorded after the final date given by which to respond.

The purpose of the exercise was to monitor and report to the HRA Board on the levels of compliance as part of the HRA duties to promote research transparency, duties that are described in the Care Act.

3. <u>The below tables are a breakdown as a comparison to the position in August 2015</u>

3.1 Phase 1 Clinical Trials (monitoring period 30 September 2013 to 30 June 2015)

	August 2015		January 2016	
Total number of Phase 1 trials with a FO during the reporting period	331		331	
Total number of Phase 1 trial registered on a publicly accessible database at the time of reporting	208	63%	254	77%
Of the total number registered, those found on ISRCTN or other	(6)	(3%)	(15)	(6%)
Of the total number registered, those found on clinicaltrials.gov	(202)	(97%)	(239)	(94%)
The number of Phase 1 trials where a deferral was allowed	49	15%	50*	15%
The number of Phase 1 trials that could not be found at the time of reporting (breakdown of response to these below)	74	22%	27	8%
Of the Phase 1 clinical trials not found or not known to have registered: **Reply received**			17	(63%)
Of the replies received, those which stated that registration not yet required (e.g trial not yet recruited / trial not yet started / trial terminated before recruitment commenced)			5	(29%) Of those where reply received
Of the Phase 1 clinical trials not found or not known to have registered: **Reply not received**			10	(37%)

*Due to a recording error, one trial did have a deferral in place but was not identified at the start of the monitoring

3.2 Medical Device Clinical Trials (monitoring period 1 January 2015 to 30 June 2015)

	August 2015		January 2016	
Total number of medical device trials with a FO during the reporting period	169		169	
Total number of medical device trials identified on a publicly	82	48%	144	85%

accessible database at the end of the monitoring period				
Of the total number registered, those found on ISRCTN	14	(8%)	20	(12%)
Of the total number registered, those found on clinicaltrials.gov	68	(40%)	88	(52%)
Total number of medical device trials not registered but details of the trial could be found on the UKCRN site	19	11%	27	(16%)
Of the total number registered, those found on researchregistry.com*			9	(5%)
The number of medical device trials that could not be found or not know to have registered; (breakdown of response to these below)	68	40%	25	15%
Of the medical device trials not found or not known to have registered: **Reply received**			6	(24%)
Of the replies received, those which stated that registration not yet required (e.g trial not yet recruited / trial not yet started / trial terminated before recruitment commenced)			5	(83%) Of those where reply received
Of the medical device trials not found or not known to have registered: **No reply received**			19	(76%)

*Researchregistry.com is a relatively new database which was not included in the list of advisable databases pre August 2015

3.3 Clinical Trials other than CTIMPs or Medical Device trials (monitoring period 1 January 2015 to 30 June 2015)

	August 2015		**January 2016**	
Total number of other trials with a FO during the reporting period	300		300	
Total number of other trials found on a publicly accessible database	144	48%	240	80%
Of the total number registered, those found on ISRCTN	75	(25%)	86	(36%)
Of the total number registered, those found on clinicaltrials.gov	69	(23%)	94	(39%)
Total number of other trials not registered but details of the trial could be found on the UKCRN site	36	12%	48	(20%)
Of the total number registered, those found on researchregistry.com*			11	(5%)
German clinical trials database			1	(0.5%)
The number of other trials that could not be found or not known to have registered	120	40%	60	20%
Of the other clinical trials not found or not known to have registered: **Reply received**			33	(55%)
Of the replies received, those which stated that registration not yet required (e.g trial not yet recruited / trial not yet started / trial terminated before recruitment commenced)			9	(27%) Of those where reply received
Of the other clinical trials not found or not known to have registered: **Reply not received**			27	(45%)

*Researchregistry.com is a relatively new database which was not included in the list of advisable databases pre August 2015

4. Summary of comments received (all clinical trials)

Responses received from applicants (These are generalised comments rather than direct quotes as similar responses were received by different applicants)	**Our response** (These are generalised comments rather than direct quotes as responses were specifically responding to the comment received)
This is a clinical trial being undertaken for academic purposes so we don't need to register.	The expectation to register applies to all clinical trials and does not differentiate between academic and non academic research.
We have been advised by our R&D department that we don't need to register (this usually related to the nature of the study being considered either non clinical or non interventional).	The expectation to register applies to all clinical trials (as defined by the first 4 study categories in Q2 of the IRAS filter page) and this is a condition of the favourable opinion, as stated in the final opinion letter. Any advice given which is contrary to this is not in accordance with the HRA position.
We stated on the IRAS form that we were not planning to register and the REC accepted this so we do not have to register this clinical trial.	The final opinion letter did state that registration of the clinical trial was a condition of the favourable opinion; this is a standard condition. As the final opinion letter which you received did not specifically state that the REC had agreed that there was no expectation to register this clinical trial, the standard condition to register is expected to be complied with.
We did not know that we needed to register	Please refer to the final opinion letter which you received. This letter states that registration of clinical trials (as defined by the first 4 study categories in Q2 of the IRAS filter page) is a standard condition of the favourable opinion.
We have no funding available for registration so we didn't do it	There is no cost attached to registering a clinical trial on certain databases, e.g www.researchregistry.com
Our study was not actually a clinical trial (although a clinical trial study category had been selected on IRAS)	As a clinical trial category was selected for Q2 on the IRAS filter page, it is expected that the study is registered on a publicly accessible database.
This study is registered on our Trust / University website	This does not comply with the condition to register the clinical trial as it does not contain the information fields to meet the World Health Organisation (WHO) requirements for a trial registry.
The research summary is published on the HRA website.	This does not comply with the condition to register the clinical trial as it does not contain the information fields to meet the World Health Organisation (WHO) requirements for a trial registry.

5. Observations and Recommendations

- Almost all of the clinical trials which were not identified on a publicly accessible database in August 2015 and are now recorded as registered were registered due to being contacted as part of this

project. This piece of work has therefore been the catalyst for registration in many cases as the clinical trials would not have been registered if contact had not been made by the HRA.

- A number of responses received to say that they did intend to register and would confirm when complete but no response received within the monitoring period.
- A large number of individuals (actual number unknown) telephoned Catherine Blewett, HRA Improvement and Liaison Manager, to query what was being asked. It was evident from these discussions that there was a significant lack of understanding in regards to the standard condition to register clinical trials. All those who telephoned Catherine to discuss registration did agree to register the clinical trial once the condition had been clarified and/or they were advised that there were proportionate mechanisms to register clinical trials available.
    - **Recommendation** - Further work to be undertaken to improve the understanding and definition of the condition to register clinical trials.
- A number of individuals referred to advice (incorrect or inaccurate advice) which they had been given by an R&D department within the NHS Trust or University.
    - **Recommendation** - Further work is advisable to target R&D departments to ensure that understanding at this level is accurate and that appropriate advice is therefore being given. This is particularly important as R&D departments are often the first place individuals will go to seek advice.

6. Next steps

The oversight of clinical trial registration has now transferred from the operations directorate to the Quality Standards directorate under Tom Smith. No additional resource is anticipated for this work. EMT is asked to advise on how this work should be taken forward based on the following options.

A. Snapshot review periodically

This option would involve undertaking the piece of work as described in this paper on a regular basis (suggest every 6 months). This would require checking against all clinical trials (except CTIMPs) which receive a favourable opinion for a 6 month period and also following up any trials not found after a further 6-8 months (some staggering would mean initial checks and following up is not at the same time) If any administrative measures are being considered for non compliance, there would need to be a 100% sample to ensure fairness.

As clinical trials commence at different time periods after ethical review, there is no guarantee that by the time of the initial check and also the follow up check that the trial has commenced/recruited. It may therefore be necessary to undertake some residual monitoring of those trials over a longer period.

B. Continuous monitoring by quality standards

This option would involve all clinical trials being monitored on an ongoing basis. As clinical trials commence at different periods after ethical review it is difficult to suggest a timeframe between a clinical trial receiving a favourable ethical opinion and checking the registration status. This may result in a significant amount of time checking and following up on clinical trials which have not yet commenced/recruited and therefore there is no requirement to have registered the clinical trial at that time.

C. Continuous monitoring by REC service

This option would involve monitoring the registration status of clinical trials via currently established REC reporting mechanisms, e.g annual progress reporting or substantial amendments. The benefit of this is that these reporting routes will confirm whether the trial has commenced/recruited and therefore whether registration is required. However, it is currently recognised that compliance with annual progress reporting is questionable as reports are often not received and there is no guarantee that a trial will require a substantial amendment.