Health Research Authority

Clinical Trial Registration

Audit of compliance for period 1 January 2016 to 30 June 2016

1. Background

Since October 2013, it has been a condition of the Research Ethics Committee (REC) favourable ethical opinion for all clinical trials to be registered on a publically accessible database. This should occur before the first participant is recruited and be no later than 6 weeks after recruitment of the first participant. Appendix 1 provides an extract of the trial registration wording from the REC favourable opinion letter. It should be noted that 'clinical trials' in this context refers to research described by the first four categories of IRAS[1] project filter question 2, which are:

- Clinical trial of an investigational medicinal product
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

Clinical Trials of Investigational Medicinal Products (CTIMPs) are legally required to be registered under the current European and UK Clinical Trial legislation. However, this legislation has specific exemption for Phase 1 trials involving healthy volunteers.[2]

The HRA recognises that in certain circumstances, for instance where details of the clinical trial could be considered commercially confidential, deferral of registration would be acceptable. A deferral mechanism is therefore in place to allow sponsors to request, on a trial by trial basis, for an agreed deferral of registration. There is an expectation that the trial will be registered when the reason for the deferral is no longer valid or immediately should the trial be terminated early for safety reasons.

The purpose of this audit, which was undertaken during August 2017, was to monitor levels of clinical trial registration compliance as part of the HRA duties to promote research transparency.

[1] Integrated Research Application System (IRAS); https://www.myresearchproject.org.uk/Signin.aspx

[2] The EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/about.html) , which is a primary registry in the World Health Organisation (WHO) Registry Network, enables the public to search for information held in EudraCT database.

2. Method

The aim of this audit was to assess the proportion of clinical trials (as defined by the first 4 study categories in Q2 of the IRAS filter page) over a specified period that met the condition of favourable opinion to register on a publicly accessible database.

Clinical Trials of Investigational Medicinal Products (CTIMPs), except for Phase 1 trials involving healthy volunteers, are always registered in the EudraCT database with a EudraCT number and they appear in the EU Clinical Trials Register. It was therefore assumed that all CTIMPs had been registered and therefore all CTIMPs except Phase 1 trials in healthy volunteers were excluded from the audit sample.

Consequently clinical trials described by the following categories were included in this audit:

- Clinical Trials of Investigational Medicinal Products (CTIMPs) – limited to Phase 1 trials involving healthy volunteers
- Clinical investigation or other study of a medical device
- Combined trial of an investigational medicinal product and an investigational medical device
- Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

The audit included clinical trials in the above categories that received a favourable opinion, favourable opinion with additional conditions, further information favourable opinion and further information favourable opinion with additional conditions from a UK REC during the period 01 January 2016 to 30 June 2016.

Clinical trials with an agreed HRA clinical trial registration deferral in place at the time of the reporting period were excluded. However, the number of valid deferrals in place for clinical trials within the audited period, categorised by study type, have been included in the report findings.

Step 1: Extracting data from the HRA Assessment Review Portal (HARP)

A management information report was extracted from HARP to identify studies within the scope of the audit. There are specific data fields on HARP for the trial registration number for studies registered on clinicaltrials.gov and the International Standard Randomised Controlled Trial Number Registry (ISRCTN), as well as an 'other reference numbers' field. The data export included this registration information where it was available (note - this information is populated in HARP either through direct import from the IRAS application form or as manual input by the REC Manager where they are advised of registration).

Note that where the data export identified trials without any registry reference number it was not feasible, due to the additional time burden and limited resources, to scrutinise each complete study record on HARP to determine if registration information had been reported, for example via progress reports or Notice of Substantial Amendment form, but not entered within registry identifier fields referenced above. The information obtained through the data export was therefore used as the starting point.

Step 2: Trial registration searches

Registration searches were conducted in August 2017 using the full study title, and if the trial could not be located with this the short title and REC Reference number were searched. The searches, via Google, sought to locate the clinical trial on a publicly accessible database. For the purposes of this step in the audit, the standard applied was for registration in any primary registry of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), usually found to be ISRCTN, or clinicaltrials.gov (this is not a primary WHO registry but is an International Committee of Medical Journal Editors (ICJME) acceptable registry).

When the study was located the registration details (name of registry and registration number) were logged on a data record sheet and the relevant study record on HARP updated.

Step 3: Follow up for studies not found

If a registry entry could not be located for a clinical trial within the scope of the audit then the Chief Investigator and Sponsor were contacted (for Phase 1 studies the Chief Investigator only was contacted) via email and asked to provide registration details or a reason for registration having not taken place. Responses were recorded on a data collection sheet and HARP was updated where registration information was provided. Responses were reviewed and categorised to determine broad themes. Where no response was received a ‘no response’ was recorded after the response cut off point.

Every best effort was made to assign the response to the most appropriate category. It must be acknowledged that some responses were not clear cut making it challenging to assign to a discrete category. Where appropriate, response categories were updated to reflect the final response received following a series of email exchange with the applicant, for example, an initial response from an applicant claimed their study was not a clinical trial and a subsequent response was received reporting that they had misunderstood the requirement to register and would register. For the purpose of this audit the final response received is the recorded category.

3. Results

Results presented include data available up to 17:00 on 29/08/2017[3]

Table 1. The number of clinical trials by study type receiving a favourable opinion registered / not registered on a public accessible registry included in the audit (registry as defined in Section2, step 2 above)

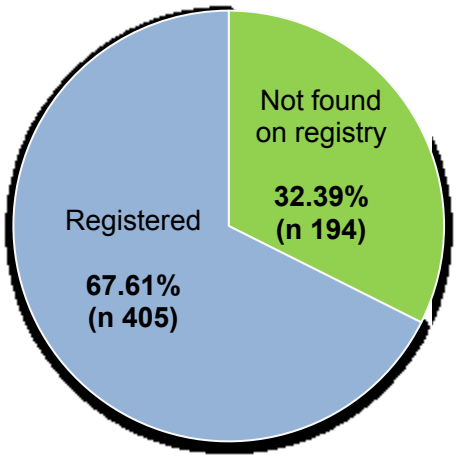
	Phase 1	Devices	Other CT	Total
	n (%)	*n* (%)	*n* (%)	*n*
Studies with favourable opinion*	84 (13.6)	206 (33.4)	327 (53.0)	**617**
Studies with HRA agreed deferral	17 (20.2)	1 (0.5)	0	**18**
Not found on a publicly accessible registry	9 (13.4)**	67 (32.7)**	118 (36.1)	**194**
Total number of studies known to be registered at baseline	58 (86.5)*	138 (67.3)*	209 (63.9)	**405**

* Includes studies that received a favourable opinion, favourable opinion with additional conditions, further information favourable opinion and further information favourable opinion with additional conditions from a UK REC

** Calculation excludes studies with a valid HRA Deferral

617 studies were included in the audit, with 18 of these studies having an agreed HRA clinical trial registration deferral in place during the monitoring period. Therefore, the total number of studies which received a favourable opinion from a UK REC, defined as a clinical trial, and did not have a valid deferral in place was over the audit period 599. Of these, 405 (67.6%) were known to be registered on a publicly accessible registry (as defined in Section 2, step 3).

Figure 1. Proportion of clinical trials known to be registered at baseline.



[3] To allow for completion of this time-limited audit, any additional responses from Chief Investigators/Sponsor received after this point have not been included.

Table 2. Breakdown of different study types at stage 1 and stage 2 of the audit to identify those registered on a public accessible registry (as defined in Section2, step 2)

	Phase 1	*Devices*	*Other CT*	*Total*
	***n* (%)**	***n* (%)**	***n* (%)**	***n***
Number of eligible studies (excludes studies with agreed deferral)	**67**	**205**	**327**	**599**
Step1: Known to be registered (through data export - registry details on HARP at time of audit)	**8 (11.9)**	**59 (28.8)**	**43 (13.1)**	**110**
• ISRCTN	0	1 (0.5)	17 (8.1)	18
• clinicaltrials.gov	8 (11.9)	57 (27.8)	25 (7.6)	90
• Other*	0	1 (0.5)	1 (0.5)	2
Step2: Known to be registered (found on registry after search) and HARP subsequently updated	**50 (74.6)**	**79 (38.5)**	**166 (79.4)**	**295**
• ISRCTN	1 (1.5)	13 (6.3)	79 (37.8)	93
• clinicaltrials.gov	49 (73.1)	66 (47.8)	85 (40.7)	200
• Other*	0	0	2 (0.6)	2
Total known to be registered (conclusion of step 1 and 2)	**58 (86.5)**	**138 (67.3)**	**209 (63.9)**	**405**
• ISRCTN	1 (1.7)	14 (10.1)	96 (45.9)	111
• clinicaltrials.gov	57 (98.3)	123 (89.1)	110 (52.6)	290
• Other*	0	1 (0.7)	3 (1.4)	4

** The Australian New Zealand Clinical Trials Registry (ANZCTR), EU Clinical Trials Register, German Clinical Trials Register (GermanCTR)*

Figure 2. The proportion of studies known to be registered by study type (Phase 1, Devices and Other Clinical Trials) at conclusion of step 1 and step 2

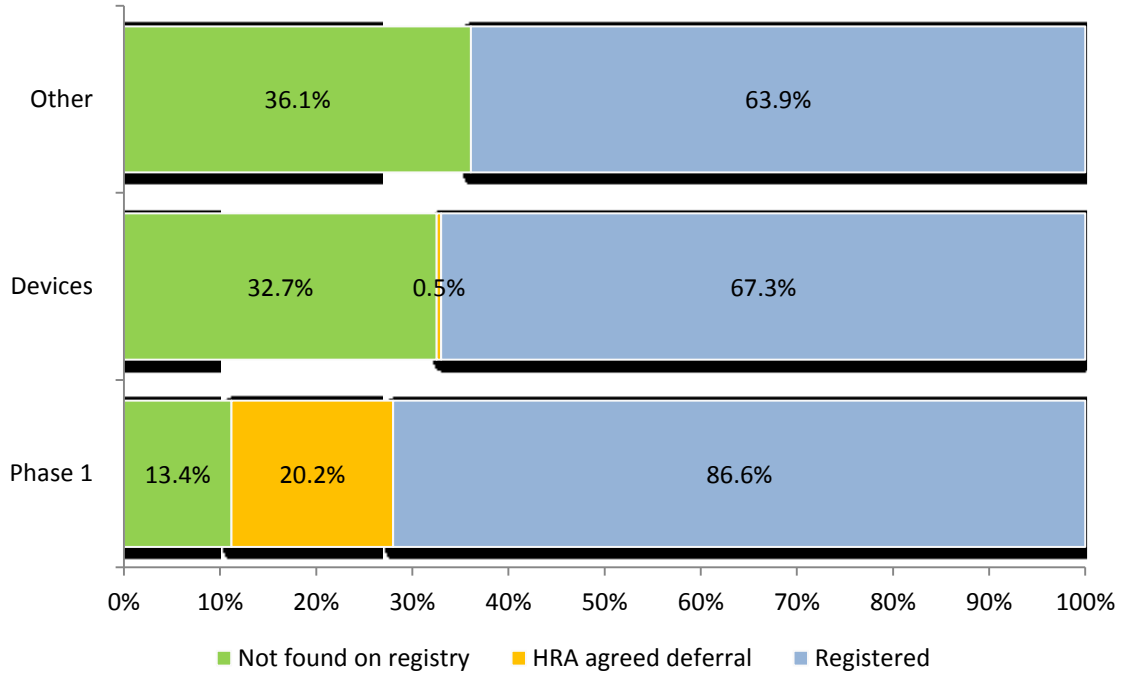
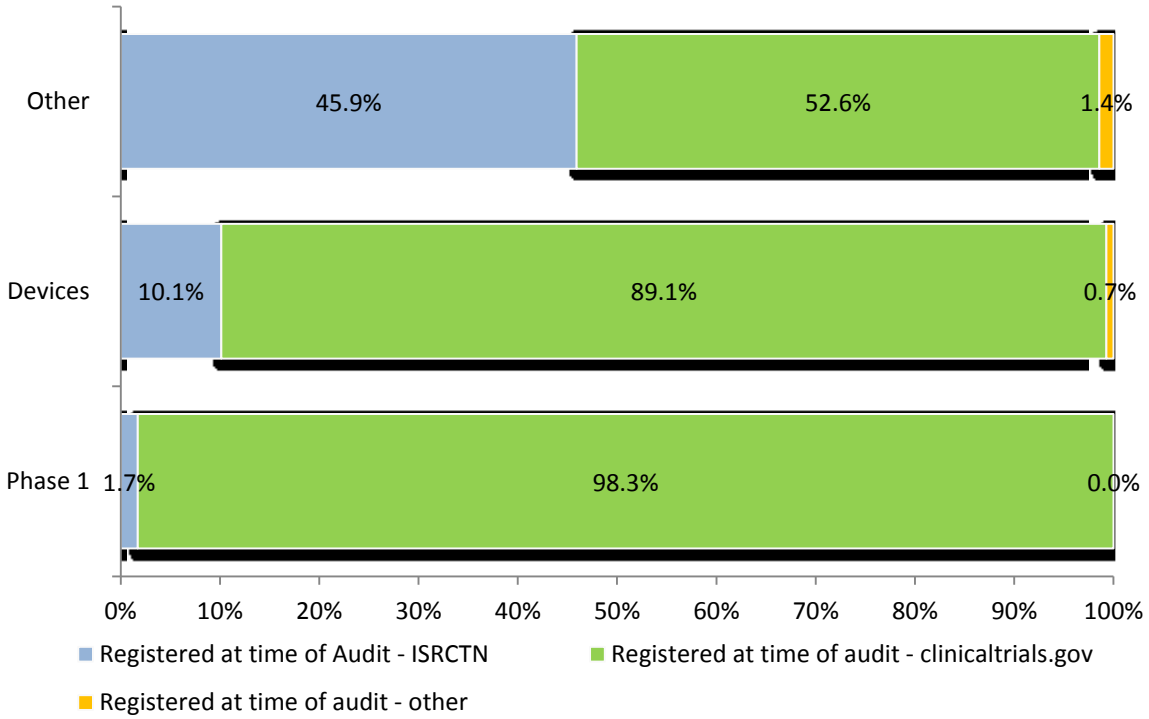


Figure 3. The proportion of studies known to be registered by register and by study type (Phase 1, Devices and Other Clinical Trials) at conclusion of step 1 and step 2



3.1 Registered studies

3.1.1 Phase 1 Clinical Trials

84 phase 1 studies were included in the audit; 17 of these had an agreed HRA clinical trial registration deferral in place. Of the phase 1 studies registered (n-58) a significant proportion of these were registered on clinicaltrials.gov (98.3%). Only 1 phase 1 study was registered on the ISRCTN registry. Eight studies were identified as being registered through the HARP data export and a further 50 were identified through Google searches.

3.1.2 Medical Device Clinical Trials

206 device studies were included in the audit; with only 1 of these having an agreed HRA clinical trial registration deferral in place. Of the device studies registered (n-138) the majority were registered on clinicaltrials.gov (89.1%) with just over 10% being registered on the ISRCTN registry. One study was register on the EU clinical Trials Register. 59 studies were identified as being registered through the HARP data export and an additional 79 were located through Google searches.

3.1.3 Clinical Trials other than CTIMPs or Medical Device trials

327 'other' clinical trial studies were included in the audit. None of these had a registration deferral in place. Of the 'other' clinical trial studies registered (n-209) just over 50% were on clinicaltrials.gov, and just under half (45.9%) were registered on the ISRCTN registry. A small proportion of this study type (1.4%) were registered on The Australian New Zealand Clinical Trials Registry (ANZCTR), and the German Clinical Trials Register (GermanCTR). 110 studies were identified as being registered through the HARP data export and a further 295 were found through Google searches.

3.2 Follow up with investigator and / or Sponsor when a study could not be found (step 3)

Table 3. Number of investigators / sponsors contacted when a study could not be found on a registry and the category of response received

	Phase 1 n (%)	Devices n (%)	Other CT n (%)	TOTAL n (%)
Contacted	**9**	**67**	**118**	**194**
No Response	4 (44.4)	26 (38.8)	43 (36.4)	**73 (37.6)**
Responses	5(55.6)	41 (61.2)	75 (63.6)	**121 (62.4)**
Will register	0	8 (19.5)	26 (34.6)	**34 (28.1***)**
*Study did not proceed **	2 (40)	6 (14.6)	7 (9.3)	**15 (12.4)**
Registered (awaiting number)	0	5 (12.2)	6 (8)	**11 (9.1)**
Applicant claimed not a CT	0	2 (4.9)	8 (10.7)	**10 (8.3)**
Now registered (following audit email)	0	3 (7.3)	7 (9.3)	**10 (8.3)**
Already registered (not found initial search)	2 (40)	5 (12.2)	3 (4)	**10 (8.3)**
*Registered on other database / website **	1 (20)	4 (9.8)	6 (8)	**11 (9.1)**
Study not started	0	4 (9.8)	5 (6.7)	**9 (7.4)**
Registered on NIHR portfolio	0	2 (4.9)	5 (6.7)	**7 (5.8)**
On AL - will deal with on return	0	1 (2.4)	2 (2,7)	**3 (2.5)**
Stated in A50 would not register	0	1 (2.4)	0	**1 (0.8)**

** Includes studies that were terminated or suspended*
*** 2 responses referred to the HRA research summary webpage as being classed as registered (one of these was a phase 1 study) 3 responses provided links to a website which included the study title only.*
**** percentage of responses*

194 follow up emails were sent to Chief Investigators/Sponsors to request confirmation of whether the trial has been registered and if not, what the reason for this was. 121 responses were received (62.4%) and categorised based on the feedback (Table 3).

A number of respondents queried the requirement to register. A reply was sent to clarify that HRA position on trial registration and a number of respondents sent a further response to confirm that they intended to register the study or had registered the study. Where this was the case and trial registry details were provided the response category on the recording sheet was updated to 'Now Registered'. The same applies for applicants who replied to say they would register (the data collection sheet was updated to 'Will register') and for those that replied to say they had made a registration application (the recording sheet was updated to Registered (awaiting number)).

3.2.1 Phase 1 Clinical Trials

Nine Chief Investigators were contacted to request confirmation of whether the trial has been registered and if not, what the reason for this was. Five responses were received. Of these, two studies were reported to be registered however were not identified through the initial search (this is likely due to variations in the study title on HARP and the registry), two studies reported to have not proceeded, and one study reported to have registered on the EudraCT database and the results had been posted there. This respondent also referenced the study details being publically available on the HRA website.

3.2.2 Medical Device Clinical Trials

67 Chief Investigators and Sponsors were contacted after their study could not be located on a registry. 41 responses were received. Nearly 20% responded to say that they would register the study; of those who specified where they would register clinicaltrials.gov and the ISRCTN Registry were most frequently referenced. 12% of respondents advised that they had registered and were awaiting the registration number. 12% of respondents advised that their study was already registered (these were not found through the initial Google search) and provided registration details. Three of these were registered on the Research Registry. Although this registry is not a Primary Registry in the WHO Registry Network, it is listed on the Research Transparency page of the HRA website as a useful link under research registries (at time at which audit was undertaken). Two respondents reported to have registered on the NIHR portfolio and another respondent advised that their trial had not yet but "intended to follow normal guidance from NIHR about public accessibility". At least 7 respondents initially claimed that their study was not a clinical trial (observation, feasibility studies were named as the type of study). One respondent noted that their local R&D team advised that registration was not necessary as the study was not a clinical trial. Of the respondents that initially claimed their study was not a clinical trial, only 2 respondents did not send a further email to confirm that they would register the study. Four respondents replied with names of websites / databases as to where their study was registered (Table 4).

3.2.3 Clinical Trials other than CTIMPs or Medical Device trials

118 Chief Investigators and Sponsors were contacted after their study could not be placed on a registry. 75 responses were received. Over 1/3 of replies advised that they would register the study. One respondent advised that they would "*review their sponsorship processes to ensure that a check on clinical trial registration is built into our sponsorship workflows on EDGE*". Five respondents reported to have registered on the NIHR portfolio. Six respondents replied with names of websites / databases as to where their study was registered (Table 4). Three respondents advised that their study was already registered (these were not found through the initial Google search) and provided registration details. Two of these were on the ISRCTN Registry and two on the Research Registry. At least 20 respondents initially claimed that their study was not a clinical trial. Examples of study types where the applicant claimed their study was not a clinical trial includes; single case design student project, feasibility study, small single arm observational, qualitative interview study. A number of respondents advised that the study was a pilot with small sample size and did not regard it necessary to register the trial. One respondent reported that they decided not to initially register after discussions at the REC meeting. A small proportion of responses alluded to inadvertently selecting the incorrect study type on

the IRAS application form. One responded started that they selected "Other CT" as it was the least inappropriate category on the IRAS filter page. One respondent who claimed that their study was not a clinical trial advised that they that had "*received confirmation from the MHRA that it is not a CTIMP and does not require a CTA*." A couple of respondents questioned whether it was worthwhile registering retrospectively, with one individual noting "*This would seem to defeat the purpose of pre-registration*." Of the respondents that initially claimed their study was not a clinical trial, over half of respondents subsequently confirmed that they would register the study or had since registered. A number of respondents asked for additional guidance on how to register and which registries where appropriate for their study type. Some respondents were under the impression that the HRA Research Summary webpage was a form of trial registration, for example, one respondent queried, "*If we register this study on www.clinicaltrials.gov then do we need to register this on HRA website too*?"

Table 4. Other sources provided by respondents to where their study was registered (this includes responses across all study types)

Aberystwyth University's online research repository / database, CADAIR.
Clinical research network portfolio of stroke projects
HRA Research Summaries website: http://www.hra.nhs.uk/news/research-summaries/
https://www.sheffield.ac.uk/medicine/prospectivepg/taught/mmedsci/currentresearch www.spvu.co.uk https://www.stgeorges.nhs.uk/education-and-research/research/clinical-research-portal/
Open science framework website. https://osf.io/sd4yh/ (log in details required)
Public Health Wales Research and Development Activity www.wales.nhs.uk/sitesplus/888/page/64145 (unable to load webpage)
The Health Foundation (www.health.org.uk)
Trusts/intranet R&D page

The databases / registries considered acceptable by the respondent were not scrutinised to assess the level of detail available / quality of information provided. Where a website links was provided the site was checked but no assessment made. Therefore, it is not possible to comment on the suitability of the various databases / registries. The study title was the only information provided on a small number of website links provided in the applicant's response.

4 Observations and Recommendations

This audit focused on the proportion of clinical trials registered that had received a favourable opinion from a UK REC. There are a number of secondary findings to report:

4.1 Follow up with Chief Investigator / Sponsors

- The response rate from investigators / sponsors when contacted regarding study registration was reasonably good, given the short response window (one week from when the email was sent and no reminder emails were issued).
- Classifying some responses into a distinct response category was sometimes difficult as some responses were either very vague or comprehensive and covered various points.
- Twenty undeliverable emails were received out of the 194 emails sent. The majority of these emails included two recipients (the sponsor and Chief Investigator), apart from Phase1 studies where only the Chief Investigator was contact. Email addresses were copied from the study record on HARP.

4.2 Definition of a clinical trial

- A number of respondents initially claimed that their study was not a clinical trial and had erroneously selected the wrong study category in IRAS.

4.3 Understanding of the requirement to register

- Awareness that the requirement to register a clinical trial as a condition of favourable opinion is variable.
- Many responders did not know how or where to register their study and what was an acceptable register for their study type.
- Many responders were committed to register, especially after further clarity around this requirement was given, and very few mentioned practical barriers to registering.

4.4 Define standards

- It is recommended that the HRA more explicitly defines the requirements that the HRA expect applicants to comply with, including which publicly accessible databases are considered acceptable for purposes of requirement to register, and that this information is publicly available to researchers / sponsors and the wider research community.
- This would allow the HRA to better monitor and improve rates of compliance and determine the appropriateness of the registry being used.

4.5 IRAS application form

- Question A50 of the IRAS application form. The section is currently headed Publication and Dissemination). Trial Registration could be added to the section header to emphasise that publication and registration are different.
- Question A50 asks 'Please give details, or justify if not registering the research'. This could be an opportunity for the committee and/or REC Manager to identify when validating / reviewing application where applicants have explicitly stated an intention not to register.
- The data export from HARP takes information from Question A5-1 on research reference numbers which includes a subsection on 'registry

reference number(s)'. There is a data field to enter the International Standard Randomised Controlled Trial Number (ISRCTN) and ClinicalTrials.gov Identifier (NCT number). There is another data field called Additional reference number(s) which pulls through to the data report as 'Other Registries'. This information also currently pulls through to the research summary page on the HRA website and is displayed as an "Additional reference number fields". It was evident from the data export from HARP that a variety of information such as insurance numbers and other ambiguous information is entered here, which is then included in the research summary dataset on the website.

- Future clinical trials regulation may not involve applying through IRAS. The HRA will consider alternate routes to capture the information currently elicited by IRAS.

4.6 Study searches

- Finding studies by full study title through a Google search generally found the study if it was registered. There were a few cases where the study title varied between what was recorded on HARP and the registry. The short title was sometimes used on the registry so it was important to use this for thoroughness. Verifying that studies matched was easier when the protocol number was given on the IRAS application form and the registry. The ISRCTN and Research Registry (not a Primary Registry in the WHO Registry Network) provide details on ethical approval and often give the REC name and REC Reference number, giving another reference point to verify that studies match.

4.7 HARP record of studies registered

- 295 study records on HARP (72.8% of the total number of studies known to be registered prior to follow up with the Chief Investigator /Sponsor) were updated with registration details identified through study searches in Google. This demonstrated that a number of Chief Investigators / Sponsors are compliant with the standard condition to register but the information about trial registration had not been captured under the study record on HARP. This may be because the details of registration had not been supplied by the Chief Investigator/Sponsor or that it had been supplied after initial submission of the IRAS application form and the data not manually added to the relevant fields in HARP. It is suggested that the process for informing RECs of registration and ensuring that registration information is added to the HARP record when received is reviewed. This review should seek to identify opportunities to facilitate the process and thereby improve the completeness of HARP records in respect research registration.

Appendix 1

Extract from the Favourable Opinion letter

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.