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80% of clinical trials in the UK are registered on publicly accessible research registries

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Research

80% of clinical trials in the UK are registered on publicly accessible research registries

Carla Denneny[1], Sue Bourne[1], Simon E Kolstoe[2]

1. Health Research Authority, Skipton House, London, SE1 6LH, UK
2. School of Health Sciences & Social Work, University of Portsmouth, PO1 2DY, UK

Correspondence to:
Dr Simon Kolstoe; simon.kolstoe@port.ac.uk

Abstract

Objective To determine levels of public registration for clinical trials reviewed and approved by research ethics committees in the United Kingdom.

Study design Audit of records

Setting Clinical trials receiving a favourable ethics opinion between 01 January 2016 and 30 June 2016

Main outcome measures Correlation between trials on the HRA maintained database and any primary registry entry on the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), or clinicaltrials.gov (this is not a primary WHO registry but is an International Committee of Medical Journal Editors (ICJME) acceptable registry) as of 29th August 2017 (14 to 20 months after the favourable ethics committee opinion).

Results Over the study period 1014 trials received a favourable ethics opinion, with 397 registered on EudraCT and 18 trials with an agreed HRA clinical trial registration deferral in place. Excluding these trials, the total number subsequently requiring registration was 599, and of these 405 were found to be registered. Follow up with the 194 investigators or sponsors of trials not found to be registered produced 121 responses with a further 10 trials having already registered, 55 commitments to register, and a variety of other responses. The overall registration rate was therefore 80% (the 18 studies with deferrals were considered not registered).

Conclusions Despite researchers and sponsors being reminded that registration of clinical trials is a condition of the research ethics committee (REC) favourable opinion when they receive the letter from the REC, a fifth of clinical trials either had not registered, or their registration could not easily be found 14 to 20 months after receiving the letter. Although there are positive indications of a culture change towards greater registration, more can be done to increase trial registration.

Key Words: Registration; Transparency; Research Registry; Research Ethics; Regulator
Word count: 3,914

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Strengths and Limitations of this Study

- In the UK the Health Research Authority (HRA) is the regulator that runs research ethics committees (RECs) and has required registration of all clinical trials since 2013.
- By comparing the HRA records with public research registries we have been able to accurately determine clinical trial registration rates.
- By comparing records held by a regulator with publicly accessible registries we have for the first time produced a "true" trial registration rate for the UK.
- Only a subset of records rather than the whole HRA database has been used due to legacy database issues.

Introduction

In England the Health Research Authority (HRA) is the administrative body that convenes and organises research ethics committees (RECs) authorised to review studies involving human participants that take place within the National Health Service (NHS) as well as falling under various legislation [1]. As of 30th September 2013 it has been a UK policy condition of a favourable ethics opinion that all clinical trials are registered on a publicly accessible database [2]. This should ideally occur before the first participant is recruited in accordance with the Declaration of Helsinki [3], or no later than 6 weeks after recruitment of the first participant. The requirement was a response to calls by groups such as the Cochrane Collaboration [4], the AllTrials campaign [5] and the World Health Organisation [6] who have argued convincingly for transparency around clinical trials in order to ensure that valuable research is not lost, and also to prevent unscrupulous researchers or investors hiding clinically or scientifically relevant results for commercial reasons [7]. Trial registration has been required for certain types of trials since 2004 by the EU[8] and since 2007 by the US FDA[9], but in the latter case the full policy is not being enforced [10] even though overall more trials are being registered [11]. Non-regulatory attempts are being made by organisations such as the International Committee of Medical Journal Editors (ICMJE) who are making registration a requirement for publication [12], but national regulatory environments also seem to be important [13,14]. Box 1 provides an extract of the trial registration wording from the REC favourable opinion letter that all researchers receive when a trial receives a favourable opinion in the UK.

Applications to NHS RECs are made using the online Integrated Research Application System (IRAS) [15] which includes a filter question (see box 2) asking researchers to define the type of study or trial. In addition to the UK policy requirement for trial registration, there is a legal obligation for registration placed on Clinical Trials of Investigational Medicinal Products (CTIMPs) under the current European and UK Clinical trials legislation [2]. All trials with a Clinical Trials Authorisation (CTA) certificate have an entry on the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database. However, the EU legislation has a specific exemption for registration details of Phase 1 trials involving healthy volunteers being made public [16], whilst other types of clinical trials are also not covered by the legal requirement to register. In order to determine compliance with its registration policy for these other types of trials the HRA conducted an audit in early 2016 looking specifically at Phase 1, Device and "Other" trial registration. The results of this 2016 audit were published on the HRA website in response to questions raised by a UK government inquiry into research integrity [2]. The inclusion criteria included Phase 1 CTIMPs receiving a favourable opinion between 30th September 2013 (when the requirement to register was put in place) and June 2015, and medical device and "other" trials/studies receiving a favourable opinion between January and

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June 2015. A registration rate of 63% was found for Phase 1 trials, and 48% for both medical devices and "Other" trials. These registration rates jumped to 77% for Phase 1, 85% for Medical Devices and 80% for "other" following email contact from the HRA reminding sponsors that registration was a condition of their favourable ethics opinion. This led the authors of the audit concluding that more was needed to be done by the HRA to highlight the registration requirements to sponsors. Efforts centred around training events and updating the wording on the IRAS form, although it was noted that there was likely to be a natural lead-in period as sponsors and researchers became more used to the new registration requirement.

This paper describes a second more systematic attempt to determine registration rates for Phase 1, medical devices and "other" clinical trials receiving a favourable opinion from RECs a number of years after the registration requirement came into force.

Box 1: Extract from the Favourable Opinion letter received by all investigators

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.

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Box 2: Filter question 2 of the Integrated Research Application System (IRAS) form

2. Select one category from the list below:

- ☐ 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
- ☐ Basic science study involving procedures with human participants
- ☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- ☐ Study involving qualitative methods only
- ☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- ☐ Study limited to working with data (specific project only)
- ☐ Research tissue bank
- ☐ Research database

If your work does not fit any of these categories, select the option below:

- ☐ Other study

Methods

Inclusion criteria

This study included all applications to UK RECs during the period 01 January 2016 to 30 June 2016 where the investigator or research team had selected one of the first four options in the IRAS filter question 2 (defining the work as a clinical trial), and the trials had then ultimately received a favourable opinion from a UK REC. Studies with a legal requirement for a public registration on EudraCT (mainly Phase II, III and IV CTIMPs) were marked as already registered.

Extracting data from the HRA Assessment Review Portal (HARP)

A management information report was extracted from the HRA's HARP database to identify trials within the scope of the study. There are specific data fields on HARP recording the research reference numbers including registration number for trials registered on EudraCT, clinicaltrials.gov and/or the International Standard Randomised Controlled Trial Number Registry (ISRCTN), as well as an '*other reference numbers*' field. This information is populated on HARP either through direct import from the IRAS application (data collected via question A5-1 of application prepared in IRAS) or as manual input by the REC Manager when they are advised of registration.

Initial Trial registration searches

For trials without a registration number logged on HARP, a registration search was conducted in August 2017 using the full trial title, and if the trial could not be located with this, the short title and REC Reference number. The manual searches via the Google search engine sought to locate the clinical trial on a publicly accessible registry. For the purposes of this search the standard applied was registration in any primary registry on the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), or clinicaltrials.gov (this is not a

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primary WHO registry but is an International Committee of Medical Journal Editors (ICJME) acceptable registry) [17]. If the trial was located the registration details (name of registry and registration number) were logged and HARP updated (for future reference if required).

Follow up for trials not found

If a registry entry could not be located using either the HARP record or manual searches then the Chief Investigator and Sponsor were contacted via email (for Phase 1 trials the Chief Investigator only was contacted) and asked to provide registration details or a reason for registration having not taken place. Only a single email was sent with no reminders. Responses obtained over the following couple of weeks were recorded and HARP was updated where registration information was provided. Responses were reviewed and categorised to determine broad themes. If an email exchange was held with the applicant the response category was updated to reflect the final response (e.g. if an applicant initially thought there was no requirement to register their trial but then did agree to register after receiving further guidance from the HRA then the trial was recorded as "will register").

Patient and Public Involvement

Patients and or public were not directly involved in the design of this work. However, the Health Research Authority convenes a "Transparency Forum" with representatives from industry, patient groups and the wider research community. This forum advises the HRA on all aspects relating to research transparency including the demand for this work.

Results

Data mining

1014 trials were initially identified using HARP, of which 397 were CTIMPs (Phase II, III and IV) already registered on EudraCT. Of the remaining 617 trials, 18 were trials with an agreed registration deferral. This deferral is allowed by the HRA in instances where public details of a (mainly Phase I but occasionally device trial) might be considered commercially confidential, although there is still the expectation that the trial will be registered on a publicly accessible registry when the reason for the deferral is no longer valid, or immediately should the trial be terminated early for safety reasons. After these exclusions 599 trials remained. Registration records could be found on either HARP or through the manual search for 405 trials, leaving 194 unregistered trials (in addition to the 18 with deferrals). Data is summarised in Figure 1, Table 1 and Table 2.

	Phase 1	Devices	Others	Total
Trials with a favourable opinion	84	206	327	617
Trials with HRA agreed deferral	17	1	0	18
Total number of trials known to be registered prior to contacting researchers	58	138	209	405
Total number of trials **NOT** known to be registered prior to contacting researchers	9	67	118	194

Table 1: *Number of included clinical trials by study type*

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	Phase 1	Devices	Other	Total
Number of eligible trials (excluding 18 trials with deferral)	67	205	327	599
Registration details found on HRA database (total)	**8**	**59**	**43**	**110**
• ISRCTN	0	1	17	18
• clinicaltrials.gov	8	57	25	90
• Other*	0	1	1	2
Registration details found after manual search (total)	**50**	**79**	**166**	**295**
• ISRCTN	1	13	79	93
• clinicaltrials.gov	49	66	85	200
• Other*	0	0	2	2
Total found to be registered	**58 (87%)**	**138 (67%)**	**209 (64%)**	**405 (68%)**
• ISRCTN	1 (2%)	14 (10%)	96 (46%)	111 (27%)
• clinicaltrials.gov	57 (98%)	123 (89%)	110 (53%)	290 (72%)
• Other*	0 (0%)	1 (1%)	3 (1%)	4 (1%)

Table 2: *Location of registration for Phase I, Devices and Other trials, and how the registrations were found. Figures in parenthesis are percentages rounded to the nearest whole number. * The Australian New Zealand Clinical Trials Registry (ANZCTR), EU Clinical Trials Register, German Clinical Trials Register (GermanCTR)*

84 Phase 1 trials were identified of which 17 had an agreed HRA clinical trial registration deferral. Of the registered Phase 1 trials (n=58) most were registered on clinicaltrials.gov and only one the ISRCTN registry. Eight trials were identified as being registered through the HARP data export and a further 50 were identified through manual searches.

206 device trials were identified with one having an agreed HRA clinical trial registration deferral in place. Of the device trials registered (n=138) the majority were again registered on clinicaltrials.gov with 10% on the ISRCTN registry. One trial was register on the EU Clinical Trials Register (this is unusual for a device trial). 59 registrations were identified through the HARP data export and an additional 79 were located through manual searches.

327 'Other' clinical trials were included. None of these had a registration deferral in place. Of those registered (n=209) just over 50% were on clinicaltrials.gov, and just under half (46%) were on the ISRCTN registry. A small proportion of this trial type (1.4%) were registered on The Australian New Zealand Clinical Trials Registry (ANZCTR), and the German Clinical Trials Register (GermanCTR). 43 registrations were found through the HARP data export and a further 166 through manual searches.

Investigator follow-up

194 follow up emails were then sent to Chief Investigators/Sponsors of trials that we could not find registration details for to request confirmation of whether the trial has been registered and if not, what the reason for this was. 121 responses were received and categorised based on the feedback (Table 3). Some respondents queried the requirement to register. A reply was sent to clarify the HRA position on trial registration and a number of respondents sent a further response.

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	Phase 1	Devices	Other	Total
Number contacted by email	9	67	118	194
No response (percentage)	4 (44%)	26 (39%)	43 (36%)	73 (38%)
Response	**5 (56%)**	**41 (61%)**	**75 (64%)**	**121 (62%)**
• *Will register*	0	8	26	34
• *Study did not proceed**	2	6	7	15
• *Registered (awaiting reference number)*	0	5	6	11
• *Applicant claimed not a clinical trial*	0	2	8	10
• *Now registered (following email)*	0	3	7	10
• *Already registered (not found in initial search)*	2	5	3	10
• *Registered on other database or website***	1	4	6	11
• *Study not started*	0	4	5	9
• *Registered on NIHR portfolio*	0	2	5	7
• *On AL – will deal with on return (but no subsequent response)*	0	1	2	3
• *Stated in A50 would not register*	0	1	0	1

Table 3: *Summary of responses to follow up emails requesting confirmation of trial registration. *Includes trials that were terminated or suspended. **Two 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 webpage which included the study title only. Other*

Nine Chief Investigators of Phase 1 trials 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 trials were reported to be registered but were not identified through the initial search (this is likely due to variations in the trial title on HARP and the registry), two trials were reported to have not proceeded, and one trial reported to have registered on the EudraCT database and the results been posted there. This respondent also referenced the trial details being publicly available on the HRA website.

67 Chief Investigators and Sponsors were contacted for device trials after their trial could not be located on a registry. 41 responses were received. Nearly 20% responded to say that they would register the trial, most commonly specifying clinicaltrials.gov or the ISRCTN Registry. 12% of respondents (n=5) advised that they had registered and were awaiting the registration number. 12% of respondents also stated that their trial was already registered (despite not being found on HARP or through our initial manual search), but provided valid 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. Two respondents reported to have registered on the NIHR portfolio and another respondent advised that their trial was not yet registered but "intended to follow normal guidance from NIHR about public accessibility". At least 7 respondents initially claimed that their trial was not a clinical trial (e.g. their response stated that the trial was an observation or feasibility trial and therefore they did not consider it as a clinical trial). One respondent noted that their local R&D team advised that registration was not necessary as the trial was not a clinical trial. Of the respondents that initially claimed their trial was not a clinical trial, only 2 respondents did not send a further email to confirm that they would register the trial. Four respondents replied with names of websites / databases as to where their trial was registered (Table 4).

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118 Chief Investigators and Sponsors of "Other" clinical trials were contacted after their trial could not be found on a registry. 75 responses were received. Over a third of replies advised that they would register the trial. 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*". Five respondents reported to have registered on the NIHR Clinical Research Network (CRN) Portfolio. Six respondents replied with names of websites / databases as to where their trial was registered (Table 4). Three respondents advised that their trial was already registered (these were not found through the initial manual 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 trial was not a clinical trial. Examples of trial types where the applicant claimed their trial was not a clinical trial included single case design student project, feasibility study, small single arm observational and qualitative interview study. A number of respondents advised that the trial 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 claimed they had inadvertently selected the incorrect study type on the IRAS application form. One response stated 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.*" Two 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 trial or had since registered. A number of respondents asked for additional guidance on how to register and which registries were appropriate for their trial 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?"*

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/
University of Sheffield post-graduate research database: https://www.sheffield.ac.uk/medicine/prospectivepg/taught/mmedsci/currentresearch
Scottish Pulmonary Vascular Unit: www.spvu.co.uk
Open science framework website. https://osf.io/sd4yh/ (log in details required)
Public Health Wales Research and Development Activity webpage
The Health Foundation www.health.org.uk
Various Trusts/intranet R&D pages

Table 4: *Alternative databases or registries named by correspondents.*

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Discussion

Compared to the HRA's registration audit in 2016 we found Phase 1 registration rates up from 63% to 87%, medical device trials up from 48% to 67% and "Other" trials up from 48% to 64%. These results are encouraging as they show there is an upward trend in registration for all types of clinical trials examined here, suggesting a possible cultural shift within the trialist community. For instance, it is likely that the Phase 1 registrations are higher because of awareness amongst industry sponsors of the legal obligation to publicly register Phase II, III and IV clinical trials, and thus the inclusion of public trial registration as a standard function of Contract Research Organisations tasked with overseeing the governance aspects of trial preparation. Likewise a number of phone-calls were made to the HRA following the email contact in the previous audit to query what was being asked, whilst none were reported during the course of this study. Following our email contact with investigators a further 10 studies were found to be previously registered (but not found in our manual search due to discrepancies in study titles and errors in reference numbers) giving slightly improved registration rates of 90% for Phase 1, 70% for Medical Devices and 65% for "Other". These figures represent the registration rate at the time of the study and do not include subsequent registrations that occurred after the sponsors and investigators had been chased. The previous HRA audit found registrations increased up to 77% (Phase 1), 85% (Devices) and 80% (Other) after chasing whilst the approximately equivalent statistics from our study were 91%, 77% and 87%. Here it is interesting to note that the Phase 1 registrations and "Other" registrations were higher, whilst the Device registrations were down slightly. Whilst it is encouraging that more registrations occur following a simple email contact, the ambition is not to have to follow up in this way.

When including the 397 trials registered on EudraCT, the overall registration rate for the studies included in our search criteria was 80%. For the purpose of calculating this percentage we decided to classify the 18 studies with valid deferrals as "not registered". This figure is broadly consistent with other studies [13,18], but is the first time a figure like this has been calculated for studies having been reviewed by RECs in the UK. This is significant because most clinical trials fall under legislation requiring them to be reviewed by UK RECs and, as a result, the REC records contain an accurate account of all trials conducted in the UK. Previously it has been very difficult for researchers to discover whether trials have even occurred as often the only record is the registry record itself. Our method of comparing data held by a regulator with registry entries is extremely effective at determining true registration rates, and the numbers reported here represents possibly the first report of a "true" registration rate, certainly at a national level.

The response rate from investigators and sponsors was also encouraging especially as most responses were received within a week. Overall the responses and reasons given for not registering were in line with other studies [14]. It was concerning that twenty of the 194 emails sent were undeliverable, indicating out of date contact information in the HARP database. A number of respondents also claimed that they had picked the wrong box on the application form, again showing that the information contained within HARP is not always accurate. Of the other respondents, 65 trials were either registered or committed to register soon after receiving our email, whilst another 18 thought they had registered (although these were not on the approved registries), making up 42 % of the studies contacted by email. Unfortunately no answer was received for 38% (73 trials) contacted by email, whilst 13% (25 trials) thought that they no longer needed to register due to either not conducting the trial, or claiming that it

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was not a clinical trial. Of most concern was the one study that stated they would not register; this is an issue that probably should have been discussed by the ethics committee when they originally reviewed the trial.

A wider issue of note concerns the 10 studies that investigators claimed were not clinical trials and therefore did not require registration. Although it is not currently UK policy condition of favourable ethics opinion that trials not in the top four categories of the IRAS filter question 2 are registered, it is difficult to see how this can be justified ethically. Whilst clinical trials and especially CTIMPs represent the most medically risky trials as far as participants are concerned, wasting research money and effort by not adequately reporting the existence of studies on a publicly accessible register is also highly problematic from an ethics perspective [19][20]. Here it is encouraging that organisations such as "Research Registry" [21] exist, enabling research of any type to be registered. More could be done to raise awareness of resources such as this because anecdotal experience of asking researchers during ethics committee meetings about study registration indicates that some investigators claim they do not know where they can register their research. Whilst registering research projects in and of itself will not prevent research waste, it is an important first step towards making research transparent because it allows future researchers to at least search out results, or even contact those who have conducted similar studies in the past, to ensure they are not duplicating efforts and thus wasting resources or participant's time [22].

The HARP database includes full copies of the IRAS form filled out by the research team with two key questions regarding research registration. Question A5-1 asks for research reference numbers including 'registry reference numbers' and gives a variety of options and types of reference numbers along with the text:

> *"The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry"*

The same text is replicated many pages later in the 'Publication and Dissemination' section of the form where Question A50 asks "Will the research be registered on a public database?", provides 'yes' and 'no' boxes, and then asks for details especially if the no box is checked. Although the guidance notes do remind researchers to also add registry numbers in section A5-1, the replication in IRAS is perhaps unfortunate. RECs have been encouraged to pay special attention to these sections and explicitly ask researchers about registration, but given that these sections were empty or included a variety of ambiguous numbers including local reference numbers and insurance numbers, this may not be happening. Indeed the fact that a manual search needed to be used alongside the information contained within these sections for 295 studies demonstrate that this data field is not being appropriately populated within the HARP database.

Putting the full trial title, or often the abbreviated trial title, into the Google search engine proved surprisingly effective for identifying registered studies, and there were only ten cases where this did not work (and registration was subsequently confirmed by email). This is again a positive finding as it means that trial details can be found by non-expert searchers using a

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popular and accessible search engine. Again, it is concerning that 36% (295 out of 802) of registered trials did not have their registration numbers correctly recorded in the HARP database. Although registration numbers may not legitimately be available at the time of REC review, it would be fairly trivial to subsequently update the HRA and RECs either in the response letter to the REC review or through a minor amendment. This is an area of improvement that the HRA may want to look at.

In conclusion, the study reported here represents the first systematic attempt to compare confidential records of clinical trials held by a national regulator with public trial registries. Registration rates have improved from initial audit figures provided by the HRA, and it is heartening to see more evidence of a culture change within the trialist community towards greater registration [11]. However, trial registration only really provides evidence that a trial has occurred. Whilst this is very important, the next step must be to ensure that trials publish their results no matter if they are positive or negative. There are ongoing discussions concerning what appropriate publication looks like [23–25], ranging from summary results posted on trial registries, through to peer reviewed journal reports, to the full release of suitably anonymised patient level data [26–28]. We do not propose an answer to this publication problem, but in the meantime the HRA and others will continue to push for 100% registration, and perhaps also look to expand this registration requirement to other types of studies reviewed by RECs.

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Competing interests: CD and SB were employed by the HRA during the audit, although CD has since left the HRA. SEK chairs an HRA research ethics committee, is a member of the HRA's Confidentiality Advisory Group and is an academic member of both the HRA's National Research Ethics Committee Advisors Panel (NREAP) and its Transparency Forum.

Data: The initial audit reports that this study is based on is available on the HRA website

Patient consent: Not required.

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Figure Legends:

Figure 1: Summary of search results: A) Research applications receiving a final favourable opinion between 1st January and 30th June 2016, falling into the first 4 categories of IRAS filter question 2. B) Total number of trials registered (812) vs unregistered (202 including 18 with valid deferrals).

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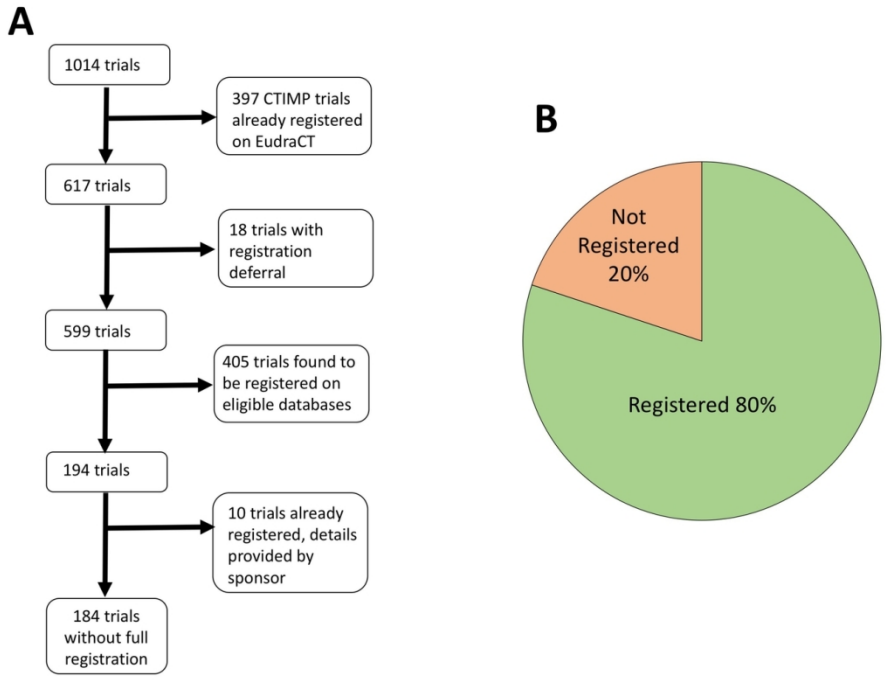

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Research

Registration audit of clinical trials approved by UK Research Ethics Committees

Carla Denneny[1], Sue Bourne[1], Simon E Kolstoe[2]

1. Health Research Authority, Skipton House, London, SE1 6LH, UK
2. School of Health Sciences & Social Work, University of Portsmouth, PO1 2DY, UK

Correspondence to:
Dr Simon Kolstoe; simon.kolstoe@port.ac.uk

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Abstract

Objective To determine levels of public registration for a cohort of clinical trials reviewed and approved by research ethics committees in the United Kingdom.

Study design Audit of records

Setting Clinical trials receiving a favourable ethics opinion between 01 January 2016 and 30 June 2016

Main outcome measures Correlation between trials on the UK research ethics committee database and any primary registry entry on the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), or clinicaltrials.gov as of 29th August 2017 (14 to 20 months after the favourable ethics committee opinion).

Results Over the study period 1014 trials received a favourable ethics opinion, with 397 (39%) registered through EudraCT and 18 trials with an agreed clinical trial registration deferral in place. Excluding these trials, the total number subsequently requiring registration was 599, and of these 405 (40%) were found to be registered. Follow up with the 194 investigators or sponsors of trials not found to be registered produced 121 responses with a further 10 (1%) trials having already registered, 55 commitments to register, and a variety of other responses. The overall registration rate was therefore 80%.

Conclusions Despite researchers and sponsors being reminded that registration of clinical trials is a condition of the research ethics committee (REC) favourable opinion when they receive the decision letter from the REC, a fifth of clinical trials either had not registered, or their registration could not easily be found 14 to 20 months after receiving the letter. The methodology trialled here proved effective, and although there are positive indications of a culture change towards greater registration, our results show that more must be done to increase publicly accessible trial registration.

Key Words Registration; Transparency; Research Registry; Research Ethics; Regulator
Word count 4,056

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Article Summary

- Registration of clinical trials on publicly accessible research registries is a matter of good research ethics. If clinical trials are not registered research organisations can hide results or trials that they do not like.
- Since 2013 UK policy has required registration of all clinical trials as a condition of research ethics committee (REC) favourable opinion.
- By comparing the REC records with publicly accessible research registries we have been able to accurately determine clinical trial registration rates.

Strengths & Limitations of the Study

- By comparing records held by a regulator with publicly accessible registries we have for the first time produced a "true" trial registration rate for the UK.
- A limitation comes from the use of only a subset of records rather than the whole REC database.

Introduction

As of 30th September 2013 it has been a UK policy condition of a favourable research ethics committee (REC) opinion that all clinical trials are registered on a publicly accessible database (see box 1 for the wording from the favourable opinion letter provided to researchers) [1]. This should ideally occur before the first participant is recruited in accordance with the Declaration of Helsinki [2], or no later than 6 weeks after recruitment of the first participant. The requirement was a response to calls by groups such as the Cochrane Collaboration [3], the AllTrials campaign [4] and the World Health Organisation [5] who have argued convincingly for transparency around clinical trials in order to ensure that valuable research is not lost, and also to prevent unscrupulous researchers or investors hiding clinically or scientifically relevant results for commercial reasons [6]. Trial registration has been required for certain types of trials since 2004 by the EU [7] and since 2007 by the US FDA [8], but in the latter case the full policy is not being enforced [9] even though overall more trials are being registered [10]. Non-regulatory attempts are being made by organisations such as the International Committee of Medical Journal Editors (ICMJE) who are making registration a requirement for publication [11], but national regulatory environments also seem to be important [12,13]. Box 1 provides an extract of the trial registration wording from the REC favourable opinion letter that all researchers receive when a clinical trial is approved in the UK.

Applications to NHS RECs are made using the online Integrated Research Application System (IRAS) [14] which includes a filter question (see box 2) asking researchers to define the type of study or trial. In addition to the UK policy requirement for trial registration, there is a legal obligation for registration placed on Clinical Trials of Investigational Medicinal Products (CTIMPs) under the current European and UK Clinical trials legislation [1]. All trials with a Clinical Trials Authorisation (CTA) have an entry on the European Union Drug Regulating Authorities Clinical Trials database (EudraCT) which is used to populate the publicly accessible EU Clinical Trial Register. However, the EU legislation has a specific exemption for registration details of Phase I trials involving healthy volunteers being made public [15], while other types of clinical trials are also not covered by the legal requirement to register. In order to determine compliance with its registration policy for these other types of trials the Health Research Authority (HRA) conducted an audit in early 2016 looking specifically at Phase I, Device and

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"Other" trial registration (although most of the HRA's functions apply to research undertaken in England, the HRA also works closely with the other countries in the UK (Scotland, Wales and Northern Ireland) to provide a UK-wide system including a research ethics service, so was able to audit UK wide records). The results were published on the HRA website in response to questions raised by a UK government inquiry into research integrity [1]. The audit authors concluded that more was needed to be done to highlight the registration requirements to sponsors, with subsequent HRA efforts centred around improved training events and updating the wording on the application form. This paper now describes a second more systematic attempt to determine registration rates for Phase I, medical devices and "other" clinical trials receiving a favourable opinion from RECs three years after the registration requirement came into force.

Box 1: Extract from the Favourable Opinion letter received by all investigators

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly 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.

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Box 2: Filter question 2 of the Integrated Research Application System (IRAS) form

2. Select one category from the list below:

- ☐ 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
- ☐ Basic science study involving procedures with human participants
- ☐ Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
- ☐ Study involving qualitative methods only
- ☐ Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)
- ☐ Study limited to working with data (specific project only)
- ☐ Research tissue bank
- ☐ Research database

If your work does not fit any of these categories, select the option below:

- ☐ Other study

Methods

Inclusion criteria

This study included all applications to UK RECs during the period 01 January 2016 to 30 June 2016 where the investigator or research team had selected one of the first four options in the IRAS (Integrated Research Application form) filter question 2 (defining the work as a clinical trial), and the trials had then ultimately received a favourable opinion from a UK REC. Studies with a legal requirement for a public registration on EudraCT (mainly Phase II, III and IV CTIMPs) were marked as already registered.

Extracting data from the HRA Assessment Review Portal (HARP)

A management information report was extracted from the HARP database[16] to identify trials within the scope of the study. There are specific data fields on HARP recording the research reference numbers including registration number for trials registered on EudraCT, clinicaltrials.gov and/or the International Standard Randomised Controlled Trial Number Registry (ISRCTN), as well as an '*other reference numbers*' field. This information is populated on HARP either through direct import from the IRAS application (data collected via question A5-1 of application prepared in IRAS) or as manual input by the REC Manager when they are advised of registration.

Initial Trial registration searches

For trials without a registration number logged on HARP, a registration search was conducted in August 2017 using the full trial title, and if the trial could not be located with this, the short title and REC Reference number. The manual searches via the Google search engine sought to locate the clinical trial on a publicly accessible registry. For the purposes of this search the standard applied was registration in any primary registry on the World Health Organization

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(WHO) International Clinical Trials Registry Platform (ICTRP) [17], or clinicaltrials.gov (this is not a primary WHO registry but is an International Committee of Medical Journal Editors (ICJME) acceptable registry) [18]. If the trial was located the registration details (name of registry and registration number) were logged and HARP updated (for future reference if required).

Follow up for trials not found

If a registry entry could not be located using either the HARP record or manual searches then the Chief Investigator and Sponsor were contacted via email (for Phase I trials the Chief Investigator only was contacted) and asked to provide registration details or a reason for registration having not taken place. Only a single email was sent with no reminders. Responses obtained over the following couple of weeks were recorded and HARP was updated where registration information was provided. Responses were reviewed and categorised to determine broad themes. If an email exchange was held with the applicant the response category was updated to reflect the final response (e.g. if an applicant initially thought there was no requirement to register their trial but then did agree to register after receiving further guidance from the HRA then the trial was recorded as "will register").

Patient and Public Involvement

The need for the audit described here was discussed at the HRA's partner "Transparency Forum" whose aim is to promote research transparency and understand opportunities, obstacles and levers[19]. Preliminary results were made available on the HRA website in response to questions from the UK House of Commons Science and Technology Select Committee[20].

Results

Data mining

1014 trials were initially identified using HARP, of which 397 were CTIMPs (Phase II, III and IV) already registered through EudraCT. Of the remaining 617 trials, 18 were trials with an agreed registration deferral. This deferral is allowed by the HRA in instances where public details of a (mainly Phase I but occasionally device trial) might be considered commercially confidential, although there is still the expectation that the trial will be registered on a publicly accessible registry when the reason for the deferral is no longer valid, or immediately should the trial be terminated early for safety reasons. After these exclusions 599 trials remained. Registration records could be found on either HARP or through the manual search for 405 trials, leaving 194 unregistered trials (in addition to the 18 with deferrals). Data is summarised in Figure 1, Table 1 and Table 2.

	Phase 1	Devices	Others	Total
Trials with a favourable opinion	84	206	327	617
Trials with HRA agreed deferral	17	1	0	18
Total number of trials known to be registered prior to contacting researchers	58	138	209	405
Total number of trials **NOT** known to be registered prior to contacting researchers	9	67	118	194

Table 1: *Number of included clinical trials by study type*

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	Phase 1	Devices	Other	Total
Number of eligible trials (excluding 18 trials with deferral)	67	205	327	599
Registration details found on HRA database (total)	**8**	**59**	**43**	**110**
• ISRCTN	0	1	17	18
• clinicaltrials.gov	8	57	25	90
• Other*	0	1	1	2
Registration details found after manual search (total)	**50**	**79**	**166**	**295**
• ISRCTN	1	13	79	93
• clinicaltrials.gov	49	66	85	200
• Other*	0	0	2	2
Total found to be registered	**58 (87%)**	**138 (67%)**	**209 (64%)**	**405 (68%)**
• ISRCTN	1 (2%)	14 (10%)	96 (46%)	111 (27%)
• clinicaltrials.gov	57 (98%)	123 (89%)	110 (53%)	290 (72%)
• Other*	0 (0%)	1 (1%)	3 (1%)	4 (1%)

Table 2: *Location of registration for Phase I, Devices and Other trials, and how the registrations were found. Figures in parenthesis are percentages rounded to the nearest whole number. * The Australian New Zealand Clinical Trials Registry (ANZCTR), EU Clinical Trials Register, German Clinical Trials Register (GermanCTR)*

84 Phase I trials were identified of which 17 had an agreed clinical trial registration deferral. Of the registered Phase I trials (n=58) most were registered on clinicaltrials.gov and only one the ISRCTN registry. Eight trials were identified as being registered through the HARP data export and a further 50 were identified through manual searches.

206 device trials were identified with one having an agreed clinical trial registration deferral in place. Of the device trials registered (n=138) the majority were again registered on clinicaltrials.gov with 10% on the ISRCTN registry. One trial was registered on the EU Clinical Trials Register (this is unusual for a device trial). 59 registrations were identified through the HARP data export and an additional 79 were located through manual searches.

327 'Other' clinical trials were included. This category includes surgery, radiotherapy, imaging investigations, mental health investigations or therapies, physiological investigations, trials of products not defined as medicines or medical devices (e.g. nutritional) and complementary or alternative therapies [21]. None of these had a registration deferral in place. Of those registered (n=209) just over 50% were on clinicaltrials.gov, and just under half (46%) were on the ISRCTN registry. A small proportion of this trial type (1.4%) were registered on The Australian New Zealand Clinical Trials Registry (ANZCTR), and the German Clinical Trials

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Register (GermanCTR). 43 registrations were found through the HARP data export and a further 166 through manual searches.

Investigator follow-up

194 follow up emails were sent to Chief Investigators/Sponsors of trials that we could not find registration details for to request confirmation of whether the trial has been registered and if not, what the reason for this was. 121 responses were received and categorised (Table 3). Some respondents queried the requirement to register. A reply was sent to clarify the UK policy position on trial registration and a number of respondents sent a further response. This email responses identified a further 10 trial that had been registered, giving an overall total of 812 out of 1014 trials with a valid registration (80%).

	Phase 1	Devices	Other	Total
Number contacted by email	9	67	118	194
No response (percentage)	4 (44%)	26 (39%)	43 (36%)	73 (38%)
Response	**5 (56%)**	**41 (61%)**	**75 (64%)**	**121 (62%)**
• *Will register*	0	8	26	34
• *Study did not proceed**	2	6	7	15
• *Registered (awaiting reference number)*	0	5	6	11
• *Applicant claimed not a clinical trial*	0	2	8	10
• *Now registered (following email)*	0	3	7	10
• *Already registered (not found in initial search)*	2	5	3	10
• *Registered on other database or website***	1	4	6	11
• *Study not started*	0	4	5	9
• *Registered on NIHR portfolio*	0	2	5	7
• *On annual leave – will deal with on return (but no subsequent response)*	0	1	2	3
• *Stated in question A50 would not register*	0	1	0	1

Table 3: *Summary of responses to follow up emails requesting confirmation of trial registration. *Includes trials that were terminated or suspended. **Two 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 webpage which included the study title only.*

Nine Chief Investigators of Phase I trials 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 trials were reported to be registered but were not identified through the initial search (this is likely due to variations in the trial title on HARP and the registry), two trials were reported to have not proceeded, and one trial reported to have registered through the EudraCT database and the results been posted there. This respondent also referenced the trial details being publicly available on the HRA website.

67 Chief Investigators and Sponsors were contacted for device trials after their trial could not be located on a registry. 41 responses were received. Nearly 20% responded to say that they would register the trial, most commonly specifying clinicaltrials.gov or the ISRCTN Registry. 12% of respondents (n=5) advised that they had registered and were awaiting the registration number. 12% of respondents also stated that their trial was registered (despite not being found on HARP or through our initial manual search) and provided valid registration details.

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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. Two respondents reported to have registered on the NIHR portfolio and another respondent advised that their trial was not yet registered but "intended to follow normal guidance from NIHR about public accessibility". At least 7 respondents initially claimed that their trial was not a clinical trial (e.g. their response stated that the trial was an observation or feasibility trial and therefore they did not consider it as a clinical trial). One respondent noted that their local R&D team advised that registration was not necessary as the trial was not a clinical trial. Of the respondents that initially claimed their trial was not a clinical trial, only 2 respondents did not send a further email to confirm that they would register the trial. Four respondents replied with names of websites / databases as to where their trial was registered (Table 4).

118 Chief Investigators and Sponsors of "Other" clinical trials were contacted after their trial could not be found on a registry. 75 responses were received. Over a third of replies advised that they would register the trial. 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*". Five respondents reported to have registered on the NIHR Clinical Research Network (CRN) Portfolio. Six respondents replied with names of websites / databases as to where their trial was registered (Table 4). Three respondents advised that their trial was already registered (these were not found through the initial manual 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 trial was not a clinical trial. Examples of trial types where the applicant claimed their trial was not a clinical trial included single case design student projects, a feasibility study, a small single arm observational and qualitative interview study. A number of respondents advised that the trial 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 register after discussions at the REC meeting. A small proportion of responses claimed they had inadvertently selected the incorrect study type on the IRAS application form. One response stated 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* (UK Medicines and Healthcare Products Regulatory Agency) *that it is not a CTIMP and does not require a CTA."* Two 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 trial or had since registered. A number of respondents asked for additional guidance on how to register and which registries were appropriate for their trial 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?"*

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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/
University of Sheffield post-graduate research database: https://www.sheffield.ac.uk/medicine/prospectivepg/taught/mmedsci/currentresearch
Scottish Pulmonary Vascular Unit: www.spvu.co.uk
Open science framework website. https://osf.io/sd4yh/ (log in details required)
Public Health Wales Research and Development Activity webpage
The Health Foundation www.health.org.uk
Various Trusts/intranet R&D pages

Table 4: *Alternative databases or registries named by correspondents.*

Comparison to previous HRA Audit

Compared to the HRA's initial registration audit in early 2016, we found Phase I registration rates up from 63% to 87%, medical device trials up from 48% to 67% and "Other" trials up from 48% to 64%. Following identifying the further 10 registered trials through our email contact with the investigators (not found in our manual search due to discrepancies in study titles and errors in reference numbers) the final registration rates were 90% for Phase I, 70% for Medical Devices and 65% for "Other". These figures represent the registration rate at the time of this study being started and do not include subsequent registrations that occurred after the sponsors and investigators had been reminded by email. The previous HRA audit found registrations increased up to 77% (Phase I), 85% (Devices) and 80% (Other) after email follow-up, while the approximately equivalent statistics from our study were 91%, 77% and 87% (figure 2).

Discussion

Including the 397 trials registered through EudraCT the overall registration rate for the studies included in our search criteria was 80%. For the purpose of calculating this percentage we decided to classify both the 18 studies with valid deferrals and the nine that had not yet started as "not registered" (although we acknowledge that these 27 studies have no policy

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requirement for registration). This 80% figure is broadly consistent with other studies [12,22], but is the first time this has been calculated for studies having been reviewed by RECs in the UK. This is significant because clinical trials conducted in the UK fall under legislation or policy requiring them to be reviewed by RECs and, as a result, the REC records contain the only complete record of all clinical trials. Previously it has been very difficult for researchers and systematic reviewers to discover whether trials have even occurred as often the only public record is the registry itself. By auditing confidential data held by a regulator and then comparing it with the public registry entries, the numbers reported here represent the first "true" registration rate (certainly at a national level).

The increase in registration rates compared to the 2016 HRA audit is encouraging as they show there is an upward trend in registration for all types of clinical trials examined here, suggesting a possible cultural shift within the trialist community. For instance, it is likely that the Phase I registrations are higher because of awareness amongst industry sponsors of the legal obligation to publicly register Phase II, III and IV clinical trials, and thus the inclusion of public trial registration as a standard function of contract research organisations tasked with overseeing the governance aspects of trial preparation. Likewise a number of phone-calls were made to the HRA following the email contact in the previous audit to query what was being asked, whilst none were reported during the course of this study. It is interesting to note that the Phase I registrations and "Other" registration rates were higher compared to the first audit, but the Device registrations were down slightly. While it is encouraging that more registrations occur following a simple email contact, the ambition is not to have to follow up in this way.

The response rate from investigators and sponsors was also encouraging especially as most responses were received within a week. Overall the responses and reasons given for not registering were in line with other studies [13]. It was concerning that twenty of the 194 emails sent were undeliverable, indicating out of date contact information in the HARP database. A number of respondents also claimed that they had picked the wrong box on the application form, again showing that the information contained within HARP is not always accurate. Of the other respondents, 65 trials were either registered or committed to register soon after receiving our email, while another 18 thought they had registered (although these were not on the approved registries), making up 42% of the studies contacted by email. Unfortunately no answer was received for 38% (73 trials) contacted by email and 8% (15 trials) thought that they no longer needed to register as the trial was not eventually conducted. While we agree that the ethical argument for registering a trial might not be as strong for trials that were never started, we do think that such trials should still be registered with a brief explanation as to why the trial was not conducted so as to avoid future researchers or systematic reviewers trying to track down trial results that never existed. However, of most concern was the study that stated it would not register - this is an issue that probably should have been discussed by the ethics committee when they originally reviewed the trial.

A wider issue of note concerns the 10 studies that investigators claimed were not clinical trials and therefore did not require registration. Although it is not currently a UK policy that studies not in the top four categories of the IRAS filter question two are registered, it is difficult to see how this can be justified ethically. While clinical trials and especially CTIMPs represent the most medically risky studies as far as participants are concerned, research money and effort can also be wasted by not adequately reporting the existence of other types of studies as well [23–25]. This is an issue that needs further consideration, and here it is encouraging that organisations such as "Research Registry" [26] exist that enable research of any type to be registered[27].

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The HARP database includes full copies of the REC application form filled out by the research team with two key questions regarding research registration. Question A5-1 asks for research reference numbers including 'registry reference numbers' and gives a variety of options and types of reference numbers along with the text:

> *"The UK Policy Framework for Health and Social Care Research sets out the principle of making information about research publicly available. Furthermore Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry"*

The same text is replicated many pages later in the 'Publication and Dissemination' section of the form where question A50 asks "Will the research be registered on a public database?", provides 'yes' and 'no' boxes, and then asks for details especially if the 'no' box is checked. Although the guidance notes do remind researchers to also add registry numbers in section A5-1, the replication in IRAS is perhaps unfortunate. RECs have been encouraged to pay special attention to these sections and explicitly ask researchers about registration, but given that these sections were empty or included a variety of ambiguous numbers including local reference numbers and insurance numbers, this may not be happening. Indeed the fact that a manual search needed to be used alongside the information contained within these sections for 295 studies demonstrate that this data field is not being appropriately populated within the HARP database.

Putting the full trial title, or often the abbreviated trial title, into the Google search engine proved surprisingly effective for identifying registered studies, and there were only ten cases where this did not work (and registration was subsequently confirmed by email). This is again a positive finding as it means that trial details can be found by non-expert searchers using a popular and accessible search engine. However, it is concerning that this search helped to identify 36% (295 out of 802) of registered trials with incorrect or absent registration numbers in the HARP database. Although registration numbers may not legitimately be available at the time of REC review, it would be fairly trivial to update RECs either in the response letter to the REC review, or through a subsequent minor amendment. This is an area of improvement that could be looked at, perhaps by requiring an amendment once the registration is confirmed.

One limitation of this audit was only including clinical trials that had been approved in a six month timeframe. This was based on a pragmatic attempt to limit the audit to about 1000 clinical trials in order to determine the practicality of the method and produce a baseline figure. If this audit is to be repeated on a regular basis more resources would be needed to deal with the couple of thousand clinical trials that are reviewed by UK RECs each year. The incompleteness of HARP records coupled with the presence of invalid email addresses also limited the information that could be obtained on each trial, but future work could attempt to determine alternative contacts within sponsoring organisations to obtain definitive data on each and every trial. A further analysis of the unregistered trials could also be interesting as a way of determining whether there are any specific types of trials that are more likely not to register.

Conclusions

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The study reported here represents the first systematic attempt to compare records of clinical trials held by a national regulator with publicly accessible trial registries. Registration rates have improved from initial audit figures provided by the HRA (figure 2), and it is heartening to see more evidence of a cultural change within the trialist community towards greater registration [10]. However, to date the research ethics service has adopted the approach of encouraging greater trial registration through education rather than sanctioning Chief Investigators or Sponsors who do not register trials. It is likely that this situation may soon change based upon recommendations made by the UK House of Commons Science and Technology Committee in their report on Clinical Trials Transparency published in October 2018 [20]. The committee recommended that measures be put in place to ensure 100% of clinical trials get registered. It is difficult to see how this target can be achieved without a more complete audit modelled on the one described here, followed by organisations such as the HRA considering the use of sanctions with sponsors or investigators who are found not to have registered their studies.

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Contributors: CD and SB designed and conducted the audit, and provided an initial report to the HRA. SEK re-analysed the results and wrote the paper.

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Competing interests: CD and SB were employed by the HRA during the audit, although CD has since left the HRA. SEK chairs an HRA research ethics committee, is a member of the HRA’s Confidentiality Advisory Group and is an academic member of both the HRA’s National Research Ethics Committee Advisors Panel (NREAP) and its Transparency Forum. He is on the board of advisors to the Research Registry.

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Data Availability Statement: The initial audit reports that this study is based on are available on the HRA website.

Patient consent: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

Figure Legends:

Figure 1: Summary of search results: A) Research applications receiving a final favourable opinion between 1st January and 30th June 2016, falling into the first 4 categories of IRAS filter question 2. B) Total number of trials registered (812) vs unregistered (202 including 18 with valid deferrals).

Figure 2: Change in registration rates between initial 2016 HRA audit and this audit, illustrating registration rates before and after email contact with researchers. Orange: 2016 HRA audit no email contact; Green: 2016 HRA audit following email contact; Blue: this study prior to email contact; Red: this study following email contact.

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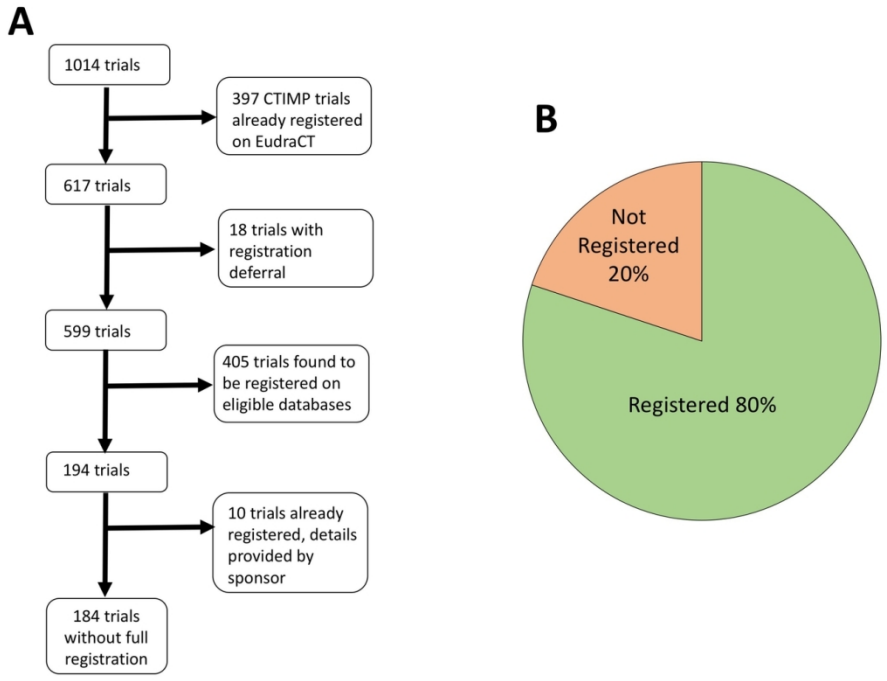

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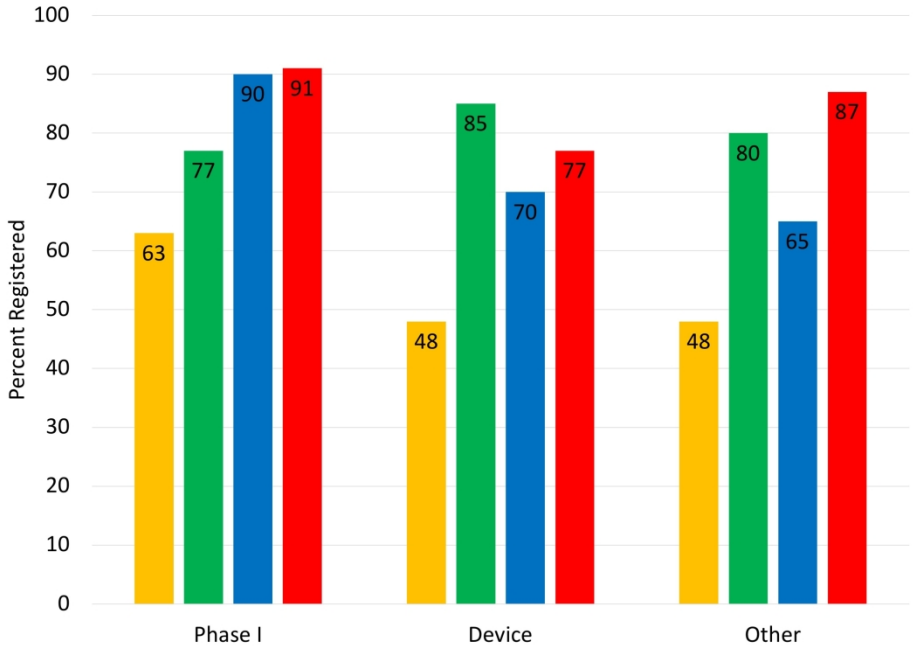

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page numbers in updated manuscript:
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2 & 3
Objectives	3	State specific objectives, including any prespecified hypotheses	Last sentence of introduction (page 3)
Methods			
Study design	4	Present key elements of study design early in the paper	Page 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 4 & 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 3 and Figure 1
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	N/A
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	N/A
Bias	9	Describe any efforts to address potential sources of bias	Page 4 (and limitation discussed in discussion)
Study size	10	Explain how the study size was arrived at	Pages 4 to 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Tables 1, 2 and 3
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 2 & 3
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	Tables 1, 2 and 3
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Pages 4 to 8
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 11 and 12
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.