Author's response to reviews

**Title:** Registration of non-commercial randomised clinical trials: the feasibility of using registration data to monitor trends in the number of trials

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Title page

Title: Registration of non-commercial randomised clinical trials: the feasibility of using these data to monitor the number of trials

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Abstract

Background
Whether the number of randomised clinical trials is rising or falling in the UK is important and controversial. A 2003 analysis suggested that the number of non-commercial trials was declining. The formation of the National Institute for Health Research in 2006 and increased research spending by the Department of Health prompts questions about the number of non-commercial trials.

Methods
UK trials were defined as those with at least one recruitment centre in the UK. Available data on all such trials was obtained from the two relevant registries, the ISRCTN register and US ClinicalTrials.gov. Data on each trial was sorted by year of start and source of funding.

Results
The number of non-commercial trials registered rose from 25 in 1990 to 188 in 1999, and to a peak of 533 in 2003, before falling back to 334 in 2009. These total trials registered was similar to but slightly above those in the 2003 study up to 1998, but then rose sharply to 2003, before falling sharply to 2007. For 2007-09, the number registered to start each year was similar to but slightly above the other main source, the UKCRN database.

Less than 10% of UK trials registered with ClinGov for most years before 2005 but rose thereafter to reach 35% by 2009.

Conclusions
for the periods of overlap, trial registration data provide fairly similar totals to other sources on the number of non-commercial trials commencing each year. The rapid rise and fall in the number of trials registered between 1999 and 2007 was due to those registered as funded by NHS Trusts. As the number of trials registered as funded by NHS Trusts has fallen, the number of UK RCTs registering with ClinGov has increased sharply so that in 2009, 30% of UK trials registering were with ClinGov.

The total number of non-commercial trial starts, excluding those funded by NHS Trusts, has been upward since around 2002. By 2009 the two main funders were NIHR and charities.

The feasibility of using registration data to monitor the number of non commercial trials has been shown but is complicated by the use of two registers, and the need to purchase the data. We recommend an annual report be commissioned to provide data on the total number of non commercial trials registering each year.

Keywords
Trial registration
Non-commercial clinical trials
ISRCTN
ClinGov

Background
Concerns have been raised about a reduced number of clinical trials conducted in the UK, both commercial and non-commercial. However the MHRA, which authorises trials of medicines, has put the number of trials registered as steady at around 1200 per year from 2002 to 2009, split roughly 75% commercial, 25% non-commercial.

Chalmers et al sounded an alarm in 2003 that the number of non-commercial trials in the UK was declining, based on a survey of the main funders. This showed around 150 trials starting in 1997, falling to 40 in 2002. From 2007 the UK Clinical Research Network portfolio database on trials being carried out in the NHS put the number of non-commercial trials starting each year in the UK at around 300.

Registration of clinical trials has become increasingly common due to statutory requirements in the US and for publication in medical journals. The revised 2008 Declaration of Helsinki, states that "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."
Although registration is not compulsory in the UK, clinical governance arrangements from 2004 have required registration.

UK triallists have registered with either the US Clinical Trials Gov Register (ClinGov) and the International Standard Randomised Controlled Trials register (ISRCTN). ClinGov, run by the United States National Library of Medicine was the first online registry for clinical trials and remains most widely used. It traces back to the Health Omnibus Programs Extension Act of 1988 (HOPE or Public Law 100-607) which mandated the development of a database of AIDS Clinical Trials Information System. It was expanded under the Food and Drug Modernization Act of 1997 (FDAMA or Public Act 105-115).

The alternative to the US registry is International Standard Randomised Control Number registry, established in 1998, and run Current Controlled Trials, part of Springer Science+Business Media of which BioMed Central is also part. CCT provides fee and open access to information about ongoing randomised clinical trials. From 2003 an administrative fee has been charged for assigning ISRCTNs to trials. This register is supported by several countries including the UK. From 2004 the UK Department of Health under its research governance framework, contracted with CCT to register trials funded by the HTA programme and ‘those funded at trust level by the NHS R&D Support Funding stream’ ISRCTNs numbers were allocated to all trials funded by previous NHS R&D programmes, and to ‘own account’ trials funded by NHS Trusts. CCT’s evidence to the House of Commons noted that less than 5% of the trials registered on the ISRCTN registry were funded by industry. Industry funded drug trials registered elsewhere. From 2004 all new and ongoing trials involving a Clinical Trial Authorisation form the MHRA had to register with the European database, EudraCT. This database is limited by being confined to drugs and being confidential.

Due to it being the first international register, some UK trials registered with ClinGov before the ISRCTN register was established in 1998. The US register allocates unique 8 digit numbers with the prefix “NCT”, while the ISRCTN registers allocate 8 digit identifiers with the prefix “ISRCTN”. Both the US and UK registers require largely the same data but with one key difference: source of funding is included in the ISRCTN but not the US. Another difference is that ClinGov provides free registration while ISRCTN requires a registration fee. This fee is met by the UK Department of Health for trials funded by it or partner agencies but not for other trials. The website Current Controlled Trials provides online access to both the ClinGov and ISRCTN registers via a meta register. ClinGov had 62,734 trials registered in November 2011 and ISRCTN had 10,153. We used the metaregister to identify UK trials (defined to include all trials with at least one recruitment centre in the UK) by register, to estimate the total number of non-commercial trials over time, and as far as possible to subdivide these by funder type.

Our aim was to establish the number of UK based non-commercial randomised clinical trials registered each year, with cross checks against other sources.

Methods
We compiled a dataset based on non-commercial randomised clinical trials due to start in the UK in any year between 1990 and 2009 from two trial registration databases, the ISRCTN register (www.controlled-trials.com) and the US register ClinicalTrialsGov (http://clinicaltrials.gov/). Data were purchased from CCT on the trials in the ISRCTN database, via a Wessex Institute small research grant. Data on UK trials in ClinGov were downloaded from the website. Data were available from 1990 in both databases due to the forerunner of ClinGov having been established in 1988 and due to data on clinical trials from the National Research Register (Ref), a prior DH database of all Department of Health funded research projects, having been backloaded onto ISRCTN. This enables comparison with Chalmer’s et al whose survey covered trials commencing each year from 1990 to 2003.

We defined UK trials as those trials with at least one centre in the UK. Criteria for eligibility were description a randomised controlled trial, a start date, a sponsor and if available, funder. Duplicates were excluded and the records sorted by year of proposed start of recruitment. Data extraction was carried out by EF, LD, AP and LD. Classification of funders was carried out independently by this group and JR, and differences reconciled through explicit criteria. The number of trials identified was compared with Chalmer’s et al 2003 survey and with the UK Clinical Research Network (UKCRN) portfolio database 2007-9.

Results and discussion
4,569 eligible records were identified as eligible after exclusion of duplicates.
The number of non-commercial trials registered rose from 25 in 1990 to 188 in 1999, and to a peak of 533 in 2003, before falling back to 334 in 2009 (Table 1). Figure 1 shows these total trials registered was similar to but slightly above those in Chalmers et al’s survey of funders for first part of the period (up to 1998), but above Chalmers et al 1999-2003. For 2007-09, the number registered to start each year was similar to but slightly above the UKCRN database.

Table 1 shows where these trials registered. Less than 10% of UK trials registered with ClinGov for most years before 2005 but rose thereafter to reach 35% by 2009.

### Table 1
**Number of UK non-commercial trials registered each year and distribution by ClinGov and ISRCTN. 1990-2009**

<table>
<thead>
<tr>
<th>Year</th>
<th>Number UK trials registered</th>
<th>% registered with ClinGov</th>
<th>% registered with ISRCTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>25</td>
<td>4.0</td>
<td>96.0</td>
</tr>
<tr>
<td>1991</td>
<td>10</td>
<td>0</td>
<td>100.0</td>
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</tr>
<tr>
<td>1993</td>
<td>42</td>
<td>16.7</td>
<td>83.2</td>
</tr>
<tr>
<td>1994</td>
<td>57</td>
<td>7.6</td>
<td>92.4</td>
</tr>
<tr>
<td>1995</td>
<td>132</td>
<td>7.6</td>
<td>92.4</td>
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<tr>
<td>1996</td>
<td>88</td>
<td>6.9</td>
<td>93.1</td>
</tr>
<tr>
<td>1997</td>
<td>132</td>
<td>8.3</td>
<td>91.7</td>
</tr>
<tr>
<td>1998</td>
<td>151</td>
<td>15.1</td>
<td>84.9</td>
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<td>1999</td>
<td>188</td>
<td>8.5</td>
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<td>2000</td>
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<td>94.5</td>
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<td>2001</td>
<td>265</td>
<td>13.6</td>
<td>86.4</td>
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<tr>
<td>2002</td>
<td>447</td>
<td>3.6</td>
<td>96.4</td>
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<td>8.3</td>
<td>91.7</td>
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<td>9.3</td>
<td>90.7</td>
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<td>2005</td>
<td>458</td>
<td>13.5</td>
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<tr>
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<td>434</td>
<td>15.7</td>
<td>84.3</td>
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<tr>
<td>2007</td>
<td>291</td>
<td>31.3</td>
<td>68.7</td>
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<tr>
<td>2008</td>
<td>284</td>
<td>31.7</td>
<td>68.3</td>
</tr>
<tr>
<td>2009</td>
<td>334</td>
<td>35.0</td>
<td>65.0</td>
</tr>
</tbody>
</table>

The source of funding is shown in Table 2. Since ClinGov does not include a field for sources of funding, the funding for trials so registered is classed as Unknown. Due to the increase in the proportion of UK trials registering with ClinGov ‘Unknown’ funding accounted for the largest share, 35% in 2009. The sharp rise in the number of registered trials from 1999 to 2003 was due almost entirely to those registered as funded by NHS Trusts (Figure 2). The proportion so registered jumped from 17% in 1999 to 72% in 2003 before falling back to 18% in 2007. By 2009, the National Institute for Health Research (NIHR), formerly NHS R&D, was the largest funder (25%), followed by the charities (17%). Cancer Research UK was followed by the Arthritis Research Council, the British Heart Foundation and the Wellcome Trust.

### Table 2
**Non-commercial randomised clinical trials UK, number registered each year by funder, 1990-2009**

<table>
<thead>
<tr>
<th>Funder</th>
<th>CHARITY</th>
<th>MRC</th>
<th>NHSR&amp;D/NIHR</th>
<th>NHS Trusts</th>
<th>OTHER</th>
<th>UNKNOWN</th>
<th>Grand Total</th>
</tr>
</thead>
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<td>14</td>
<td>7</td>
<td>3</td>
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<td>1</td>
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<td>85</td>
<td>33</td>
<td>1</td>
<td>16</td>
<td>188</td>
</tr>
<tr>
<td>2000</td>
<td>41</td>
<td>24</td>
<td>73</td>
<td>84</td>
<td>2</td>
<td>13</td>
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<tr>
<td>2001</td>
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<td>12</td>
<td>39</td>
<td>134</td>
<td>2</td>
<td>37</td>
<td>265</td>
</tr>
<tr>
<td>2002</td>
<td>56</td>
<td>13</td>
<td>27</td>
<td>329</td>
<td>6</td>
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<td>2003</td>
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<td>10</td>
<td>32</td>
<td>388</td>
<td>5</td>
<td>44</td>
<td>533</td>
</tr>
<tr>
<td>2004</td>
<td>63</td>
<td>11</td>
<td>38</td>
<td>269</td>
<td>8</td>
<td>41</td>
<td>430</td>
</tr>
</tbody>
</table>
2005  77   15   40   252   11   63   458  
2006  85   15   30   222   11   71   434  
2007  75   16   47   55    7   91   291  
2008  69   12   64   36    2   91   284  
2009  59   15   89   45    8  118   334  
**Grand Total**  738  292  984  1891  76  668  4569

Notes:  
Charity includes CRUK and a small number of educational grants from pharmaceutical companies.  
Other includes a small number of investigator funded projects and PhD studies.  
NHS R&D includes all NHS funded projects with the exception of those RCTs with funder indicated as NHS trust.  
Unknown indicates that either the funding field was missing (almost all instances) or had not been completed (rare).
The total number of UK non-commercial trials registered was similar to Chalmers et al 1993 – 2002 and to the UKCRN portfolio database for 2007-09. This suggests, as expected, that almost all trials register.

The number of non-commercial trials registered over the past 20 years has increased from under 200 before 2000 to around 300 per annum from 2007-9. A rapid rise in the total from 1996 to a peak in 2003 of over 500 and subsequent fall to 2007 was evident. This was due mainly to trials registered as funded in ISRCT by NHS Trusts, which have not previously been identified as major funders. No new funding became available to NHS Trusts around this time. Governance of trials increased after the EU Directive of 1999 which became UK law in 2004 with the Medicines for Human Use (Clinical Trials) Regulations. The strong encouragement of trial registration around that time in the UK may explain the rise in the number registered.

The decline in the number of trials registered as funded by NHS Trusts after 2003 might be linked to changes in funding. Each hospital had a largely notional self-declared research fund which had historically covered a range of activities including SIFTR, Special Health Authorities, ‘tasked’ monies for general practice research and ‘own account’ research. In 2006/7 some £500m or some 80% of NIHR (NHS R&D up to 2006) budget was hospital based. These funds were successively known as: Culyer Budget 1, infrastructure support, Priorities and Needs Funding, Support for Science. What was termed ‘own account’ research was funded by these funds. These considerable funds were withdrawn over three transition years from 2006/7 reducing the scope for NHS trusts to fund research.

The rise in the proportion of UK trials registering with ClinGov rather than ISRCTN is notable. This rose from 10-15% before 2007 to over 30% 2007-9. Although ISRCT charges for registration, these charges are met by the Department for Health for trials funded by the main funders, specifically NIHR, MRC and the charities. It seems likely that those trials registering with ClinGov were from other funders, such as own account trials in trusts. Whatever the reason, the rise in the use of ClinGov was unfortunate because of its lack of a field on the funding of the trial. This means that in 2009, the largest group of trials were those with unknown funding. If registration data are to be of use in monitoring trends in non commercial trials the source of funding must be known.

**Conclusions**

Overall, for the periods of overlap, trial registration data provide fairly similar totals to other sources on the number of non-commercial trials commencing each year. The rapid rise and fall in the number of trials registered as funded by NHS Trusts between 1999 and 2007 may be due to changes in the governance and funding of research within NHS hospitals. It remains to be seen how many of the ‘own account’ trials registered as funded by NHS trusts report their results.

As the number of trials registered as funded by NHS Trusts has fallen, the number of UK RCTs registering with ClinGov has increased sharply so that in 2009, 30% of UK trials registering were with ClinGov. It is likely that these were largely those trials previously registered as funded by NJS trusts but this cannot be established without more detailed investigation.

Leaving aside trials registered as funded by NHS trusts, the overall has been upward since around 2002. By 2009 the two main funders were NIHR and charities. The role of the MRC, already reduced, seems likely to shrink as NHS trials become the responsibility of NIHR. However, due to the increased use of ClinGov by 2009, the largest group of trials registered in that year had no data on funder. Further work to understand how these trials are being funded and registered with ClinGov seems an obvious priority.

The feasibility of using registration data to monitor the number of non commercial trials is complicated by the use of two registers, and the need to purchase the data. However it is feasible to compile these data. We recommend an annual report be commissioned to provide data on the total number of non commercial trials registering each year.

**List of abbreviations**

ISRCTN International Standard Randomised Controlled Trial Number
CCT Current Controlled Trials
ClinicalTrialsGov is a service provided by the US National Institutes of Health.
Competing interests
None of the authors have any competing interests.

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Alison Price¹ (A.M.Price@soton.ac.uk), 
Ruairidh Milne¹ (R.Milne@soton.ac.uk), 
Tom Walley² (T.Walley@liverepool.ac.uk).
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Endnotes
None
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