Medical Research Ethics at Top UK Universities
Performance, Policies and Future Plans

Failure to register and report clinical trials harms patients, wastes NHS resources, and slows down the development of new treatments and cures

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1 EXECUTIVE SUMMARY

Overview

This study examines the clinical trial transparency policies and practices of 16 leading British medical universities. Drawing on data obtained through Freedom of Information requests and searches of clinical trial registries, it finds that UK universities frequently fail to comply with the legal, regulatory and ethical standards governing the conduct of medical research in humans.

Why it matters

Failure to register and report clinical trials harms patients, wastes NHS resources, and slows down the development of new treatments and cures. For example, doctors prescribing the drug Lorcainide to patients who had suffered heart attacks inadvertently killed over 100,000 people because the results of a single clinical trial remained hidden, and the UK government bought Tamiflu at a cost of £424 million before discovering that the drug’s effectiveness was questionable. The best research is useless if its results remain inaccessible. Universities urgently need to step up their game and ensure that their staff members register and fully report every single trial they participate in.

Laws, regulations and best practices

Growing awareness of the immense cost of hidden clinical trials has led to the adoption of legal and regulatory requirements and ethical standards aimed at getting all trials registered and all results reported. However, the UK’s Health Research Authority currently cannot ensure compliance because it lacks the necessary resources and sanctions mechanisms.

Universities’ current performance

In total, the top 16 medical universities in the UK have only posted results for 5.8% of clinical trials. Out of a total of 3,540 trials conducted, only 206 have posted results. The results of the remaining 3,334 trials are difficult or impossible to find.

<table>
<thead>
<tr>
<th>Rank</th>
<th>University</th>
<th># Trials total</th>
<th># no results</th>
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<th># with results</th>
<th>% with results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Keele</td>
<td>17</td>
<td>12</td>
<td>70.6%</td>
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<td>29.4%</td>
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<tr>
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<td>Dundee</td>
<td>211</td>
<td>162</td>
<td>76.8%</td>
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<tr>
<td>3</td>
<td>Cambridge</td>
<td>142</td>
<td>130</td>
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</tr>
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</tr>
<tr>
<td>6</td>
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<tr>
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<td>London School of H&amp;T</td>
<td>292</td>
<td>281</td>
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<tr>
<td>16</td>
<td>Swansea</td>
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</tr>
<tr>
<td></td>
<td>TOTAL</td>
<td>3,540</td>
<td>3,334</td>
<td>94.2%</td>
<td>206</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

¹ Cardiff University claims that the total number of applicable trials is 37, with 36 of those missing results.
Numerous examples show that due to universities’ failure to post the results of their trials and other weak data management practices, registry entries on clinical trials conducted in the UK have become a tangled patchwork of partial, inconsistent and potentially unreliable data.

At the same time, the scope and strength of university policies on clinical trials registration and results posting varies widely. Many universities seem to have an incomplete understanding of the relevant legal, regulatory and ethical frameworks.

**Universities’ future plans**

Two British universities are already on the road to excellence in reporting the results of their medical research. The University of Aberdeen is set to become the world’s first university to carry out an audit of its existing registry entries. The University of Dundee is actively strengthening its data management systems and has already begun uploading missing trial results onto registries.

**Research funders**

Universities’ operating context is rapidly evolving. Recently, over a dozen major global medical research funders, including four funders in the UK, declared that they will soon require their grantees to pre-register all trials, post their results on registries within 12 months, and ensure that registry entries are complete, accurate, and kept up to date.

**Recommendations**

Hidden clinical trials pose a substantial health risk to British citizens and are a drain on public funds. The cost of continued inaction by far outweighs the cost of resolving the problem.

The UK government should:
1. Assume political leadership and commit to solving the problem
2. Launch a national strategy to secure the results from past clinical trials
3. Launch a national audit system for future clinical trials

UK universities should:
1. Centralize oversight of all existing registry entries
2. Audit their clinical trial registration and reporting performance
3. Adopt strong policies
4. Post full trial reports online
2 INTRODUCTION

WHY IT MATTERS: SAVING LIVES, IMPROVING NHS SPENDING, FINDING CURES

Clinical trials conducted in human patients are the keystone of modern medicine. Typically, a clinical trial examines whether a new drug, medical device or procedure is safe and effective at improving patients’ health. Government regulators rely on the results of clinical trials to decide whether to allow new drugs onto the market, and doctors rely on them to advise their patients on which drugs to take.

Since the 1980s, experts have warned that the information currently available on clinical trials is incomplete and frequently biased. As a result, patients, doctors and even regulators cannot access complete and reliable information on how safe a new medicine is, or whether it will actually help people to get better.

Failure to register and report clinical trials harms patients, wastes NHS resources, and slows down the development of new treatments and cures. For example, doctors prescribing the drug Lorcainide to patients who had suffered heart attacks inadvertently killed over 100,000 people over the course of the 1980s because the results of a single clinical trial remained hidden. More recently, the UK’s Department of Health bought around 40 million doses of Tamiflu at a cost of £424 million. In one year, 0.5% of the entire NHS budget was spent on the drug, which was given to around 240,000 people in Britain. When independent researchers finally got hold of all the evidence needed to evaluate the effectiveness and safety of Tamiflu – which took them four years – they found that its effectiveness was questionable and its negative side effects had been underplayed.

Experts agree that this problem is solvable. Registering all clinical trials before they begin and then posting their full results on dedicated trial registries can enable regulators, doctors and patients to base their decisions on the best available evidence, and speed up the discovery of new treatments and cures. In recent years, trial registration and reporting have become globally recognized as ethical imperatives in medical research, and a growing body of laws and regulations seeks to ensure that researchers do the right thing.

British universities have a clear moral obligation to ensure that all members of staff adhere to global ethical norms governing medical research in human volunteers. Furthermore, as publicly funded institutions tasked with generating and disseminating knowledge for the public good, British universities have a duty to ensure that all members of staff comply with existing laws and regulations and enable other researchers to build on their insights and discoveries.

Britain is proud of being a global leader in medical research, and British universities house some of the world’s top medical research teams. However, the best research is useless if its results remain hidden. Universities urgently need to step up their game and ensure that their staff members register and fully report every single trial they participate in.

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CASE STUDY: THE HIDDEN COST OF HIDDEN HEPATITIS C TRIALS

Hepatitis C infection is linked to around 700,000 deaths a year globally, and 160,000 people are estimated to live with the virus in England alone. Treating all those infected would cost a third of the UK’s entire drugs budget because pharmaceutical companies have priced recently developed antiviral medicines at about £30,000 per patient. But how safe and effective are these new drugs? Do they really save lives?

To answer these questions, the Cochrane Collaboration recently set out to identify all relevant clinical trials and review their results. In theory, this should be quick and easy, as there are only 16 WHO-recognised trial registries in the world. In practice, the gaps left in these registries by universities, pharmaceutical companies and other research institutions make it extremely difficult to identify all relevant trials and chase down their results. The passage below describes the many steps Cochrane researchers had to take to find all existing evidence on these prohibitively expensive but potentially life-saving drugs.

“We searched the Cochrane Hepato-Biliary Controlled Trials Register (Gluud 2015), Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE (OvidSP), Embase (OvidSP), Science Citation Expanded (Web of Science), LILACS (Bireme), and BIOSIS (Web of Science) in order to identify relevant trials. We also searched the Chinese Biomedical Literature Database (CBM), China Network Knowledge Information (CNKI), the Chinese Science Journal Database (VIP), and the Wanfang Database...

We searched the bibliographic references of identified randomised clinical trials and review articles in order to find randomised clinical trials not identified by the electronic searches and handsearches. We contacted the principal authors of the identified randomised clinical trials to inquire about additional randomised clinical trials that they might know.

We also searched Google Scholar, The Turning Research into Practice (TRIP) Database, and on-line trials registries such as ClinicalTrials.gov, European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), the Food and Drug Administration (FDA) (www.fda.gov), as well as pharmaceutical company sources for ongoing or unpublished trials.

Additionally, we handsearched Hepatology, New England Journal of Medicine, JAMA, BMJ, PLoS Medicine, and Annals of Internal Medicine for relevant trials.

We also searched for unpublished and grey literature trials.”

Source: “Direct-acting antivirals for chronic hepatitis C” Cochrane library of systematic reviews, June 2017

The Cochrane team eventually managed to locate and review 138 relevant clinical trials, and concluded that the expensive new drugs did not seem to have “any clinical effects”.3

This is not an isolated or extreme case. Until governments step in to ensure that all trials are registered and all registry entries are complete, accurate and up-to-date, lengthy treasure hunts for existing medical evidence will continue to waste government agencies’ and scientists’ valuable time – time that could instead be spent on developing new treatments and cures.

3 The Cochrane team’s conclusion has been contested by other scientists and the Association of the British Pharmaceutical Industry. The debate about the new drugs’ safety, effectiveness and cost-effectiveness continues, as does a separate debate about whether the prices charged by industry are fair. TranspariMED takes no position in these debates.
LAWS, REGULATIONS AND BEST PRACTICES

Overview

Growing awareness of the immense cost of hidden clinical trials has led to the adoption of legal and regulatory requirements aimed at getting all trials registered and all results reported. Global best practices go beyond current legal and regulatory requirements, and define the gold standard for the field. The table below provides a quick overview of current legal and regulatory requirements in the UK versus global best practices.

<table>
<thead>
<tr>
<th></th>
<th>UK legal and regulatory requirements</th>
<th>Global best practices</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial registration</td>
<td>Maximum 6 weeks after recruitment of the first participant, covers all trials</td>
<td>All trials, before recruitment of the first participant</td>
</tr>
<tr>
<td>Results posting</td>
<td>Within 12 months of completion, for drug trials only</td>
<td>All trials, post results within one year of completion</td>
</tr>
</tbody>
</table>

Trial registration

- **UK regulatory requirement (UK Health Research Authority)**

The UK’s Health Research Authority (HRA) has made trial registration within six weeks of the recruitment of the first UK participant mandatory. When applying for Research Ethics Committee approval, which every interventional trial involving human participants needs to secure before going ahead, researchers have to commit to subsequently registering their trial on a public registry. Trial sponsors can apply with the HRA for permission to defer registration for some types of trials, but such deferral is conditional on “assurances that the studies will be registered later”. The HRA requirement covers “[A]ll clinical trials of medicines, devices or other clinical interventions.” The responsibility for ensuring that a trial is registered rests with the trial sponsor.

Overall, the HRA’s standard is very strong and has been flagged as a positive example for ethics regulators in other countries. However, it has two weaknesses. First, the six week time lapse allowed between recruitment and registration falls short of global best practices (see below).⁴ Second, there is a lack of effective sanctions; the results of a 2015 HRA audit report suggest that many trials are still not being registered as required.⁵

- **Global best practice (World Medical Association, World Health Organization, AllTrials)**

The World Medical Association’s Declaration of Helsinki, the most widely recognized global standard governing medical research ethics, states that “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject”. Crucially, it also notes that “No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.” This means that registration before recruitment is an ethical imperative for all researchers at British universities,

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⁴ The HRA “expects registration of all clinical trials before the first participant is recruited” [emphases added], but this is not a binding requirement.

⁵ The HRA plans to repeat this audit in autumn 2017 and will publish the results in due course.
despite the HRA having set the bar somewhat lower. The World Health Organization and the AllTrials campaign\(^6\) have also called for pre-registration of all interventional clinical trials.

**Results posting**

- **UK legal requirement (European law)**

  Since 2014, it has been mandatory for British trial sponsors to post the summary results of most types of clinical trials on the European clinical trials registry EudraCT\(^7\) within 12 months of trial completion (6 months for paediatric trials). The relevant guidelines apply to all interventional trials testing the efficacy and/or safety of a medicine, called CTIMPs.\(^8\) Under the same guidelines, sponsors are also required to retrospectively post the summary results of older CTIMPs.

The guideline is limited in its breadth, because trials of medical devices and non-drug health interventions are not covered, but its time frame of 12 months for results posting is fully in line with global best practices.

As this study documents, many UK universities have repeatedly failed to post summary results onto EudraCT for trials that have long been completed, and thus appear to be in violation of the guideline. However, the underlying legislation was developed and adopted by the European Union, so while it is binding for all trial sponsors across the EU, it falls to national authorities to enforce compliance. As the European Medicines Agency explained:

> “The European Medicines Agency (EMA) is not responsible for the completeness or accuracy of this [registry] information. This is primarily the responsibility of the sponsor of the trial and the national authorities of the Member States where the trial is authorised... [The relevant guideline] sets out that it is the responsibility of the Member States to ‘verify that for clinical trials authorised by them the result-related information is posted to the Agency’... There are no sanctions such as fines or criminal charges defined at the European level in the event that the sponsor does not follow the requirements of the guidance on posting the results. However, member states may have some provisions in relation to sanction at national level.”\(^9\)

In the UK, the relevant national authority is the Health Research Authority (HRA). According to the HRA, all trials listed on EudraCT are by definition CTIMPs\(^10\) and are thus required to post summary results within 12 months.\(^11\) However, HRA Chief Executive Janet Wisely has noted that the HRA currently lacks the resources needed to monitor compliance, and due to the lack of supporting UK national legislation is unable to impose effective sanctions on trial sponsors who violate these and other clinical trial transparency rules.\(^12\)

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\(^6\) Full disclosure: TranspariMED’s founder worked for the AllTrials campaign during 2016-2017, but has no current financial or organizational ties to AllTrials. This study was conducted independently of AllTrials and was not reviewed by AllTrials prior to publication. Any errors are the sole responsibility of TranspariMED.

\(^7\) Technically, trials are registered and summary results are posted first on EudraCT, which is not publicly accessible, and only then transferred to its publicly accessible twin registry, the EU Clinical Trials Register, and a third linked registry aimed at the general public is currently in development. However, in the interests of clarity, this study consistently refers to EudraCT as ‘the European registry’.

\(^8\) This useful crib sheet explains what kinds of trials are defined as CTIMPs.

\(^9\) Email communication from the EMA press office, 30 June 2017.

\(^10\) Email communication from the HRA Clinical Trial Helpline, 30 June 2017.

\(^11\) There are some exceptions relating to the public availability of data on phase 1 drug trials, but these are a small minority of CTIMPs. None of the trials discussed in detail in this study were purely phase 1 trials.

\(^12\) The HRA confirmed upon request that “[r]eporting of clinical trials results is not mandated by the current UK Clinical Trials Regulations themselves but by other EU Regulations”. Email communication from the HRA press office, 23 June 2017.
Please see the statements by regulators and policy recommendations, further below, for additional details.

- **Global best practices (World Health Organization and AllTrials)**

Global best practices in the field have been set out by the [World Health Organization](https://www.who.int), which in 2015 demanded that every interventional clinical trial’s “key outcomes are to be made publicly available within 12 months of study completion by posting to the results section of the primary clinical trial registry.” The [AllTrials campaign](https://alltrials.net) has also demanded that a “summary of results, including information on the primary and any secondary outcomes measured and statistical analysis, should be posted where a trial was registered within one year of completion of a trial.”

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13 Note that neither the WHO nor AllTrials regard academic publication as a satisfactory substitute for results posting on registries that offer such a function.
3 RESULTS POSTING

UNIVERSITY PERFORMANCE RANKING

In total, the top 16 UK universities have only posted results for 5.8% of clinical trials involving their researchers on the European and American registries where they were originally registered. Out of a total of 3,540 trials conducted, only 206 have posted results. The results of the remaining 3,334 trials are difficult or impossible to find.¹⁴

Keele University performs strongest, having posted results for 29.4% of its trials, or 5 out of 17 trials total. The University of Dundee comes second with 23.2% of its trials (49 out of 211) posting results. All other universities have posted results for less than one in ten of their clinical trials. The worst performers are Swansea with 0% (not a single result posted for 18 trials total), Kings College with 0.9% (only 2 out of 235 trials), and Cardiff with 1.1% (only 1 out of 87 trials).¹⁵

| Clinical trial results posting performance of top 16 UK medical universities |
| Keene  | 29.4% |
| Dundee | 23.2% |
| Cambridge | 8.5% |
| Oxford | 7.8% |
| Queen Mary (QMUL) | 6.0% |
| University College London | 5.9% |
| Newcastle | 5.2% |
| Manchester | 5.1% |
| London School of H&T | 3.8% |
| Imperial College London | 3.4% |
| Edinburgh | 2.5% |
| Exeter | 2.3% |
| Glasgow | 1.6% |
| Cardiff | 1.1% |
| King's College London | 0.9% |
| Swansea | 0.0% |

This study identified 3,334 clinical trials involving researchers from top UK universities that have not posted results on the main European and American registries. The three universities with the largest numbers of trials that have failed to post results, Imperial College London (564 trials without results), University Oxford (544 trials) and University College London (466 trials), between them have failed to post results for over 1,500 trials.

¹⁴ While a minority of these trials are still ongoing, the number of all completed trials that have not posted results is likely to be even higher because data from a third major registry (ISRCTN) was not included in this data set. Please see the Annex for more details.

¹⁵ Cardiff University claims that the correct figure is 2.7% (1 out of 37 trials). Please see the next footnote for more details.
**Number of trials that have not posted results on registries, per university**

<table>
<thead>
<tr>
<th>Rank</th>
<th>University</th>
<th># Trials total</th>
<th># no results</th>
<th>% no results</th>
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<tr>
<td>1</td>
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</table>

**TOTAL** | 3,540 | 3,334 | 94.2% | 206 | 5.8%

A [2014 U.S. government study](#) estimates the typical cost of a single clinical trial at £3-15 million, depending on the phase of the trial and other variables. Assuming the low cost estimate of £3 million per trial, the 3,334 trials missing results consumed over £10 billion in scarce medical research funds. If UK universities do not post the results of these trials on registries, their discoveries will remain difficult or impossible to access, adding to the estimated [£131 billion in medical research](#) that are currently being wasted worldwide every year.

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Cardiff University has challenged the accuracy of the data presented in this section. The university claims that the total number of applicable trials is 37, with 36 of those missing results. These alternative figures would translate into 2.7% of trials with results posted and 97.3% of trials without results posted. Please see the statement of Cardiff University and TranspariMED’s comment on that statement, both further below, for more details.
**TYPOLOGY OF PROBLEMS DETECTED**

Clinical trial registries were created to give patients, doctors, researchers and regulators quick access to comprehensive and unbiased evidence on the benefits and side effects of drugs, medical devices and treatments. However, due to universities’ failure to post the results of their trials and other weak data management practices, registry entries on clinical trials conducted in the UK have become a tangled patchwork of partial, inconsistent and potentially unreliable data. This harms patients, wastes NHS resources, and slows down the development of new treatments and cures.

The table below provides a typology of the bad practices encountered in the course of conducting this study, together with the problems caused and the wider consequences.

<table>
<thead>
<tr>
<th>BAD PRACTICES</th>
<th>PROBLEMS CAUSED</th>
<th>CONSEQUENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to set strong policies and centrally track all trials involving university staff(^1)</td>
<td>Universities fail to prevent, deter and detect ethics violations and weak research practices</td>
<td>Ethics violations and weak research practices widespread at UK universities</td>
</tr>
<tr>
<td>Weak results reporting practices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to share results in any form</td>
<td>Trial results are lost forever</td>
<td>Patients are harmed because the full benefits and side effects of medicines remain unknown</td>
</tr>
<tr>
<td>Failure to post results on registries</td>
<td></td>
<td>Scarce NHS funds are wasted on drugs of dubious effectiveness and safety</td>
</tr>
<tr>
<td>Failure to link to academic journal articles within trial registries</td>
<td></td>
<td>New treatments and cures take longer to develop</td>
</tr>
<tr>
<td>Failure to include trial number(s) in the abstracts of journal articles</td>
<td>Trial results get overlooked</td>
<td>Precious research funding is wasted</td>
</tr>
<tr>
<td>Weak data management practices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure to complete all required data fields in registries</td>
<td>Important information on trial design, conduct and results remains hidden</td>
<td>Impossible to reliably interpret the results of individual trials</td>
</tr>
<tr>
<td>Failure to ensure data is consistent across different registries (^2)</td>
<td>Important information on trial design, conduct and results is not consistent</td>
<td>Impossible to compile reliable systematic reviews and meta-analyses</td>
</tr>
</tbody>
</table>
| Failure to regularly update registry entries                                   | Impossible to reliably determine:  
- which trials are currently recruiting volunteers  
- who is currently studying what  
- which trials have been completed | Patients find it hard to identify and enrol in trials that could help them and others  
Trials are needlessly duplicated and gaps in knowledge are left unfilled  
Laws and regulations mandating results posting may become hard or impossible to enforce |
| Failure to cross-link trials registered in multiple registries                | Hard to gain comprehensive overview of research on any drug or condition        | Registries fail to fulfil their original purpose and promise                  |

Examples of bad practices within the universities covered by this study are provided in the following section.

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\(^1\) Demonstrated by the failure of all universities to ensure that registry entries are complete, correct, and up-to-date, and that all trial results are posted on time. Note also that several universities failed to correctly identify all trials completed during 2015 in their responses to the FOI requests.

\(^2\) Inconsistencies encountered in the course of compiling this study include the following: primary and secondary outcomes, trial sponsor, participant number, trial status, results status, and completion date. Additional data fields may also have contained inconsistencies; compiling an exhaustive catalogue of inconsistencies was beyond the scope of this study.
RAPID EXTERNAL AUDIT RESULTS BY UNIVERSITY

Overview

TranspariMED audited a sample of trials involving staff from each of the top 16 UK medical universities to determine which universities’ data entries on clinical trial registries provide a complete, accurate and up-to-date record of their past and present clinical trials (please see the Annex for details on the methodology used).

Not a single university’s registry entries fully met these criteria, indicating that central oversight of clinical trials reporting is currently weak or non-existent at all 16 universities. Many universities’ FOI responses also indicated weak central oversight. Some universities seemed unable to correctly answer a seemingly simple Freedom of Information (FOI) question about the number of trials they had sponsored that were completed during 2015, and the number of those trials that had not posted results. Other universities responded to the same question by stating that they themselves did not know how many of their trials had been completed in 2015 or had posted results. Weak results reporting and data management practices currently appear to be the norm rather than the exception within many, if not all, of the universities included in this study.

The examples below bring into focus the negative consequences of universities’ failure to make the results of their medical research easily accessible. The list of trials with missing or difficult to locate results includes attempts to find better treatments or cures for widespread and in some cases life-threatening conditions, including:

- arthritis
- asthma
- bipolar disorder
- cancer (several different kinds)
- diabetes
- dengue fever
- Duchenne muscular dystrophy
- leukaemia
- malaria
- MRSA (better known as the drug-resistant ‘hospital superbug’)
- multiple sclerosis

At the same time, many of the problems flagged below would be easy for universities to fix. For example, adding links to already published academic journal articles to existing registry entries would require very little effort.

Cambridge

Clinicaltrials.gov lists a total of 18 diabetes-related trials sponsored by the University of Cambridge that have been completed but have failed to post results. Among these are two trials involving children suffering from diabetes, NCT02129868 and NCT01778348, which tested a new device that automatically administers insulin during the night. Because the result have not been posted, parents of children will diabetes, family doctors, and researchers looking for new ways to manage the illness cannot benefit from the discoveries made by trials run by the University of Cambridge.
Children were also the focus of trial NCT00607074, which was sponsored by the University of Cambridge but took place in a village in Bangladesh. The water-borne infectious disease studied, Giardia, is widespread in developing countries, can cause malnutrition in smaller children, and has the potential to interfere with their physical and mental development. Researchers from Cambridge gave two different treatment courses to 222 infants aged between 3 and 15 months to see which treatment was better. The study was completed in 2008 and its results were published in an academic journal in 2009. However, the university failed to subsequently also post the results on the registry, making them hard to discover for doctors and public health agencies in developing countries. The registry notes that the university has not updated the relevant entry since 2008, indicating weak follow-up of completed trials.

In addition, the University of Cambridge has also not posted results for trial 2011-005606-30, which was conducted to find new ways to help patients suffering from multiple sclerosis. The trial set out to recruit 86 patients; as long as its results remain hidden, other people living with the disease will be unable to benefit from the discoveries made. A further multiple sclerosis trial, NCT00395200, has not posted results even though it has long been completed and its results have already been published in two academic journals. Yet another multiple sclerosis trial, NCT01044576, was completed years ago and has not posted results; a PubMed search for the trial number does not bring up any related articles, suggesting that the trial’s results have not been published in the academic literature.

Cardiff

In 2007, Cardiff University registered a large multinational trial on EudraCT (2007-003798-16) that set out to study whether a new chemotherapy treatment could increase remission rates and improve overall survival in patients with leukaemia and another form of blood cancer. The Cardiff-sponsored trial aimed to recruit thousands of patients in the UK, Ireland and Denmark and was scheduled to run for six years. Ten years on, the British and Danish arms of the trial are still listed as “ongoing”, while the Irish arm is listed as “completed”. The trial has not posted any results on EudraCT.

Meanwhile, the same trial was also registered on the ISRCTN registry, where it is listed as having ended in 2014. The ISRCTN entry links to five separate academic papers discussing the trial’s results. For users of the EudraCT registry, these journal articles are difficult to find because the university failed to ensure that the EudraCT number was included in the article’s abstracts.

Furthermore, the number of total trial participants reported is inconsistent, with the UK and Danish versions on EudraCT citing 2,700 participants versus 2,800 in the Irish version and the ISRCTN entry. (The ISRCTN entry originally stated yet another figure, 2,500, but that was subsequently changed to 2,800.) In addition, the ISRCTN entry only lists the UK and Denmark as trial sites; the Irish arm of the trial is not mentioned there.

Cardiff University’s failure to provide reliable data on this potentially life-saving trial and make its results easily accessible indicates weak data management practices within the institution.

Dundee

The University of Dundee’s trial 2013-003573-10 set out to discover whether vitamin D supplementation can improve Hepatitis C cure rates. The trial aimed recruit 100 people suffering from Hepatitis C as volunteer participants. Its results had not been posted at the time of
TranspariMED’s rapid external audit, but were subsequently posted on 13 May 2017, almost eighteen months after trial completion (see also the university’s statement, further below).

The University of Dundee’s trial 2007-000012-90 set out to evaluate whether patients with osteoarthritis or rheumatoid arthritis could benefit from a different treatment to the current standard of care. In total, 13,682 patients volunteered to participate in this trial. Even though the trial was completed in 2015, no results have been posted. The university commented in its FOI response dated 24 March 2017 that “the full report has been published by the European Heart Journal and upload to EudraCT is in process”, but as of 24 June 2017, the relevant link had still not been added to the registry entry. Furthermore, a PubMed search for the trial number returned no results because university researchers departed from best practice by not including the trial number in the abstract; a PubMed search for the trial’s title also did not bring up a link to the paper. Such weak data management practices mean that even if results are published in journals, patients elsewhere may not benefit from the contribution made by the over 13,000 people who volunteered to participate in the University of Dundee’s large-scale study.

In its statement (see further below), the university explained that:

“The reasons for delay in posting results for both trials was that there were mandatory reporting requirements to the UK Regulatory Authority, the MHRA, that the University, had to fulfil.”

Edinburgh

The University of Edinburgh’s trial 2013-004706-25 set out to discover whether it was feasible to recruit large numbers of pregnant women suffering from Gestational Diabetes Mellitus, a potentially fatal disease, to participate in a subsequent bigger trial. In order to test feasibility, 40-50 pregnant women were to be recruited, with one group being administered glibenclamide instead of the usual insulin treatment. Completed in 2015, it has not posted results, making it difficult for pregnant women elsewhere to seek what may be a more effective treatment.

Trial 2006-003509-18 tested what effects a drug had on kidney functions in healthy volunteers and in patients with chronic kidney disease, a total of 114 people. Completed in 2015, it has still not posted results.

Trial 2013-005327-16 has also not posted results on the European EudraCT registry. However, researchers did post results for the same trial on the American Clinicaltrials.gov registry.

Similarly, trial 2013-005338-39, which set out to study a possible new treatment for cysts in 120 people suffering from arthritis, was prematurely ended in October 2015 according to EudraCT data. However, on Clinicaltrials.gov, the same trial (number NCT02154789) is still listed as “not yet recruiting”. Such data inconsistencies between registries indicate weak data management practices within the University of Edinburgh.

Exeter

The University of Exeter has failed to post results for six clinical trials registered on Clinicaltrials.gov aimed at discovering new ways to help people with diabetes. In total, 4,437 patients with diabetes participated in these six trials, all of which have reportedly been completed; these volunteers’ contribution to the discovery of new treatments will have been in vain if the university fails to make the results of the trials accessible. The university has also failed to post results for one diabetes trial
that was registered on EudraCT; trial 2009-013100-32 was registered in 2009 and was only scheduled to last for nine months, but is still listed as “ongoing”, indicating weak data management practices at the university.

The University of Exeter has also yet to post results for a trial (2004-004231-53) that was completed seven years ago. The trial involved 23 volunteers who had survived a stroke. Whether its results have been published elsewhere or have remained completely unreported is unclear; PubMed searches for the trial number and trial title did not return any results. The discoveries of this trial seem to be in danger of being lost forever.

Glasgow

The University of Glasgow reported in response to the FOI request that only one CTIMP it co-sponsored was completed in 2015, and that this trial had posted results. This statement is not fully accurate. While the trial referenced by Glasgow (2009-011542-25), which involved 69 women with inoperable cervical cancer, has indeed posted results on EudraCT, Glasgow’s team failed to also post the results on Clinicaltrials.gov, where the same trial had also been registered. This indicates weak data management practices within the university.

The University of Glasgow has also failed to post results on Clinicaltrials.gov for at least seven different cancer trials that were completed before 2013. One of these studies, NCT00003998, involved over 1,000 patients with ovarian cancer. At the time, university researchers noted that “It is not yet known which combination chemotherapy regimen is more effective for treating ovarian epithelial cancer”, but afterwards they failed to post their results. However, they did link to three academic papers that presented the results. Confusingly, the same trial has also been registered separately on the ISRCTN registry (ISRCTN31374767), but only one of the academic papers is linked there. Also, while the Clinicaltrials.gov registry identifies the University of Glasgow as the trial sponsor, ISRCTN names Cancer Research UK as the trial sponsor; furthermore, there are gaps in the data entered into both registries.

Imperial College London

In its FOI response, Imperial College London (ICL) declined to provide information identify trials it had sponsored that ended during 2015. ICL explained that:

“[T]here is currently no requirement for information other than confirmation of registration to be recorded centrally. Consequently, the College does not have a single, centrally held record of when clinical trials are completed, or if the results of its clinical trials have been posted on a public clinical trials registry... To obtain the information requested... would require the individual records of each of these hundreds of trials to be inspected to extract this data... [The workload involved] would exceed the appropriate time limit under the Freedom of Information Act...

The College is currently reviewing its standard operating procedures in relation to clinical trials, including the nature and extent of the central records it holds... However, as there is no legal requirement to keep a central record or to report on the information requested, the College will have to consider whether the creation and maintenance of such a central record is necessary.”

A search of EudraCT shows that Imperial College London has not posted results for 12 trials involving children and teenagers. One of these trials, number 2006-003833-33, illustrates how the university’s failure to share results may both harm patients and slow down medical progress. Several years ago,
ICL researchers ran a trial of a then new drug that many hoped might slow the progression of Duchenne muscular dystrophy. There are around 2,500 people in the UK living with Duchenne’s, a chronic progressive disease that starts in early childhood and for which there is no cure. Many children with the disease do not survive beyond their teens. During the trial, ICL researchers injected nine teenagers aged 12-17 “to evaluate the safety and tolerability” of the new drug. The trial was completed in 2009, but ICL did not post the results on EudraCT. (A search of PubMed using the trial number and trial title suggests that the results were not published academically, either.)

An ICL staff member explained in an email that “the principal investigator for the Duchenne muscular dystrophy trial referred to in the report (2006-003833-33) left Imperial College before the trial ended and the research was therefore not concluded at the College.” However, according to the European Medicines Agency, the responsibility for results posting rests with the trial sponsor, not with the principal investigator: “The sponsor has the duty to post the summary results directly into EudraCT within 6 or 12 months after the end of the trial.”

As a result, researchers elsewhere trying to help children with Duchenne’s could not find out whether the new drug was safe or not. Sure enough, soon afterwards, a different team of researchers in the United States again tested the same drug, this time on 19 children aged 5-15, once again to evaluate its “safety and tolerability”. The children participating in the American trial reported numerous adverse reactions, including tachycardia, nausea, vomiting, abdominal pain, headaches, and “influenza like illness”. (We only know this because, in contrast to the ICL team, the American researchers were diligent and posted their findings on the Clinicaltrials.gov registry; they also published a journal article and linked to it on the registry.)

In September 2016, the drug was approved by U.S. regulators amid concerns that the available evidence from past clinical trials was not sufficient to warrant approval. A search of OpenTrials suggests that worldwide, the drug has been tested in only eight clinical trials, of which two seem to still be underway. Of the six completed trials, two – including the ICL trial – have not posted results, so globally there are only four trials of this drug that have made their results available on registries.

Imperial College has also failed to post results on other registries. For example, the university sponsored a clinical trial that set out to recruit women with breast cancer to determine the “efficacy and tolerability” of two different treatment options. The trial (NCT00963729) was registered on Clinicaltrials.gov in 2009 and completed in 2011, but ICL has still not posted its results on the registry. The same trial was apparently also registered on EudraCT, where it is still listed as “ongoing”; EudraCT has added a note stating that trial results have been “Removed from public view”. The trial was additionally registered on ISRCTN, which is the only registry entry that contains a link to the 2014 journal article that discusses the trial’s results. However, the journal article only discusses the results for a cohort of 44 women who fully participated in the trial. Meanwhile, Clinicaltrials.gov reports 756 participants, EudraCT reports 40 participants, and ISRCTN reports 716 participants.

Such data gaps and inconsistencies indicate weak data management practices within the university, and make it extremely difficult for systematic reviewers and other researchers to correctly gauge and evaluate a trial’s contribution to current medical knowledge.

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19 Please see the sections on university statements and the EMA’s statement, both further below, for more details.

20 The EMA press office explained that: “The EU Clinical Trials Register displays a notification saying ‘Removed from public view’; results were submitted on 11-Jul-2015 but due to a system error all trial results that had been were removed from public view. The system was made available again on 13 January 2016. The summary results have gradually been made available for public access from that date, once the information has been reviewed and verified by the sponsors. We will be looking to contact the sponsor to ask them to verify the status of their results to enable public access.”
**Keele**

Keele University registered a trial on the ISRCTN registry (ISRCTN23378642) that was completed during 2015 but has not posted results. The university explained in its FOI response that “The results have not been published yet but once they are available a link to the results will be added to the ISRCTN record”.

A Keele University trial (2010-021257-39) involving 93 patients who had suffered a stroke is listed as “ongoing” on EudraCT but is listed as “completed” on Clinicaltrials.gov. The same trial has posted results on EudraCT, but has not posted results on Clinicaltrials.gov. These data inconsistencies across registries indicate weak data management practices within the university.

A different Keele University sponsored trial, called “Management of Asthma in School-age Children on Therapy”, was completed several years ago. Keele’s researchers explained that “Asthma remains the most common medical condition seen in children in primary care and the most frequent cause for medical paediatric hospital admission. It affects 1 in 8 children nationwide... We do not have the scientific information about how to treat children with asthma who are not well controlled on low-dose ICS therapy.” They started the trial in order to find out, and registered it separately on three registries. On Clinicaltrials.gov (NCT01526161), the trial is listed as having been “completed” in 2011, but no results have been posted there, and no publications have been linked. On EudraCT (2008-000511-16) the same trial is listed as “ongoing”, even though the trial results sheet linked there states that trial was completed, albeit in 2010. (The results sheet itself links to a PDF copy of a journal article describing the trial’s results.) Meanwhile, ISRCTN lists the same trial (ISRCTN03556343) as “completed”, giving 2011 as the end date, and links to the same journal article. However, the ISRCTN entry does not contain the corresponding trial identification numbers used on the other two registries. Because the journal article’s abstract only contains the ISRCTN trial number, PubMed searches for the trial’s other two registration numbers did not return any results. This means that any researcher using Clinicaltrials.gov as her point of departure would miss the results of this trial, in which 229 children with asthma had participated. While it is laudable that Keele’s researchers made the effort to post or link trial results twice in two separate registries, their omission to also post results on the third registry apparently went unnoticed by the university, indicating weak data management practices within the institution.

**King’s College London**

King’s College London (KCL) sponsored trial ISRCTN25691213 in 2009. The trial set out to enrol 40 children aged 7-15 years suffering from learning disabilities and hyperkinetic disorder to see whether their lives could be improved by taking the drug atomoxetine. KCL’s researchers did not link any academic articles reporting the results on that registry, and ISRCTN administrators noted in 2016 that they had been unable to locate any related publications even though the trial is recorded as having been completed in 2010 on their registry. Meanwhile, the same trial appears to have also been registered on EudraCT, where it continues to be listed as “ongoing” (again without results having been posted), indicating weak data management practices within the university. Even though the trial apparently ended in 2010, doctors and parents of children with learning disabilities and hyperkinetic disorder cannot find out whether atomoxetine’s benefits outweigh its harms – or vice versa.

King’s College London has sponsored or co-sponsored several other trials that appear likely to have completed long ago, but that are nevertheless still listed as “ongoing” and have failed to post results. For example, one KCL trial (2005-005072-32) set out to discover whether the drug quetiapine could
prevent the development of manic episodes in 50 patients suffering from bipolar disorder. The trial was registered in 2005, but twelve years later on continues to be listed as “ongoing”, which seems unlikely to be correct considering the short-term outcome measures used. KCL has not posted any results for the trial on EudraCT, and a PubMed search for the trial number does not return any results, suggesting that the research team failed to make its findings accessible to the broader medical research community.

Another KCL trial that seems to be incorrectly listed as “ongoing” is trial 2006-002330-38, which set out to enrol 120 patients whose bodies were rejecting a kidney transplant. The trial was registered in 2006 and should have ended three years after the last patient had been recruited. However, the trial is still listed as “ongoing”, no results have been posted, and a PubMed search for the trial number does not flag any related academic papers. Researchers and doctors outside KCL thus have no easy way of discovering whether the new drug holds out hope for other patients with this potentially life-threatening condition, or even whether the trial was completed as planned or abandoned early.

None of these three trials has contributed to global progress in medical research or helped other doctors and patients to make better treatment choices because KCL failed to ensure that its researchers make their findings accessible to the wider medical community.

**London School of Hygiene and Tropical Medicine**

A search of Clinicaltrials.gov shows that 115 malaria trials registered in 2014 or earlier involving London School of Hygiene and Tropical Medicine (LSHTM) researchers have not posted results on that registry. Examples include trial NCT00131794, which examined whether a vaccine could protect children against malaria, enrolling 1,200 infants aged 18-24 months in the small African country of Guinea-Bissau. Over a decade later, the trial has not posted any results on the registry, and a PubMed search for the trial number does not return any academic publications discussing its results. Another malaria vaccine trial (NCT00121823) conducted in adults in the Gambia has also failed to post results on the registry, and a PubMed search for the trial number does not return any results.

Both trials were completed during 2003-2004 and retrospectively registered in 2005. This is positive, as pre-registration was not common at the time, and the decision to retrospectively register these trials indicates a willingness by the university to add its ‘old’ trials to the global medical research map. While the findings of both trials have been published academically, these publications could be made easier to locate.

In several cases, the London School of Hygiene and Tropical Medicine has failed to keep registry entries up to date. A search of Clinicaltrials.gov shows that the university was involved in 28 trials whose status is currently listed as “unknown”. For example, trial NCT01476358 examined whether giving newborn babies a large dose of Vitamin A could boost their immune systems. In total, 100 babies in the Gambia were scheduled to receive the vitamins, with another 100 receiving a placebo. The LSHTM-sponsored trial was scheduled to finish in 2013, but since the university has not updated the registry entry since 2012, its registry entry leaves unclear whether the trial was completed or

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21 University comment: “published: https://www.ncbi.nlm.nih.gov/pubmed/17300629. Found by googling the title of the paper. Noted that the NCT reference number was not provided in the paper. Noted that the record was not updated after completion. However, the best practices referred to in this paper came out after the paper was published, and clinicaltrials.gov only introduced a results section in 2008.”

22 University comment: “published: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398130/. Found by googling NCT00121823 which is listed in the methods section. Noted that results are not posted on clinicaltrials.gov”

23 University comment: “This is per the ICMJE criteria for publication that required registration from 2005 onwards.”
what researchers may have discovered. A search of PubMed for the trial’s number and title did not return any results.24

Similarly, the findings of trial NCT01236274 will remain difficult to locate unless the university updates its registry entries. The observational study of 90,000 people in the UK set out to determine whether taking antipsychotic drugs increases the risk of heart attacks. The researchers noted that “[t]he use of antipsychotics is associated with a rise in cardiovascular events. Previous studies investigating the effect of antipsychotic agents on the risk of Myocardial Infarction (MI) led to conflicting results with reports of either no association or a positive association… the relationship between cardiac events and the use of antipsychotic drugs is not clear.” The study was scheduled to complete in 2013, but the university has not updated the registry entry since 2010, and a search of PubMed for the trial’s number did not return any results. Clinicaltrials.gov automatically indexes journal articles related to a trial, but it was unable to detect a journal article discussing the trial’s results because LSHTM researchers did not follow best practices and failed to include the trial number in its abstract.25 This indicates weak data management practices by the university and its staff.26

**Manchester**

The University of Manchester in its FOI response stated that only one trial (2009-010725-39) sponsored by the university was completed in 2015, and that this trial had not posted results. The university explained that “the data from this trial has not been posted on a public clinical trials registry. The MHRA approved earlier this year a request from the trial team to upload the data at a later date. Please note, the trial team have already published the data [in a journal] in 2016 which included a plain English summary”. The trial in question is listed as “ongoing” rather than “completed” on EudraCT, but on the ISRCTN registry, the same trial is listed as “completed”, indicating weak data management practices within the university. After TranspariMED flagged the issue with the university, it promptly took action to resolve the problem.27

EudraCT lists two additional trials sponsored by Manchester as completed but still missing results.

Trial 2004-002440-96 was completed in 2006. After reviewing an early draft of this study, the University of Manchester commented that it had in fact never sponsored this trial.28 TranspariMED accepts that the university bears no responsibility whatsoever for the lack of results for this trial. (It seems likely that the actual trial sponsor, South Manchester University Hospitals NHS Trust, had erroneously listed the university as a co-sponsor in the relevant registry entry.) This case highlights that the problem of unreliable registry entries is not limited to trials sponsored by universities.

Trial 2007-002571-14 set out to test an innovative treatment for MRSA, commonly known in the UK as the drug-resistant ‘hospital superbug’, in 65 patients with diabetic foot ulcers. The trial was completed in 2009, but no results have been posted, and a PubMed search for the trial number and

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24 University comment: “published: https://www.ncbi.nlm.nih.gov/pubmed/24708735. NCT reference is in abstract in a section entitled “trial registration”. Noted that results are not on clinicaltrials.gov and status states not known.”

25 They did include the trial number in the full text, but Clinicaltrials.gov and PubMed cannot locate it there.

26 University comment: “published: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404491/. Found by googling the NCT reference. NCT reference is in the methods section. Note that this is not a trial, but a case-control study”

27 University comment: “we have contacted the principal investigator and asked him to register the status of this project from ongoing to completed on the EudraCT database”

28 Statement by the University of Manchester: “We are confident that Manchester did not sponsor the 2004-002440-96 trial, and this is documented in our records. We have contacted the listed sponsor of that trial to request they update the EudraCT database so that reference to the University is removed.”
trial title returns no results. While the trial’s results have been published in a journal, hospital administrators who are struggling to manage MRSA may miss that publication because the trial’s identification number was not included in the article.

**Newcastle**

The University of Newcastle stated in its [FOI response](https://www.foi.nsw.gov.au/foi/displayFoia2015?caseid=174730) that no trials sponsored by the university were completed during 2015. EudraCT only lists [eight Newcastle trials](https://www.clinicaltrialsregister.eu), all of which are listed as “ongoing”, suggesting that no trials were completed during 2015.

However, the University of Newcastle’s EudraCT entries alone do not provide a complete picture of Newcastle’s performance regarding trials that ended in 2015. Trial NCT02701959 was registered with Clinicaltrials.gov but not with EudraCT. That trial was completed in 2015, and it has not reported results. Furthermore, at least two trials involving University of Newcastle researchers that are listed as “ongoing” on EudraCT have actually been completed, indicating weak data management practices within the university. Trial 2004-001622-24 was registered over a decade ago, finished recruiting in 2009, and [ended on 15 January 2014](https://www.foi.nsw.gov.au/foi/displayFoia2015?caseid=174730), but continues to be listed as “ongoing”. Trial 2008-006916-39 is also still listed as “ongoing”, but a corresponding entry on Clinicaltrials.gov suggests that the trial was in fact completed in January 2016.

**Oxford**

In response to the [FOI request](https://www.foi.nsw.gov.au/foi/displayFoia2015?caseid=174730), the University of Oxford declined to provide information on university-sponsored trials that were completed during 2015, arguing that this information was “reasonably accessible by other means” because it was publicly available on three clinical trial registries: Clinicaltrials.gov, EudraCT, and ISRCTN. This response would be appropriate if the data uploaded onto public trial registries by the university was complete and correct. However, because the university has failed to adequately track and manage its registry entries, comprehensive information on its trials is not publicly available as claimed.

For example, trial ISRCTN94236001 set out to research a possible treatment for recurrent Ewing’s Sarcoma, a rare cancer that mostly afflicts teenagers and young adults. Ewing’s sufferers on average only have 14 more months to live after the cancer recurs. The trial set out to recruit 40 patients with a “life expectancy of at least 4 months” to study the effects of a drug on the tumour and ascertain its safety and tolerability. Ten of the study patients were to receive the drug in an Oxford hospital. The trial was registered on three separate registries; it has posted results on none of them. (The trial’s Clinicaltrials.gov entry explicitly identifies the University of Oxford as the party responsible for providing information.) This means that other medical researchers cannot discover whether a promising new cancer drug has been found to be safe, slowing the progress of research into new treatments or a cure.

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29 University comment: “[T]he results for trial 2007-002571-14 have been published by the research team - [http://care.diabetesjournals.org/content/diacare/30/2/370.full.pdf](http://care.diabetesjournals.org/content/diacare/30/2/370.full.pdf)"

30 It is unknown whether the university in its FOI response overlooked this trial because it (a) was not a CTIMP, (b) was not registered on EudraCT, and/or (c) was conducted by the university’s School of Agriculture Food and Rural Development rather than by a medical school.

31 Oxford University commented in an email that: “Regarding the Ewing’s Sarcoma trial you mentioned ([https://www.isrctn.com/ISRCTN94236001](https://www.isrctn.com/ISRCTN94236001)), the research team is currently analysing the genomic data and the mechanisms picked up in the biomarker directed trial, and will be submitting for publication later this year. The data would not normally be made available before the paper is published.” TranspariMED strongly disagrees that the posting of summary results on registries can wait until after publication in a journal. Please see the section containing universities’ statements (further below) for more details.
In addition, due to inconsistent data, it is unclear when the trial was completed. The ISRCTN entry states that the trial ended in February 2015. The corresponding Clinicaltrials.gov entry states that the trial was completed in July 2016. Meanwhile, on EudraCT, the same trial is still listed as “ongoing” in the UK. This example demonstrates that data on the university’s trial performance is not “reasonably accessible” by searching its registry entries as claimed by the university, because due to the university’s weak data management practices, external researchers cannot reliably determine when a trial was concluded.

Furthermore, a search of Open Trials shows that the findings of one trial (ISRCTN03147572) that has not posted results on ISRCTN have in fact been published in a PubMed indexed journal. The trial had explored whether it was safe to give a statin to people suffering from dengue fever in order to prepare the ground for later investigations into that statin’s potential to help dengue patients. In total, 330 people in Vietnam who suffered from dengue volunteered to participate in the trial. According to the paper “Dengue endangers billions of people in the tropical world, yet no therapeutic is currently available.” Searching ISRCTN for new treatments for dengue, other researchers into the disease could easily miss this important document because University of Oxford staff failed to upload the link onto the registry.

**Queen Mary University of London**

In its FOI response, Queen Mary University of London (QMUL) stated that only eight trials sponsored by the university were completed in 2015, and that four of these trials have not posted results. A review of registry entries by the university suggests that this is probably incorrect, and shows that QMUL fails to effectively keep track of the clinical trials conducted by its staff.

In its narrative response to the FOI request, QMUL supplied the Unique IDs [i.e. trial numbers] of the four trials it had identified as having ended during 2015 and not having posted results. The narrative information provided by QMUL on these four trials does not match the corresponding entries in clinical trial registries:

- QMUL identified trial 2009-016675-29 as completed during 2015 and not having posted results. (The trial’s results were posted on EudraCT shortly after the FOI response was sent, on 07 April 2017). However, the results sheet uploaded onto EudraCT states that the trial ended in February 2016, not during 2015, as reported by the university. Furthermore, the trial’s main page on EudraCT continues to list the trial as “ongoing”.
- QMUL identified trial ISRCTN01253916 as having been completed during 2015. However, the trial is listed on ISRCTN as having ended in March 2016, not during 2015.
- QMUL identified trial NCT01911910 as completed during 2015 and not having posted results. Clinicaltrials.gov notes that “The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years.” The status of the entry was last verified by QMUL in October 2014. Thus, visitors to the American registry have no way of discovering that the trial has ended, let alone when it ended.
- QMUL identified the fourth 2015 trial missing results as “008188 QM” in its FOI response. This is not a standard trial Unique ID number, and searches run for this number and for the trial’s title returned no results on Open Trials, EudraCT, Clinicaltrials.gov or ISRCTN.

A search of ISRCTN returned five additional QMUL trials recorded as completed during 2015 that have not posted results: ISRCTN72085021, ISRCTN83599025, ISRCTN40785133, ISRCTN22975026, and ISRCTN13028601.
A look at QMUL trials completed prior to 2015 also suggests weak results posting performance by the university. At least five QMUL trials registered on EudraCT that were completed prior to 2015 have failed to post their results:

- Trial 2005-003464-30 set out to discover whether it was worthwhile to screen people for hypothyroidism. Even though the trial was completed in 2009, medical researchers and health policy experts scanning EudraCT cannot discover the answer as no results have been posted.
- Trial 2007-004269-16 set out to study growth failure in children with Crohn’s disease, which remains incurable. QMUL researchers planned to recruit twelve children aged 10-16, all suffering from “severe growth failure”. The trial was completed in 2010 but its results have not been posted, preventing other researchers looking for a cure for the disease from building on the QMUL team’s discoveries.
- Trial 2006-006652-35 explored a new treatment with the potential to help people to better recover from kidney transplants. The trial, which set out to enrol 40 kidney transplant patients in the UK, was completed in 2012. Because the trial’s results have not been posted, it remains unclear whether other transplant patients could be helped by this new treatment.
- Trial 2010-022334-92 tested a new way to help people to stop smoking with the help of 120 British volunteers, and trial 2011-005565-20 compared the effects of e-cigarettes against those of nicotine inhalators. Smoking tobacco continues to kill nearly six million people a year worldwide, but even so, QMUL researchers failed to post results after the two trials were completed in 2011 and 2013, respectively.

The total number of old QMUL trials that have failed to post results is likely to be significantly higher. In total, EudraCT lists 51 clinical trials sponsored by QMUL. Of those, only six have posted results. Many of the remaining 45 trials are listed as “ongoing” – suggesting that results posting is not overdue – but some of these have actually been completed. For example, trial 2011-001192-39, which recruited patients with advanced prostate cancer, is listed as ongoing but actually ended in June 2014.\(^{32}\)

**Swansea**

The EudraCT registry lists two trials sponsored by Swansea University as “ongoing” and not having posted results. However, it seems that both of these trials were completed years ago. Also, both trials have published results in the academic literature, but these results are difficult to find for EudraCT users. Inconsistencies between data provided on EudraCT and ISRCTN indicates weak data management practices within Swansea University.

Trial 2007-002876-32 set out to recruit 2,974 hospitalized elderly patients taking antibiotics. The trial appears to have begun in 2008 and was scheduled to last just three years, but continues to be listed as “ongoing”. No results have been posted on EudraCT, and a search for the trial number in PubMed also returned no results because the EudraCT trial number was not included in any abstracts. However, the same trial was separately registered on ISRCTN, where it is listed as “completed” and two academic papers discussing its results are linked. The two registry entries have not been cross-linked.

Worryingly, it is not clear exactly what Swansea researchers were trying to discover with this trial. According to ISRCTN, the trial had only two primary outcome measures, both focusing on the occurrence of diarrhoea, plus nine secondary outcome measures. Meanwhile, on EudraCT, the same

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\(^{32}\) Trial 2006-004511-21, which started in 2007, is also listed as “ongoing”, which seems unlikely. The researchers involved have already published two journal articles (see here and here) about the trial’s findings, but have not posted any results on EudraCT.
trial lists six primary end points. Such ambiguity facilitates a widespread form of research misconduct known as outcome switching and directly undermines the original rationale of trial registries, which were set up to provide access to data that is free from bias in addition to being comprehensive.

The second trial listed on EudraCT as sponsored by Swansea, trial 2008-001968-36, investigated treatment options for patients with acute severe steroid resistant ulcerative colitis. Around 146,000 people in the UK suffer from this disease, which is a chronic (life-long) condition whose causes remain unclear and for which there is no cure. Even though the trial began nearly a decade ago, it is still listed as “ongoing” on EudraCT, has not posted results there, and a PubMed search for the trial number did not return any results. However, a separate ISRCTN entry for the same trial notes that it was completed in 2014, and published some results in a June 2016 journal article whose abstract omitted the EudraCT number. As with the first Swansea trial, entries in the two registries have not been cross-linked, and the pre-defined primary outcomes differ between trials.

According to their ISRCTN entries, both Swansea-sponsored trials discussed above were funded by UK taxpayers via the NHS National Institute for Health Research, which funds over £1 billion of research each year, including around 750 randomised controlled trials at a time. Researchers later pointed to the ulcerative colitis trial as an example of how “bureaucratic processes of ethical and research and information governance approvals” made trials difficult and expensive to run in the UK. The recommendations presented further below highlight that the problem of hidden results can be resolved without increasing the regulatory burden on researchers in the UK.

University College London

In its FOI response, University College London (UCL) stated that 14 trials sponsored by the university were completed in 2015, and that only 3 of these trials had posted results. (The university noted that 3 of the trials that had not posted results were Phase I studies.) This statement appears to be incorrect, as one of the trials identified as having been completed during 2015 (trial 2013-003363-64) seems to actually have been completed in 2016.

In its FOI response, UCL provided the names and identification numbers of eleven trials completed during 2015 that have not posted results.

Notably, UCL researchers have failed to post the results of four cancer trials concluded during 2015. Between them, these trials aimed to recruit 870 cancer patients as volunteers. Two of the trials involved potentially life-saving treatments for people suffering from ovarian cancer (2008-000837-23) and mantle cell lymphoma (2006-001965-41); UCL’s researchers explicitly set out to discover whether their new treatments would improve “overall survival” among trial participants. A third trial (2013-003469-32) aimed to discover whether a cancer’s growth could be slowed in patients who were so ill that their cancer was regarded as “inoperable, advanced, recurrent or metastatic”. The fourth trial (2006-003203-40) aimed to recruit 32 children suffering from primary bone cancer.

Another trial’s registry entry (NCT01398072) shows that UCL’s data management practices are weak. The purpose of the trial was to develop an optimal antibiotic regime for long-term therapy in people suffering from stable Chronic Obstructive Pulmonary Disease (COPD). When the UCL-sponsored trial was first registered in 2011, the researchers explained that this illness “is the cause of considerable deaths, and... a major cause of hospital admission in the UK... there is little information available about the use of long term antibiotics in the treatment of this disease. Therefore the purpose of this study is to identify the best antibiotic regime for treating patients... The information we get from this study may help us to treat future patients with COPD better.” The trial, which aimed to include 200
patients, was scheduled to last just 13 weeks. Six years later, it has still not posted any results. UCL has not updated the trial’s status since 2012, leading a Clinicaltrials.gov administrator to comment that “The recruitment status of this study is unknown. The completion date has passed and the status has not been verified in more than two years.” Researchers and doctors outside UCL are still waiting for the university to post the trial’s results so that they can “treat future patients with COPD better”, as originally promised.
4 POLICIES

OVERVIEW OF UNIVERSITY POLICIES

The scope and strength of university policies on clinical trials registration and results posting varies widely. **Responding to Freedom of Information (FOI) requests**, some universities reported having no relevant policies whatsoever. Others pointed to policies adopted by clinical trial units or research partnerships between the university and, typically, a local NHS Trust. Yet other universities shared policies that were unambiguously internal and, in some respects, very strong.

A review of the documents provided by universities showed that it is difficult to define what constitutes a relevant policy. For example, many universities regard Standard Operating Procedures for the conduct of clinical trials as policies. Others have formed clinical trial partnerships with other organisations, and regard the policies of these partnerships as internal to the university itself. Some documents shared by universities merely mandate compliance with complex legal or regulatory standards without providing actionable guidance.³³ Yet others seem to have been developed in response to the ICMJE’s adoption of a trial registration policy; in some of these cases, it is unclear whether the university requires staff to register all trials, or merely advises staff that publishers may reject their papers if trials had not been pre-registered. One university claimed to have relevant policies, but the documents it shared contained no policies on either trial registration or results posting, suggesting a lack of clarity about policies within the institution itself.

The section below flags some strong and weak policy elements encountered in order to support universities’ efforts to strengthen their policies.

EXAMPLES OF STRONG POLICIES

**Trial registration**

Keele University has a trial registration policy that clearly and fully meets global best practices as set out in the Declaration of Helsinki. According to Keele’s **SOP11**, all clinical trials must be registered before the first participant is recruited:

“All clinical trials must be registered on a public database prior to the start of participant recruitment.”

An excellent aspect of the policy is that it applies to all Keele staff and students:

“This SOP applies to all individuals undertaking functions outlined herein. This includes all core Keele CTU [Clinical Trials Unit] staff and all other academic, research, management or admin staff, or students working on Keele University sponsored/ Keele CTU managed clinical research projects through site agreements, service or other contractual arrangements.”

The London School of Hygiene and Tropical Medicine also has a trial registration policy that meets global best practices and covers all staff and students (**SOP-028-01**). In addition, it clearly defines responsibilities:

³³ Busy medical research staff seem unlikely to review and analyse legal texts that can be hundreds of pages long.
“For clinical trials, it is the responsibility of the Sponsor to ensure that their trial is registered on a public database. For LSHTM Sponsored clinical trials this responsibility is delegated to the Chief/Principal Investigator.”

Results posting

Keele University has put very strong policies and procedures in place for CTIMPs that are sponsored by the university. However, these policies only apply to CTIMPs sponsored by the university, rather than to all trials conducted at Keele.

The clarity with which Keele’s CTIMP sponsorship policies allocate responsibilities is exemplary. For example, tool TEM01 explicitly discusses who will bear responsibility for compliance if multiple sponsors are involved. Tool TEM03 explicitly makes the Chief Investigator responsible for trial registration, for posting the results of CTIMPs on the EudraCT registry within the required timelines, and for generally ensuring that all applicable laws and regulations are complied with. In addition, the CI must provide an “E-mail confirmation of EudraCT [registration]” to the university to allow it to verify compliance (SOSOP01).

Accountability is further boosted by requiring the Chief Investigator to sign a statement (TEM3). The CI has to commit to take “full responsibility for the conduct and delivery of the research as proposed” and “comply with the University’s and CTU’s policies and procedures... the Principles of Good Clinical Practice, the Protocol and... the relevant legislation”. Where the CI delegates responsibilities to other team members, (s)he has to document this in a “Delegation Log”; even so, the CI has to explicitly confirm that “ultimately I retain responsibility”.

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34 Note that while a university can delegate tasks – which LSHTM does with admirable clarity – the ultimate responsibility for ensuring that all trials are indeed registered cannot be delegated and rests with the university.

35 Note that further up the accountability chain, the university retains ultimate responsibility for ensuring that the conduct and delivery of all its research complies with all applicable laws, regulations, policies and ethical standards.
TYPOLOGY OF WEAK POLICY ELEMENTS

Several of the top 16 UK medical universities reported that they had no trial registration and/or results posting policies whatsoever. Others reported that they did have policies and shared relevant documents. A review of these documents, plus documents shared by the universities of Aberdeen, Bristol, and Nottingham, identified numerous weaknesses. The table below provides a typology of weaknesses encountered across the policy documents reviewed.

<table>
<thead>
<tr>
<th>Weakness</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Not formal</td>
<td>A statement that is not reflected in any formally endorsed policy document is not a formal policy. Staff members are unlikely to be aware of informal expectations, and compliance cannot be enforced.</td>
</tr>
<tr>
<td>Not binding</td>
<td>Some documents merely state that staff “should” register or report trials, or mix words like “should” and “must” within the same section, leaving unclear whether the policy is binding or not. This could suggest to staff that it is acceptable not to pre-register trials or post the results of trials on registries.</td>
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<tr>
<td>Limited scope</td>
<td>The Declaration of Helsinki makes pre-registration of all clinical trials a non-negotiable ethical imperative for all medical researchers. Similarly, the WHO regards results posting (or results reporting in journals if registries do not have a posting function) as best practice for all trials. Limiting policies’ scope to only some types of trials, such as CTIMPs or university-sponsored trials, is insufficient to ensure that all university staff adhere to the minimum ethical standards governing interventional medical research conducted in humans during the conduct of all trials that they are involved with.</td>
</tr>
<tr>
<td>Not public</td>
<td>Some policies are reportedly contained within SOPs that are only accessible to university staff, and are not public. While there may (or may not) be valid reasons not to put SOPs into the public realm, there is no reason why policies on trial registration and results posting should not be public. The same applies to audit reports. Several universities argued that their existing trial audit reports were confidential as they contained commercial secrets. However, audit data on trial registration and reporting performance does not contain any commercial secrets, and so should be made public.</td>
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<tr>
<td>Not consistent</td>
<td>In some cases, two separate policy documents spelled out different standards, potentially leaving staff unclear about expectations.</td>
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<tr>
<td>Not updated</td>
<td>Documents provided by several universities state that ICMJE rules do not require phase 1 trials to be pre-registered. In fact, this has been an ICMJE requirement since 2008. Standards in this field are constantly evolving, so scheduling regular policy updates is essential.</td>
</tr>
<tr>
<td>Not precise</td>
<td>If policies fail to clearly and unambiguously define who is responsible for ensuring that trials are registered and their results posted, and within what timeframes, staff members will remain unclear about their responsibilities. Also, in case of non-compliance, nobody can be held to account.</td>
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</table>

36 Aberdeen, Bristol, and Nottingham shared documents in response to FOI requests whose wording was identical to the FOI requests submitted to the top medical universities covered by this report. These documents were included in the review to inform the development of the typology.

37 Example: “The [university] PI or TM should complete the ISRCTN for the study. The CTU Governance & QA Officer should be involved in completing the ISRCTN application… It is the responsibility of the CI, CTU PI and the Study Co-ordinator (SC) and other members of the Study Team, as appropriate, to gain the appropriate regulatory approvals for the study.” [emphases added] However, a publications consultant who reviewed an early draft of this section pointed out that responsibilities may vary depending on whether commercial sponsors or other third parties are involved in a trial.
Not explicit

Merely telling staff members that they must comply with certain laws or standards leaves expectations unclear and seems unlikely to drive positive behaviour. Medical researchers cannot realistically be expected to go through several hundred pages of text line-by-line to determine what their obligations are.

Not audited

Some universities reported some form of auditing activity related to clinical trials in their FOI responses. However, no university reported systematically auditing the trial registration and results posting performance of its staff members. In addition, the results of existing audits are currently not made public.

The University of Aberdeen is set to become a pioneer in this regard. It plans to conduct an audit of its existing registry entries.

Not enforced

One university provided a document stating that staff members had to update registry records every six months. A subsequent search of the U.S. registry showed that the most entries there had not been updated within the past six months, even though the university could easily have monitored staff compliance in this regard.

Not sanctioned

Few of the policy documents explicitly spell out sanctions for non-compliance, or offer rewards for outstanding performance.

Not known

Policies can only drive positive behaviour if staff members know about them. One university’s FOI team reported the existence of trial registration and results posting policies, but a subsequent review of the documents referred to in the FOI response showed that they contained no such provisions.

All universities’ FOI responses including their policy documents were archived online. Individual universities’ policies (or responses noting that no applicable policies exist) can be directly accessed through the links provided in the table below.

<table>
<thead>
<tr>
<th>University</th>
<th>Document links</th>
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<tr>
<td>Cambridge</td>
<td>Cambridge FOI response</td>
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<td>Cardiff</td>
<td>Cardiff FOI response</td>
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<td>Dundee</td>
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<td>Keele</td>
<td>Keele FOI response</td>
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<td>King’s College London</td>
<td>KCL FOI response</td>
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<td>London School of Hygiene &amp; TM</td>
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<td>Swansea</td>
<td>Swansea FOI response</td>
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<tr>
<td>University College London</td>
<td>UCL FOI response</td>
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5 STATEMENTS BY UNIVERSITIES

OVERVIEW OF UNIVERSITY STATEMENTS

TranspariMED contacted all universities with a draft of this study and asked them to provide a formal response for inclusion in the final study.

Eight universities (Cambridge, Exeter, Glasgow, Keele, King’s College London, QMUL, Swansea, University College London) did not respond. The responses of the other eight universities are reproduced below in full, as is the University of Aberdeen’s response to an earlier pilot study.

Two of these statements stand out:

- The University of Aberdeen shared a trial-by-trial review of its EudraCT entries and pledged to carry out an audit of its existing registry entries as well as strengthening related processes and procedures. To the best of TranspariMED’s knowledge, this will make Aberdeen the first university in the world to undertake an institution-wide audit of clinical trials as recommended by the AllTrials campaign.
- The University of Dundee reported that it had already started the process of updating registry entries, uploading missing trial results onto registries, linking published papers to registries, and inserting missing trial registry numbers into PubMed abstracts in 2016. It added that it was also in the process of improving existing systems for keeping its registry entries up to date.

In addition, the University of Manchester reported already having contacted the principal investigator of one trial featured in this study to ask him to update its register entry.

INDIVIDUAL UNIVERSITY STATEMENTS

Aberdeen

In May 2017, the University of Aberdeen became the first university in the UK to pledge an audit of its existing trial registry entries in response to the findings of a pilot study by TranspariMED.

While the University of Aberdeen was not among the 16 universities covered by the present study, its formal statement from May 2017 is reproduced here as an example of the positive steps a university can take to ensure that all its registry entries are complete, accurate and up-to-date:

“The University of Aberdeen is committed to ensuring transparency in research, avoiding selective publication, and making results readily available to the public. We already ensure that publication and dissemination of results is brought up in our GCP training so that researchers are made aware of their responsibilities as early as possible, and weekly checks are made on Clinicaltrials.Gov to review any problem records and act upon them. There is no requirement to post results onto this register as none of our trials have as yet fallen under the FDA regulations. This audit report has helped highlight areas where improvements can be made. We plan to carry out an audit of the of the (known) registry entries and to review our oversight processes. Also, all trial protocols risk assessed for sponsorship shall be required to include a statement confirming UoA commitment to register trials and report results.”
Cambridge

Cambridge did not respond to repeated requests for a statement.

Cardiff

Cardiff University on 15 June 2017 emailed a question about how the quantitative data for the university had been generated. TranspariMED replied on the same day, pointing to the Annex of the report, which had been shared with the university in its original email, and offered help should the university have further questions. On 22 June 2017, the deadline for supplying a statement, the university wrote the following email:

“We’ve had a look at the figures you sent over and our analysis doesn’t give a figure of 87 trials linked with Cardiff University. Running the same search methodology, there are 72 trials on the EudraCT and ClinicalTrials.gov registries that involve Cardiff University (a number of trials are listed on both databases). 27 of those trials are either still recruiting, analysing data or did not commence, and as such are not due to submit results yet. The actual figure of trials that have not uploaded results on to those databases is 45. 9 of these are also led by other organisations, and therefore Cardiff University is not responsible for maintaining the entries on EudraCT and ClinicalTrials.gov.”

- Comment by TranspariMED

The statement by Cardiff University is disappointing. If the figures supplied by the university are correct, it has posted results for only one single trial across both major trial registries, while it has failed to post results for a minimum of 36 trials. This would mean that Cardiff University has posted results for less than 2.7% of trials. In other words, 97.3% of clinical trials for which the university accepts responsibility have failed to post results. This is not a performance that any institution conducting medical research in human volunteers should be proud of.

The single trial for which Cardiff University appears to have posted results illustrates the impossibility of external researchers collecting precise data on the university’s results posting performance. The trial investigated a possible new drug combination to treat advanced cancers in patient volunteers with an “[e]stimated life expectancy greater than three months” who were “not amenable to curative treatment with surgery or radiotherapy”. The trial is still listed as “ongoing” on EudraCT (2007-007615-82), where it has posted results. On Clinicaltrials.gov, the same trial (NCT01090466) is listed as having been “completed” in 2010, but has not posted results. The same trial was also registered on ISRCTN (trial number ISRCTN31546330), again giving a trial end date of 2010, again without results. Furthermore, the description of the trial’s primary and secondary end points is inconsistent across all three registries, and the target number of participants given on

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38 While TranspariMED has no reason to believe that the figures reported by the university are incorrect, Cardiff University did not supply a data table that would enable external researchers to independently verify its figures. Furthermore, the claim that “27 of those trials are either still recruiting, analysing data or did not commence, and as such are not due to submit results yet” is also unverifiable due to the university’s weak data management practices. As the discussion of trial 2007-003798-16 in this study (which was shared with the university when the statement was requested, and which the university has not challenged) and the discussion of trial 2007-007615-82 (see below) show, Cardiff trials listed as “ongoing” or “still recruiting” in registry entries cannot reliably be assumed not to have been completed years ago.

39 A manual review of Cardiff University entries on a third registry, ISRCTN, shows that 25 entries there with completion dates prior to 30 June 2016 are also missing results, meaning that the total number of Cardiff trials without results is likely to be even higher than the 36 reported by the university. However, there may be some overlap between these ISRCTN entries and trials that have been registered on the other two registries; TranspariMED did not check for such overlaps.
ISRCTN differs from that stated in the other registries; a PubMed search for all three trial numbers returns no results. While Cardiff University is identified as the trial’s sponsor on EudraCT and ISRCTN, the Clinicaltrials.gov entry does not even mention Cardiff University, instead listing “Wales Cancer Trials Unit” as the sole sponsor. Thus, due to the university’s weak data management practices, an external researcher without access to internal university documents cannot even determine with 100% confidence whether this is a Cardiff-sponsored trial in the first place.

Following receipt of Cardiff’s statement, TranspariMED successfully replicated the headline figures cited in the study using the original methodology. The methodology of this study, which had been shared with the university, states that:

“Despite the inevitable limitations of this study, TranspariMED is confident that the data presented here are sufficient to demonstrate that medical researchers at all the top 16 UK universities frequently deviate from best practices in the field, and that some universities are more successful than others in ensuring that staff post the summary results of clinical trials on registries. In addition, TranspariMED is confident that the data in this study are sufficient to demonstrate that all 16 universities need to review and update their existing registry entries, and take steps to ensure that in future, all new future registry entries will be comprehensive, correct, and kept up to date.”

TranspariMED is confident that the data presented in this study are sufficient to demonstrate that Cardiff’s researchers frequently deviate from best practices in the field. They are also sufficient to demonstrate that some universities are more successful than others, as a results posting rate of 2.7% would still leave Cardiff near the bottom of the league, far behind stronger performers like Keele (29.4%) and Dundee (23.2%). Finally, the data are sufficient to demonstrate the need for Cardiff University to review and update its existing registry entries.

TranspariMED hopes that Cardiff University will, at a minimum, revisit the registry entries it has already identified as deficient and post the summary results for these 36 clinical trials onto the relevant registries.

Dundee

The University of Dundee provided the following statement [emphases in the original]:

“The University of Dundee welcomes the opportunity provided by TranspariMED to respond to the findings of their study. We acknowledge the importance of full, transparent reporting of all trial results in a way that allows patients, funders, clinicians and policymakers to access the results easily. We acknowledge that our past performance in making all our trials results fully available has not been consistent with best practice standards. However, since identifying this issue in December 2016, we have been working with investigators and colleagues to rectify this and to update the backlog of trials that were missing publicly available data. Significant work has also been ongoing since April 2016 to upload missing results for CTIMPs to EudraCT and its sister publicly accessible registry the EU CT Register, which became publicly available in January 2016.

Since December 2016, when the AllTrials team first alerted us of these issues with respect to other publicly accessible registries, we have been working with investigators and colleagues to further upload missing trial results to those registries, link published papers to registries, and insert missing trial registry numbers into PubMed abstracts. We are also in the process
of improving existing University systems to provide better oversight of the processes for keeping registry entries up to date.

We would like to make two clarifications in the interest of accurate reporting:

1) With respect to the two CTIMPs quoted in the report, ViaDUCT (2013-003573-10) and SCOT (2007-000012-90). Results for the former are now on EudraCT and available to the public on EU CT Register.\(^4\) The latter is registered on EudraCT, and results posting is in progress so these will be publicly available via EU CT Register. **The reasons for delay in posting results for both trials was that there were mandatory reporting requirements to the UK Regulatory Authority, the MHRA, that the University, had to fulfil.**

2) With respect to comments on page 29 of the draft report, The University would like to clarify that the Tayside Medical Sciences Centre (TASC) policies are indeed University Policies. TASC is a formalised collaboration between the University of Dundee (UoD) and NHS Tayside. UoD has granted authority to TASC to manage this aspect of UoD’s business and the post of R&D Director, is a joint UoD-NHST post, with formalised, delegated authority given to that post by both organisations.

As this recent report has reminded us, there is plenty of work still to do, but we expect the changes that we have put in place to improve the standard of our trial reporting going forward.”

**Comment by TranspariMED**

It is extremely encouraging that the University of Dundee is already taking strong action to complete its registry entries. The university should be applauded for its positive efforts to further improve its contribution to medical progress.

Regarding the university’s comment on its policies, the early draft of the study reviewed by universities made a binary distinction between ‘internal’ and ‘external’ policies. TranspariMED accepts that this dichotomy was insufficiently nuanced and has revised the text of the study accordingly.

**Edinburgh**

The University of Edinburgh provided the following statement:

“We do not recognise the figures quoted in this report and have concerns about the methodology used to obtain them. It is not clear how clinical trials have been defined and which research studies have been included or excluded in the analysis. Registrations made in clinicaltrials.gov will include more types of research than just clinical trials. The studies that are highlighted from Edinburgh do not match with our data for these trials. We are disappointed that you have not included the detailed information that we provided in our response to your initial enquiry:


\(^4\) The results were posted on 13 May 2017, shortly after review by TranspariMED. TranspariMED has changed the wording in the relevant paragraph of the study to reflect this recent positive development.
“The University of Edinburgh is committed to transparent reporting of our research, as demonstrated by our endorsement of the AllTrials campaign. We endeavour to publish all of our research outcomes in order to accelerate the public benefits from them. We also have a commitment to demonstrate the value of our work for the Research Excellence Framework. We welcome improvements to registration and reporting of clinical trial results under EudraCT and clinicaltrials.gov.

“We hold comprehensive records of all past and present clinical trials, and are regularly inspected by the Medicines and Healthcare products Regulatory Agency to ensure compliance with the Clinical Trials Regulations. As detailed in our response, we have robust policies and processes regarding registration and reporting of clinical trial information and results. These policies have been developed jointly with NHS Lothian – not delegated – as we co-sponsor all clinical research studies. These Standard Operating Procedures are formal, internal and binding on staff from both organisations, ensuring that all parties are clear on their responsibilities. Our policies and SOPs are publicly available through http://accord.scot, which is linked to both the University and NHS Lothian websites. Training in relevant SOPs is provided to staff working on clinical trials in Edinburgh, and all clinical trials are regularly monitored for compliance with the protocol and relevant SOPs.

“We will continue to work with our researchers to promote proactive reporting of results in clinical trial registries.”

- **Comment by TranspariMED**

The university notes in its statement that “[t]he studies that are highlighted from Edinburgh do not match with our data for these trials.” TranspariMED revisited all trials mentioned in the section of the study discussing individual trials by the University of Edinburgh. These are four trials, some of them registered in more than one registry:

- Every single registry entry identifies the University of Edinburgh as a sponsor or co-sponsor
- All four items flagged are clinical trials
- Five out of six registry entries cite 2015 as the year of trial completion, yet the university listed none of them in its response to the FOI question about trials ending in 2015 that have not posted results on registries

<table>
<thead>
<tr>
<th>EudraCT</th>
<th>Other registries</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-004706-25</td>
<td>None</td>
<td>The registry entry identifies “University of Edinburgh (ACCORD)” as the trial sponsor. “NHS Lothian (ACCORD)” is listed as the second sponsor. The trial has not posted results on the registry. Even though the registry states “2015-11-01” as “Date of the global end of the trial”, this trial was not identified by the university in response to TranspariMED’s FOI request. While this was primarily a feasibility study whose primary endpoint is recruitment rates, the protocol of the trial states that it also studied drug safety and efficacy against placebo, and thus qualifies as a clinical trial. The registry entry itself identifies it as being a Phase 4 trial.</td>
</tr>
<tr>
<td>2006-003509-18</td>
<td>None</td>
<td>The registry entry identifies “University of Edinburgh (ACCORD)” as the trial sponsor. “NHS Lothian (ACCORD)” is listed as a second sponsor. The trial has not posted results on the registry. Even though the registry states “2015-01-09” as “Date of the global end of the trial”, this trial was not identified by the university in response to TranspariMED’s FOI request. While this was primarily a feasibility study whose primary endpoint is recruitment rates, the protocol of the trial states that it also studied drug safety and efficacy against placebo, and thus qualifies as a clinical trial. The registry entry itself identifies it as being a Phase 4 trial.</td>
</tr>
</tbody>
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41 FOI question 9: “Please provide the name and unique identification number of each clinical trial that was sponsored by the university and was completed during the calendar year 2015 that has not posted its results on a public clinical trials registry as of today”. The university named three trials in response. None of the four trials listed here were named in its response.
Either the “data for these trials” held by the University of Edinburgh is incorrect, or the registry entries are incorrect, or both. It would appear to be the responsibility of the university to ensure that registry entries bearing its name accurately reflect the medical research being conducted at the university.

Regarding the university’s statement that “[w]e are disappointed that you have not included the detailed information that we provided in our response to your initial enquiry [FOI request], TranspariMED has linked all universities’ FOI responses within the study; Edinburgh’s FOI response is publicly available. Questions 1-4 were related to policies. Questions 5-9 were related to practices. In the interests of maximum transparency, the university’s answers to questions 5-9 are reproduced below:

“You asked how many clinical trials sponsored by the University were completed during the calendar year 2015, how many have been registered, and how many have entered study results. Six clinical trials sponsored by the University were completed during 2015. All six trials are registered on a public clinical trials registry. Three of the trials have not
yet entered results or links to publications.”

In its FOI response, the university listed three trials it had identified as having been completed during 2015 and not having posted results on registries, and provided details on their status:

- **NCT02142699** “Data analysis ongoing”
- **ISRCTN62133820** “Final study report has been submitted to sponsor. Publication planned.”
- **NCT02080377** “Results submitted to journal for publication”

(Note that not yet having published trial results in an academic journal is not a valid reason for delaying the posting of summary results on trial registries. Please see TranspariMED’s comment on Oxford University’s statement, further below, for a detailed discussion.)

TranspariMED’s subsequent research identified four additional trials sponsored by the university that appear to have been completed during 2015 and have not posted results on a registry (see the table above). In addition, the inconsistencies observed in the two registry entries for trial 2013-005338-39 / NCT02154789 (see the table above) indicated weak data management practices by the university. Therefore, TranspariMED assessed the university’s FOI responses regarding trial numbers as unreliable and did not cite them in the draft study.

TranspariMED thus calculated the headline results posting figures for the University of Edinburgh in the same way as for all other universities. While the methodology used has some drawbacks – as highlighted in the university’s response, and in the methodology section of this study – it allows the generation of comparative data by external researchers. In future, once Edinburgh and other universities have improved the quality of data provided in their registry entries to the point where external researchers can confidently generate precise and accurate results posting figures by reviewing and assessing registry entries one-by-one, TranspariMED will adjust and refine its methodology accordingly. At present, given the unreliability of data uploaded by universities themselves, alternative approaches such as assessing all registry entries one-by-one would not yield precise figures.

Regarding the university’s comment on its policies, the early draft of the study reviewed by universities made a binary distinction between ‘internal’ and ‘external’ policies. TranspariMED accepts that this dichotomy was insufficiently nuanced and has revised the text of the study accordingly. TranspariMED has also clarified the definition used within the methodology section.

It is extremely encouraging that the University of Edinburgh has voluntarily chosen to support the AllTrials campaign. It is also encouraging that it is confident that it “hold[s] comprehensive records of all past and present clinical trials” – something that few UK universities currently seem to do. This indicates that despite present shortcomings, the university takes the issue seriously and is determined to improve its performance.

In this context, the university may wish to consider AllTrials’ suggestion that universities:

> “Conduct regular public audit of compliance with your own policies, setting out proportion of registered trials, proportion of trials with reported results, and proportion of trials with Clinical study reports or equivalent reports posted online”

Once the university has resolved the data quality issues within its registry entries, and audited its internal records and made them publicly available, external researchers (after verifying the accuracy
of the university’s own data through cross-checking with registry entries) will be able to rapidly and precisely determine the university’s results posting performance.

**Exeter**

Exeter did not respond to repeated requests for a statement.

**Glasgow**

Glasgow did not respond to repeated requests for a statement.

**Imperial College London**

In an email, Imperial College London declined to provide a formal statement in response to the study:

“We will not be making an statement in response to your report, but you have our full FOI response. For information, the principal investigator for the Duchenne muscular dystrophy trial referred to in the report (2006-003833-33) left Imperial College before the trial ended and the research was therefore not concluded at the College.”

- **Comment by TranspariMED**

Staff mobility is often cited as a factor that contributes to universities’ low results posting rates and other data management problems. TranspariMED hopes that this study will increase awareness among universities about their obligations as trial sponsors.

According to the European Medicines Agency, “[t]he sponsor has the duty to post the summary results directly into EudraCT within 6 or 12 months after the end of the trial.” Similarly, it is the trial sponsor who is responsible for ensuring that Clinicaltrials.gov entries are updated not less than once every 12 months. (Please see the EMA’s and FDA’s statements further below for more details.)

While universities may legitimately choose to delegate certain tasks to research staff, this does not absolve them of their ultimate responsibility for compliance with legal and regulatory demands and adherence to global ethical standards. Thus, the onus is upon the university to ensure that summary results are promptly posted for the Duchenne muscular dystrophy trial 2006-003833-33.

**Keele**

Keele did not respond to repeated requests for a statement.

**King’s College London**

King’s College London did not respond to repeated requests for a statement.

**London School of H&TM**

The London School of Hygiene and Tropical Medicine did not provide a formal statement, but it did insert some comments related to individual trials in the draft study. These are reproduced verbatim below:
Comment on trial NCT00131794:
“published: https://www.ncbi.nlm.nih.gov/pubmed/17300629. Found by googling the title of the paper. Noted that the NCT reference number was not provided in the paper. Noted that the record was not updated after completion. However, the best practices referred to in this paper came out after the paper was published, and clinicaltrials.gov only introduced a results section in 2008.”

Comment on trial NCT00121823:
“published: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398130/. Found by googling NCT00121823 which is listed in the methods section. Noted that results are not posted on clinicaltrials.gov”

Comment on the sentence “Both trials were retrospectively registered in 2005”:
“This is per the ICMJE criteria for publication that required registration from 2005 onwards.”

Comment on trial NCT01476358:
“published: https://www.ncbi.nlm.nih.gov/pubmed/24708735. NCT reference is in abstract in a section entitled “trial registration”. Noted that results are not on clinicaltrials.gov and status states not known.”

Comment on trial NCT01236274:
“published: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404491/ Found by googling the NCT reference. NCT reference is in the methods section. Note that this is not a trial, but a case-control study”

- Comment by TranspariMED

TranspariMED welcomes the university’s detailed feedback on these four registry entries. As TranspariMED notes in the study, the retrospective registration of the first two trials in 2005 is entirely positive. The fact that the results for all four trials have been published in academic journals is also very positive. TranspariMED hopes that the university will take action to ensure that the summary results of these trials are soon posted onto the relevant registries.

Manchester

The University of Manchester provided the following statement:

“We take the issue of openness and transparency very seriously – and as a matter of course ensure that the trials we sponsor are registered appropriately on a public database.

We are confident that Manchester did not sponsor the 2004-002440-96 trial, and this is documented in our records. We have contacted the listed sponsor of that trial to request they update the EudraCT database so that reference to the University is removed.

In terms of the 2015 trial [2009-010725-39], we have contacted the principal investigator and asked him to register the status of this project from ongoing to completed on the EudraCT database.

However, we are investigating why the results of trial 2007-002571-14 were not published.”
In a subsequent email message, a staff member of the university reported that:

“[T]he results for trial 2007-002571-14 have been published by the research team - http://care.diabetesjournals.org/content/diacare/30/2/370.full.pdf”

- Comment by TranspariMED

TranspariMED accepts that the University of Manchester bears no responsibility whatsoever for the lack of results for trial 2004-002440-96, which TranspariMED had included in the study based on an incorrect registry entry made by a third party.

It is excellent that the university has already taken steps to towards updating the registry entry for trial 2009-010725-39. TranspariMED hopes that the university will also ensure that the results of trial 2007-002571-14 are posted onto the relevant registry in order to make them more accessible.

Newcastle

Newcastle University provided the following statement:

“Newcastle University follows the necessary procedures as it is mandatory only to register CTIMPs (clinical trials of investigational medicinal products or ‘drug trials’) on EudraCT which we do in all those cases either directly or with our NHS Trust partner. The registration of other trials is deemed to be good practice, and is agreed through the Health Research Authority via the research ethics committees, and we may register with sites such as clinicaltrials.gov or ISRCTN.”

- Comment by TranspariMED

Newcastle University’s apparent belief that the registration of clinical trials other than CTIMPs is not mandatory is mistaken. The registration of all clinical trials is mandatory, rather than just “good practice”. Trial registration is a condition of ethics approval in the UK and an ethical obligation according to the Declaration of Helsinki.

Oxford

Oxford University did not provide a formal statement for inclusion in this report.

However, a member of Oxford University’s media relations team sent the following email:

“I’ve checked through the methodology section and I can’t work out how you have reached this figure. Additionally, it isn’t clear whether this is the number of trials currently taking place, to have taken place to date or in a specific year. Also, many of our researchers work in collaboration with scientists from other institutions - does this figure include those working with other teams?

“Regarding the Ewing’s Sarcoma trial you mentioned (https://www.isrctn.com/ISRCTN94236001), the research team is currently analysing the genomic data and the mechanisms picked up in the biomarker directed trial, and will be submitting for publication later this year. The data would not normally be made available before the paper is published.”
TranspariMED strongly disagrees with Oxford’s apparent assertion that the posting of summary results on registries can wait until after a journal has published a trial’s findings. The trial that Oxford referred to in its response (ISRCTN94236001) is a cancer trial that ended in February 2015. The process of academic publication tends to be slow. Even assuming that Oxford’s researchers submit their findings to a journal this summer, and that the journal decides to accept the paper, the trial’s findings are likely to only get published in 2018—three years after the trial was completed. If the first journal rejects the paper, the researchers will be forced to submit the same paper to a second and maybe a third journal, restarting the cycle from scratch every time and pushing out the likely publication date to 2019 or beyond.

The World Health Organization has explicitly demanded that “key outcomes are to be made publicly available within 12 months of study completion by posting to the results section of the primary clinical trial registry... [This] represent[s] the longest possible acceptable timeframe for reporting and shorter timeframes are strongly encouraged.” The WHO’s statement on this issue makes clear that the global body expects results posting on registries prior to results publication in journals to be the norm, not an exception.

Medical progress is slowed down when the findings of cancer trials are kept from public view for the years it can take until a journal finally publishes them. This is presumably not in the interests of the cancer patients who volunteered to participate in the Oxford trial, nor the many Ewing’s Sarcoma sufferers elsewhere whose lives may depend on the rapid discovery of a cure. (Note that the Oxford trial was funded by taxpayers, not by a private company.) Indeed, one of the key advantages of trial registries is that they allow medical researchers worldwide to gain rapid access to the newest discoveries being made in their field—but only if those making the discoveries share them by posting results.

While university researchers need to publish in journals, they can do so after having posted the summary results in trial registries because most major medical journals do “not consider as prior publication the posting of trial results in any registry”. Thus, there appears to be no compelling reason for medical researchers at Oxford not to share their results as rapidly as possible, and within 12 months of trial completion at the very latest.

In order to address the university’s methodological concerns, TranspariMED replicated its original findings and on 16 June 2017 shared them with the university, noting in an email that:

“[I’ve] just run the same searches using the same methodology and found no indication that the original results were flawed. Please see the attached document for details... However, I’m aware that the data generated using this methodology is not 100% precise, as discussed in the section of the methodology titled “Limitations”. I hope this answers your question. If not, I remain available to discuss further.”

TranspariMED did not receive any further communications from the university after this date.
Queen Mary (QMUL)

QMUL did not respond to repeated requests for a statement.

Swansea

Swansea did not respond to repeated requests for a statement.

University College London

UCL did not respond to repeated requests for a statement.
6 STATEMENT BY RESEARCH FUNDERS

Since May 2017, over a dozen leading medical research funders have signed up to a joint statement that has major implications for British universities. This rapidly growing global group of funders, which includes the UK’s National Institute for Health Research, the Medical Research Council, the Wellcome Trust, and the Department for International Development, will in future require grantees to pre-register all trials, post their results on registries within 12 months, and ensure that registry entries are complete, accurate, and kept up to date.

Crucially, each participating funder has agreed to actively “monitor registration and endorse the development of systems to monitor results reporting on an ongoing basis” and make this monitoring data public. Universities and researchers who fail to meet the new disclosure standards may get their funding cut off:

“When a PI [principal investigator] applies for new funding, they may be asked to provide a list of all previous trials on which they were PI within a specified timeframe and their reporting status, with an explanation where trials have remained unreported.” Future grant applications will be expected to include “specific time bound commitments” on sharing results.

The funders’ statement emphasizes that the proposed measures to ensure better results sharing are highly cost-effective:

“The costs of disseminating the results of research are a minor component of the overall costs of conducting such research, and results reporting is an essential component of the research enterprise. The resource allocation, public health and scientific benefits - together with the need to meet ethical imperatives - far outweigh the costs.”

The funders’ statement sets out four key expectations:
1. Trials should be registered before the first subject receives the first medical intervention
2. Registry entries should be complete, accurate, and be kept up to date
3. Summary results should be posted on registries within 12 months of primary study completion
4. Results should also be published in an open access journal within an “indicative timeframe” of 24 months after completion

The funders’ statement has been strongly welcomed by the AllTrials campaign and the Cochrane Collaboration. TranspariMED also strongly welcomes this promising new initiative, and will closely follow its evolution and impact over the coming months and years.

Defined as “the last visit of the last subject for collection of data on the primary outcome”.

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7 STATEMENTS BY REGULATORS

CAN REGULATORS ENFORCE RULES ON RESULTS POSTING?

Universities’ responses to TranspariMED’s FOI requests indicate that not all academic institutions have a full understanding of current legal and regulatory requirements regarding the posting of trial results.

In addition, TranspariMED’s study shows that the top UK universities frequently fail to update their registry entries and ensure that entries are complete and consistent. In particular, many trials that have been completed years ago remain listed as “ongoing”. Also, some trials that are listed as “completed” cite completion dates that contradict the dates stated elsewhere (e.g. on other registries). This raises the question whether regulators will be able to monitor trial sponsors’ performance and enforce existing laws and rules that mandate results posting for some clinical trials within set timeframes, typically within 12 months of trial completion. Can trial sponsors ‘game the system’ by indefinitely listing such trials as “ongoing” on registry entries?

TranspariMED approached the UK’s Health Research Authority (HRA), the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) and asked them to clarify matters and answer some specific questions.

- The EMA stated that “The sponsor has the duty to post the summary results directly into EudraCT within 6 or 12 months after the end of the trial”.
- The FDA pointed to 42 CFR 11.64, according to which sponsors are obliged to update clinical trial registration information “not less than once every 12 months”.

TranspariMED’s questions and regulators’ responses are reproduced below in full.
STATEMENT BY THE UK HEALTH RESEARCH AUTHORITY

Question by TranspariMED

Can you please clarify whether or not the UK Clinical Trial Regulations or any other current legislation or regulation applicable in the UK (including European Union law) mandates the posting of summary results on trial registries?

Response by the Health Research Authority

Reporting of clinical trials results is not mandated by the current UK Clinical Trials Regulations themselves but by other EU Regulations – see www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002127.jsp&mid=WC0b01ac058004d5c1 for details.

The requirement for transparency and in particular reporting the results of clinical trials will become more structured with the new EU Clinical Trial Regulation. Under the new Regulation, which should come into force in 2019, sponsors will have to by law upload both a technical summary and a lay summary, the contents of which will be structured by law.

The requirement to report lay summaries of clinical trial results will become mandatory under the new EU Clinical Trials Regulation, but that requirement is to report the results on the forthcoming EU Clinical Trials Portal, not on other trial registries.

Also, it will only apply to clinical trials of investigational medicinal products, not other types of clinical trials, e.g. of medical devices or surgery.

Our current guidance (www.hra.nhs.uk/?p=200866) asks sponsors of clinical trials to feed back the summary findings of studies to the participants in those studies (excluding phase I studies), but this is not mandatory.

More information can be found here: http://www.hra.nhs.uk/resources/during-and-after-your-study/transparency-registration-and-publication/

HRA spokesperson
23 June 2017
STATEMENTS BY THE EUROPEAN MEDICINES AGENCY

First set of questions by TranspariMED

1. Are there laws and/or rules setting out how often trial sponsors have to update and/or verify EudraCT entries? If yes, please provide a link to the law(s)/rule(s), and very briefly explain or link to supporting monitoring, compliance and sanctions mechanisms by the EMA.

2. Given that registry entries alone currently cannot be used to reliably determine the completion dates for many trials, will the EMA in practice be able to enforce new laws mandating CTIMP results posting on EudraCT within 6/12 months? If yes, please briefly explain what other data sources will be used, and how compliance will be monitored and enforced.

3. Will trial sponsors be able to ‘game the system’ and avoid sanctions for not posting results within 6/12 months by indefinitely listing trials as “ongoing” on registry entries?

Response by the European Medicines Agency to first set of questions

The European Medicines Agency maintains the EU Clinical Trials Register [EudraCT] from a technical point of view. This means the Agency is responsible for the development, maintenance and coordination of the EudraCT. The information in the register is provided by the company or organisation responsible for the clinical trial (i.e. the trial sponsor) to the national competent authority(ies) of the member state(s) where the trial will be conducted. The protocol-related information is a component of the sponsor’s clinical trial application. The national competent authority (NCA) subsequently uploads into EudraCT the information, together with the clinical trial authorisation and the opinion from the relevant ethics committee. The information is then made public through the EU Clinical Trial Register.

The sponsor is responsible for notifying the end of the clinical trial to the respective National Competent Authority (NCA) and Ethics Committee where the trial was conducted. The sponsor has the duty to post the summary results directly into EudraCT within 6 or 12 months after the end of the trial. [note: highlighting added]

There are some exceptions to these rules. One of these relates to Phase 1 clinical trials which are not made public and do not appear in the register. The other relates to the protocol-related information on those clinical trials, that are conducted outside of the European Union and the European Economic Area and fall within the scope of the paediatric Regulation; these are directly uploaded by the trial sponsor.

For background reading:
The requirements for information from EudraCT to be made public are given in Article 57 of Regulation (EC) No 726/2004 and Article 41 of the Paediatric Regulation (EC) No 1901/2006. These are further detailed in the Commission guidelines available from the Chapter V of Eudralex Volume 10 of the rules governing medicinal products in Europe, which can be consulted here.

In addition, it is worthwhile to point out that the new clinical trial Regulation No. 536/2014 has been shaped with the goal to facilitate the conduct and supervision of clinical trials throughout their lifecycle. Once the Regulation will apply, data entry by the sponsor will be improved, the supervision by the Member State will be facilitated and the quality of public information will be improved with phase 1 data made available.
On a related note, you may be aware that since October 2016, the Agency publishes the clinical data that form the basis of the regulatory decision for medicinal products authorised by the European Commission. On EMA’s clinical data publication website you can find the clinical reports submitted by pharmaceutical companies to EMA for assessment in the context of a marketing authorisation procedure falling under the EMA’s clinical data publication policy.

Given that EudraCT does not contain clinical study reports but rather summaries of clinical trial results, EMA’s clinical data publication policy is a separate and complementary transparency initiative. Clinical study reports of clinical trials contained in EudraCT will only be made publicly available in the Agency’s website if they become part of a marketing authorisation application submitted to the Agency.

Edoardo Iannone, Media and Public Relations Service, European Medicines Agency
09 June 2017

Second set of questions by TranspariMED

A - Questions on Trial 2006-003833-33 (Duchenne)

A1 - Who is the party responsible for posting the summary results for this trial onto the registry?

A2 - Is the party identified in your answer above currently in violation of European law(s) and/or regulation(s)?

A3 – Please detail the steps the EMA has taken to date to ensure that results for this trial are posted on the registry (e.g. reminder emails to responsible party, imposition of sanctions or fines, etc)

B - Questions on Trial 2006-003596-12 (Breast cancer)

B1 - Who is the party responsible for posting the summary results for this trial onto the registry?

B2 - Is the party identified in your answer above currently in violation of European law(s) and/or regulation(s)?

B3 – Please detail the steps the EMA has taken to date to ensure that results for this trial are posted on the registry (e.g. reminder emails to responsible party, imposition of sanctions or fines, etc)

C - Questions on Trial 2012-000616-28 (Ewing’s Sarcoma)

C1 - Who is the party responsible for posting the summary results for this trial onto the registry?

C2 - Is the party identified in your answer above currently in violation of European law(s) and/or regulation(s)? If not, if no results are posted in future, from what date onwards will the party be in violation of European law(s) and/or regulation(s)?

C3 – Please detail the steps the EMA has taken to date to ensure that results for this trial are posted on the registry (e.g. reminder emails to responsible party, imposition of sanctions or fines, etc)

D – General questions
D1 – Please briefly explain how the EMA determines whether and when a study has been completed. (Please note that some trials seem to be incorrectly listed as “ongoing” on the registry.)

D2 – What are the legal consequences for violating the applicable European law(s) and/or regulation(s) (e.g. sanctions, fines, criminal charges, etc)?

D3 – Who is responsible for detecting such violations?

D4 – Who is responsible for imposing sanctions etc?

D5 – In how many instances have these sanctions etc been imposed to date (26 June 2017)?

Response by the European Medicines Agency to second set of questions

As stated in the previous response, the Agency is in charge of the maintenance of EudraCT and its public-facing system, the EU Clinical Trials Register from a technical point of view.

The information is originally provided by the company or organisation responsible for the clinical trial. The protocol related information is a component of the sponsor application to a national competent authority for authorisation to conduct a trial. Please note that authorisation to conduct a clinical trial is given by Member State(s) where the trial is going to take place. There is no central authorisation for clinical trials and EMA is not involved in this process.

The protocol-related information is loaded into the EudraCT database by the national competent authority. The national competent authority adds to this information on the authorisation of the clinical trial and the opinion from the relevant ethics committee.

Once the trial has ended, the sponsor has the duty to inform the national competent authorities by submitting the declaration of the End of Trial Form, https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/declaration_end_trial_form.pdf

Upon receipt of the declaration of the end of the trial from, the national competent authority enters the end date of the trial in EudraCT and the information is made public if the trial is publicly available.

The results-related information on clinical trials conducted in the EEA or outside of the EEA is shown as posted into EudraCT by the sponsor/marketing authorisation holder. The European Medicines Agency (EMA) is not responsible for the completeness or accuracy of this information. This is primarily the responsibility of the sponsor of the trial and the national authorities of the Member States where the trial is authorised.

Detailed guidance on posting and publication of result-related clinical trials information is provided in a European Commission Guideline. This guideline also sets out that it is the responsibility of the Member States to “verify that for clinical trials authorised by them the result-related information is posted to the Agency”.

There are no sanctions such as fines or criminal charges defined at the European level in the event that the sponsor does not follow the requirements of the guidance on posting the results. However, member states may have some provisions in relation to sanction at national level. For details on how individual Member States handle this, I would suggest you directly contact the respective National
Competent Authorities that will be capable to offer assistance on the topic. Please find here a complete list of the authorities in the Member States.

With respect to the trials you have mentioned specifically, please see links to their respective dedicated pages on the EU Clinical Trials Register, as well as links to the national authorities responsible for their authorisation, who you may wish to contact with regards to your questions.

Trial 2006-003833-33 (Duchenne), MHRA;
Trial 2006-003596-12 (Breast cancer), MHRA;
Trial 2012-000616-28(Ewing’s Sarcoma), MHRA and Medicines Evaluation Board.

The EU Clinical Trials Register displays a notification saying “Removed from public view”; results were submitted on 11-Jul-2015 but due to a system error all trial results that had been were removed from public view. The system was made available again on 13 January 2016. The summary results have gradually been made available for public access from that date, once the information has been reviewed and verified by the sponsors.

We will be looking to contact the sponsor to ask them to verify the status of their results to enable public access.

Edoardo Iannone, Media and Public Relations Service, European Medicines Agency
30 June 2017
STATEMENTS BY THE U.S. FOOD AND DRUG ADMINISTRATION

First set of questions by TranspariMED

1. Are there laws and/or rules setting out how often trial sponsors have to update and/or verify CT.gov entries? If yes, please provide a link to the law(s)/rule(s), and very briefly explain or link to supporting monitoring, compliance and sanctions mechanisms by the FDA.

2. Given that registry entries alone currently cannot be used to reliably determine the completion dates for many trials, will the FDA in practice be able to enforce the FDAAA 2007 provisions (and provisions in the subsequently issued related rule) on mandatory results posting on CT.gov within a set time frame? If yes, please briefly explain what other data sources will be used, and how compliance will be monitored and enforced, including for non-US trial sponsors.

3. Will trial sponsors be able to ‘game the system’ and avoid sanctions for not posting results for trials subject to the FDAAA 2007 results posting provision (and provisions in the subsequently issued related rule) by indefinitely listing trials as “ongoing” on registry entries?

Response by the U.S. Food and Drug Administration to first set of questions

Information regarding ClinicalTrials.gov and the laws and regulations pertaining to submission of clinical trial information can be found on FDA’s website at https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/FDAsRoleClinicalTrials.govInformation/default.htm

A link to the HHS regulations at 42 CFR Part 11 is included on this site. Of note, the requirements for updating of information for applicable clinical trials can be found at 42 CFR 11.64. In addition, the preamble to the final rule establishing 42 CFR Part 11 describes when a clinical trial with sites outside the U.S. may be an applicable clinical trial (see 81 Fed. Reg. 65010-15).

The FDA has incorporated the primary ClinicalTrials.gov compliance/enforcement activities into its existing compliance program structure. Specifically, these activities are formally part of the FDA’s Bioresearch Monitoring (BIMO) program. During BIMO inspections, the FDA evaluates and collects information related to clinical trials; in light of this, the BIMO program is the most appropriate framework for addressing potential violations of the ClinicalTrials.gov statutory and regulatory requirements.

As it has done in the past, the FDA will undertake activities to encourage compliance with ClinicalTrials.gov requirements similar to those types of activities the agency takes to encourage compliance with other statutory provisions, although such actions will be tailored to the unique requirements of ClinicalTrials.gov. For example, typically when the FDA believes there may be a violation of the law, it sends a warning letter to give notice of the potential violation and an opportunity for voluntary correction. FDAAA requires the agency to send a notice of non-compliance once the agency has determined that there is a violation. This provides a party with an opportunity to correct the violation.

Lauren Smith Dyer, Office of Media Affairs, FDA
07 June 2017
Second set of questions by TranspariMED

A - Questions on Trial NCT00963729 (Breast cancer)

A1 - Who is the party responsible for posting the summary results for this trial onto the registry?

A2 - Is the party identified in your answer above currently in violation of U.S. law(s) and/or regulation(s)?

A3 – Please detail the steps the FDA has taken to date to ensure that results for this trial are posted on the registry (e.g. reminder emails to responsible party, imposition of sanctions or fines, etc)

B - Questions on NCT02546544 (Ewing’s Sarcoma)

B1 - Who is the party responsible for posting the summary results for this trial onto the registry?

B2 - Is the party identified in your answer above currently in violation of U.S. law(s) and/or regulation(s)?

B3 – Please detail the steps the FDA has taken to date to ensure that results for this trial are posted on the registry (e.g. reminder emails to responsible party, imposition of sanctions or fines, etc)

C – General questions

C1 – Please briefly explain how the FDA determines whether and when a study has been completed. (Please note that some trials seem to be incorrectly listed as “ongoing” on the registry.)

C2 – What are the legal consequences for violating the applicable U.S. law(s) and/or regulation(s) (e.g. sanctions, fines, criminal charges, etc)?

C3 – In how many instances have these sanctions etc been imposed to date (26 June 2017)?

Response by the U.S. Food and Drug Administration to second set of questions

The FDA cannot comment on specific trials, however, more information about the FDA’s oversight of ClinicalTrials.gov is included below.

The National Library of Medicine (NLM) of the National Institutes of Health (NIH) operates the ClinicalTrials.gov data bank. Under Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and its implementing regulations (42 CFR Part 11), sponsors or investigators of certain clinical trials (“responsible parties”) must submit specific registration and results information to the data bank. The data bank also includes many clinical trials not subject to FDAAA or 42 CFR part 11 as that is not required to submit a clinical trial to the data bank.

The FDA has authority for certain enforcement activities under provisions of FDAAA and through a delegation of authority from the Secretary of Health and Human Services. FDAAA amended the Federal Food, Drug, and Cosmetic (FD&C) Act to include specific prohibited acts for failing to submit required registration and results information to the ClinicalTrials.gov database and submitting false or misleading information to the ClinicalTrials.gov database. Under FDAAA, the FDA has the authority to issue a Notice of Noncompliance to the “responsible party” of an “applicable clinical trial” for
violations of these prohibited acts. These prohibited acts also may be the subject of an injunction action or criminal prosecution brought by the Department of Justice. The FDA also may assess civil monetary penalties for such violations. Please note that, as indicated above, not all trials listed on the ClinicalTrials.gov are “applicable clinical trials.”

If the FDA identifies a potential violation, the agency may notify the responsible party and, if the FDA determines that there was a violation, it may, as appropriate, initiate administrative proceedings for civil monetary penalties or the process for civil or criminal court actions. To date, no civil monetary penalties have been assessed under the statute.

Lauren Smith Dyer, Office of Media Affairs, FDA
30 June 2017
8 RECOMMENDATIONS

RECOMMENDATIONS TO THE UK GOVERNMENT

1. Assume political leadership and commit to solving the problem

Hidden clinical trials pose a substantial health risk to British citizens and are a drain on public funds, making this a political issue that requires urgent and decisive government intervention. Ensuring that the results of all clinical trials are made publicly accessible would directly benefit patients, reduce cost pressures on the NHS, and provide a boost to medical research in the UK and beyond.

The cost of continued inaction by far outweighs the cost of resolving the problem. The annual NHS budget is over £120 billion. The evidence gaps on one single drug, Tamiflu, have already cost British taxpayers £424 million. Ensuring that NHS decision-makers can access the full evidence on the benefits and harms of drugs, devices and treatments would carry a negligible cost compared to the savings it would generate.

Taking action would help to boost the UK’s profile as a global leader in medical research excellence internationally, and would enjoy strong domestic support:

- **The National Institute for Health and Care Excellence (NICE)** has publicly stated that it “strongly believe[s] that all clinical trial data should be made available so that those with responsibility for developing guidance and making treatment decisions have all the necessary information to hand to help them do so safely and efficiently.”
- **The Health Research Authority (HRA)** has formally endorsed calls for comprehensive trials registration and reporting as “entirely consistent with our remit to protect and promote the interests of patients and the public in health research.”
- **The Medical Research Council (MRC)** “has, for many years, strongly supported the position that clinical trial results must be published in a timely manner”.
- **The British Medical Association (BMA)** has warned that “Doctors need accurate and unbiased information on the efficacy and safety of different treatments to help them prescribe properly, safely and most effectively for their patients. If data from clinical trials are withheld or otherwise not available, doctors cannot be sure of the risks and benefits of using particular drugs thus risking avoidable harm to patients and wasting scarce NHS resources.”
- **Over 700 other groups**, including leading professional associations and patient advocacy groups, have also expressed their support for clinical trials transparency by joining the AllTrials campaign.

Despite the best intentions and efforts of UK public institutions and expert bodies, the problem remains unresolved due to a lack of sustained top-level political support. The government must heed the United Nations’ recent call and deliver on David Cameron’s 2015 promise by assuming political leadership on this important and urgent public health issue, and must act to solve the problem once and for all.
2. **Launch a national strategy to secure the results from past clinical trials**

The government should formulate, fund and implement a national strategy to secure the results from clinical trials conducted in the past.

Most of the medicines that UK citizens take today were developed years or even decades ago. However, much of the research into their benefits and harms – including publicly funded research – remains hidden from view. Time is running out. If the government does not act quickly, research findings that could save countless lives will be lost forever as researchers retire and old archives get cleared out.

The costs of securing this data are *marginal* compared to the many billions of pounds it cost to generate the data in the first place. The data itself would provide a boost to medical research across the UK and improve decision-making by the NHS and NICE, making this a highly cost-effective intervention.

3. **Launch a national audit system for future clinical trials**

The government should design, fund and implement a comprehensive national audit system to ensure that all future clinical trials conducted in Britain are registered and fully and accurately report results.

Every single clinical trial conducted in the UK requires approval from one of Britain’s 68 Research Ethics Committees (RECs). *A pilot project has conclusively demonstrated* that the records of these committees can be used to track whether trials have been registered, have posted results, and have been accurately reported.

Scaling up this pilot nationally and coupling it with an effective sanctions regime would ensure that all future clinical trials conducted in Britain are registered and report their full results. Such a national audit system would require few additional staff, representing a miniscule investment in context of the NHS’ overall £120 billion budget and payroll of over one million employees.

Setting up a national audit system would not generate additional red tape, costs, or approval times for researchers conducting clinical trials in the UK. Rather, it would use already gathered data to ensure and verify that existing regulations and best practices are being followed in every single trial. This would provide Britain with a very strong competitive advantage as a location for top quality clinical research and drug development. Against a backdrop of rising concerns about publication bias and other forms of evidence distortion, “Successfully trialled in the UK” would rapidly become the ultimate quality hallmark for new drugs, devices and treatments worldwide.
RECOMMENDATIONS TO UNIVERSITIES

Overview

This study shows that the results of many clinical trials conducted at British universities remain hidden or are hard to find. Clearly, universities’ current systems, procedures and processes require an overhaul.

The status quo is not acceptable. Posting the results of clinical trials is an ethical obligation. Being transparent about methods and results is a key element of research excellence, as is the effective communication of research findings. Major funders are increasingly making results posting a funding criterion for future medical research grants.43

UK universities need to live up to their reputation as global centres of excellence in clinical research. To get ahead of the transparency curve, they should:

1. Centralize oversight of all existing registry entries
2. Audit their clinical trial registration and reporting performance
3. Adopt strong policies
4. Post full trial reports online

1. Centralize oversight of all existing registry entries

Universities should review and redesign their current systems, procedures and processes. In particular, universities should centrally monitor and track existing registry entries for all clinical trials they are involved with,44 and clearly define responsibilities and timelines to ensure that any problems detected are rapidly resolved.

2. Audit clinical trial registration and reporting performance

At a minimum, universities should conduct an annual audit of existing registry entries for all clinical trials they are involved with and publish the full audit reports.

Universities aspiring to excellence should consider conducting more in-depth audits that can also detect non-registration of trials and outcome switching.

TranspariMED’s recent pilot study provides an overview of possible audit approaches, and a section of an audit report recently disclosed by the University of Edinburgh contains some useful pointers. Note that the resources required to conduct an audit can be minimized by considering auditors’ data requirements when designing wider systems, procedures and processes.

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43 The UK Medical Research Council and the Wellcome Trust recently announced that:
“Reporting of previous trials realises the value of funding; therefore the contribution made from reporting previous trials, whatever their results, will be considered in the assessment of a funding proposal. When a PI applies for new funding, they may be asked to provide a list of all previous trials on which they were PI within a specified timeframe and their reporting status, with an explanation where trials have remained unreported.”

44 For example, the University of Bristol recently centralized control over its Clinicaltrials.gov account. “Prior to this, anyone could set up an account naming the University as the umbrella organization [sponsor],” a spokesperson explained. “At the point of setting up the central account we took on this legacy and are currently in the process of working with researchers to ensure that the University of Bristol’s account reflects studies appropriately.”
3. **Adopt strong policies**

Trial registration and results posting are ethical imperatives and key elements of excellence in clinical research. British universities should adopt policies that are in line with global best practices in the field and are backed up by effective monitoring and sanctions mechanisms.

4. **Post full trial protocols and reports online**

A large body of research shows that summary results posted on registries and articles published in academic journals by themselves are **not sufficient** to allow external researchers and regulators to fully evaluate the findings of a trial.

The AllTrials campaign has called for **all trial reports to be made public**: “All trial reports (Clinical Study Reports or their equivalent in non-commercial settings) should be posted online in full, with only minimal redactions.” In October 2016, the European Medicines Agency led the way by beginning to **proactively release trial reports** that it holds on file.

Universities should follow the positive example set by the EMA, and work with **pro-transparency research funders** to develop mechanisms for posting online full trial reports (including the original research protocols) at the same time summary results are posted.
9 ABOUT TRANSPARIMED

TranspariMED works to end evidence distortion in medicine

Failure to register and fully report clinical trials harms patients, wastes taxpayers’ money, and slows down the development of new treatments and cures.

TranspariMED uses research-driven advocacy to develop and promote policy solutions to this ongoing public health crisis.

TranspariMED was set up in March 2017 by transparency campaigner Till Bruckner. It currently receives no external funding; any future funding will be promptly and fully disclosed on its website. TranspariMED supports the AllTrials campaign and actively encourages other organizations to do the same, but is independent from AllTrials. The content of this study is the sole responsibility of TranspariMED. For breaking news and views, follow TranspariMED on Twitter.

Past publications

Bruckner, Till. “Grantees, Reveal Thy Findings: A Push By Funders for Transparency in Medical Research” Inside Philanthropy, 28 July 2017

Bruckner, Till. “Medical research in Bristol violates international transparency guidelines” The Bristol Cable, 20 July 2017

Bruckner, Till and Ellis, Beth. “Clinical Trial Transparency: A Key to Better and Safer Medicines” Bristol (UK), 28 April 2017, DOI: 10.13140/RG.2.2.21249.35686

TranspariMED. 2017. “Clinical Trials Transparency” Poster presentation at Evidence Live conference, Oxford (UK), 21 June 2017


AllTrials & TranspariMED. 2017. “Sustainable access to innovative therapies: The need to take action on clinical trials transparency” Joint submission to the OECD Sustainable access to innovative therapies online consultation, London & Bristol (UK) and New York (USA), 28 April 2017 [copy available upon request]

TranspariMED. 2017. “Distortion of Medical Evidence: Urgent Need for Decisive Political Action” Evidence submitted to the UK House of Commons Science and Technology Committee inquiry into research integrity, Bristol (UK), March 2017

Forthcoming publications

TranspariMED. 2017. “Global Standards on Clinical Trials Transparency - An Overview”


Thank you

TranspariMED would like to thank the media and policy teams at the UK Health Research Authority, the European Medicines Agency, and the U.S. Food and Drug Administration for unfailingly responding to questions in a timely manner and for putting considerable effort into helping to explain and clarify the complex legal and regulatory framework surrounding clinical trials.

TranspariMED would also like to thank the UK universities who chose to engage; many of them provided useful insights into individual clinical trials and broader systemic issues. Additional thanks go to three researchers who provided feedback and comments on earlier draft sections of this study.

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ANNEX: METHODOLOGY AND LIMITATIONS

METHODOLOGY

University selection

Universities were selected based on three external rankings:
- Guardian University League Tables 2018: Medicine
- Complete University Guide League Table Ranking 2018: Medicine
- QS World University Rankings by Subject 2017: Medicine

Every university that was featured among the UK top ten in any of these surveys was included, yielding a total of 16 universities overall. The table below shows the top ten in each ranking.

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Rapid external audit

TranspariMED searched trials involving university staff (see also below) to check which universities’ data entries on registries provided a complete, accurate and up-to-date record of their past and present clinical trials. In particular, TranspariMED sought to identify trials currently listed as “ongoing” that had in fact already been completed, or seemed highly likely to have been completed, in order to determine whether universities’ registry entries provided reliable data and could thus form the basis for a precise external assessment of results posting performance.

Each search continued until TranspariMED had detected and documented incorrect or otherwise flawed registry data entries, thereby demonstrating that the registry entries of a particular university were too flawed to form the basis for a precise external assessment of the number of trials with overdue results. TranspariMED then moved on to the next university.

At times, the search was broadened to triangulate data and/or to highlight that universities’ weak data management practices were not confined to EudraCT and ClinicalTrials.gov registry entries alone. In such cases, TranspariMED variously searched the ISRCTN registry for additional trials, searched PubMed for relevant articles in academic journals, and/or searched OpenTrials to check whether the same trial had been registered on multiple registries.

Not a single one of the 16 universities surveyed had a complete, accurate and up-to-date record of all its past and present clinical trials. These data quality issues made a precise assessment of
universities’ results posting performance for trials completed more than one year ago impossible, forcing the researcher to fall back on a heuristic approach to gathering comparative results posting data (see below, and also the section on “Limitations”). However, the audit did demonstrate that all 16 universities currently have weak data management practices, providing a sufficient evidence base for advocating with universities to address and resolve the problem.

(Note that the aim was never to provide a comprehensive catalogue of each university’s failings, which would by far have exceeded the scope of this study. The onus is on universities to ensure full compliance with best practices across their portfolios of trials by themselves conducting line-by-line audits of all their existing registry entries and fixing all problems detected, not on external researchers to identify and document every single shortcoming within their large portfolios.)

The rapid external audit took place during May and early June 2017.

Measuring universities’ results posting performance

TranspariMED searched the two of the most widely used clinical trial registries, EudraCT and Clinicaltrials.gov, to identify trials in which university staff had been involved. Within each registry, TranspariMED then searched for the total number of trials registered, and for the number of trials that had not posted or linked results within the registry entry. The search methodology varied slightly by registry as each registry has unique search features. Quantitative data was extracted and compiled during 24-25 May 2017.

- **EudraCT was searched** for all entries containing the university’s exact name (placed in inverted commas), and then searched the resulting population of trials for those that have not posted results. The searches that generated EudraCT results posting figures were conducted during on 24 May 2017.
- **Clinicaltrials.gov was searched** using the site’s new beta search function. It was searched by entering the university’s name into the “Sponsor / Collaborators” search window (without inverted commas; search limited to “exact match” only), and then searched the resulting population of trials for those that have not posted results. The searches underlying Clinicaltrials.gov summary statistics were conducted during 24-25 May 2017.

Collecting and assessing universities’ policies

University policies were obtained through Freedom of Information requests. Identically worded Freedom of Information requests were submitted to all universities on 24-25 January 2017, all of them requesting data current as of 24 January 2017. The full text of the FOI questions and universities’ individual FOI responses to these questions are linked to in this study.

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45 For technical reasons, universities’ results posting performance on a third major registry, ISRCTN, were not included in this study. Please see the section on “Limitations” below for more details.

46 In the case of Swansea, the sponsor for one trial is listed as “University of Wales Swansea”, while the sponsor of a second trial is listed as “Swansea University”. In this case, the search term “Swansea University” was used; this captured both trials. The episode illustrates how inconsistent data entry by universities can complicate research. (The third trial was not sponsored by the university, but was lead by a professor at its medical school.)

47 In addition, Aberdeen, Bristol, and Nottingham shared documents in response to FOI requests whose wording was identical to the FOI requests submitted to the top medical universities covered by this report. These documents were included in the review to inform the development of the typology. The FOI request with Cardiff was filed at a later date.
Data validation with universities

Results were shared with each university’s press office, using the relevant contact email addresses listed online, to enable institutions to review the data on their policies and performance and, if appropriate, ask for corrections to be made. In addition, universities were invited to provide a statement for inclusion in the report. The initial emails were sent on 12 June 2017, and reminder emails were sent on 16 June. Universities were given until COB on 22 June 2017 to respond. In total, eight out of the 16 universities responded.

In cases in which universities supplied additional information on specific trials, this information was integrated into the text of the final study and/or flagged in footnotes where those trials were discussed.

In the draft shared with universities, TranspariMED had rated universities’ policies according to their scope and strength, in the process excluding a priori all policies not exclusive to universities themselves (such as policies of joint clinical trial partnerships formed with local NHS Trusts) from consideration due to those policies being “not internal”. Several universities persuasively argued that this dichotomous approach was misplaced, and TranspariMED abandoned the approach and reworked the relevant section of the study.

LIMITATIONS

TranspariMED did not systematically search for trials that were not registered on the two registries covered, attempt to determine non-registration or retrospective registration rates, or check for inconsistencies in outcome reporting across trial protocols, results posted, and/or journal articles; all this was beyond the scope of this study.

Also, this study does not distinguish between non-reporting and bad reporting of trials. Non-reporting means that a trial has never reported results, neither by posting a result on a registry nor through academic publication. Bad reporting means that a trial has reported results somewhere, somehow, but that these results are difficult to locate because they are not linked to from the trial’s registry entry. The whole point of registries is to make medical research information easy to locate. Doctors and patients do not have the time to go on lengthy treasure hunts for badly indexed research results, so for many registry users, non-reporting and bad reporting have identical, negative consequences: while one is worse than the other, both are bad practices.

The online search functions on the two registries are slightly different and thus yielded results that are not fully comparable. The Clinicaltrials.gov search only returned trials in which a university was an official sponsor, co-sponsor or collaborator, while the EudraCT search additionally returned some trials in which university staff members were involved but in which the university did not act as a sponsor. As the ethical imperative to report trial results applies to all researchers, and universities are responsible for ensuring that their staff do not violate ethical norms in the course of conducting medical research in humans (irrespective of a trials’ formal sponsorship arrangements), all EudraCT data returned by the search are relevant. Conversely, Clinicaltrials.gov data presented in this study is likely to underrepresent relevant trial numbers. At the same time, Clinicaltrials.gov contains some

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48 A [2015 HRA audit report](#) indicates that despite the ethical imperative to register trials and clear REC rules in this regard, many trials conducted in the UK are still not registered, presumably including some trials conducted at universities. Sadly, [outcome switching also remains common](#). Universities setting out to audit their own performance should include non-registration, retrospective registration and outcome switching in the scope of their audits, building on existing audit approaches. Please see TranspariMED’s 2017 [rapid external audit pilot study](#) for a discussion of different audit approaches.
studies that are not clinical trials. For the purposes of this study, a clinical trial is defined as a study that is registered on a clinical trials registry.

This study does not include data from another widely used registry, ISRCTN, because it currently has no search function allowing users to rapidly generate summary data showing how many trials have (or have not) reported and linked results. ISRCTN plans to add such a search function in future,\(^49\) which will hopefully allow ISRCTN data to be included in a follow-up study of the same universities. Universities should note that posting results is an ethical obligation regardless of where a trial was registered, and any internal audit of registry entries should include entries on ISRCTN and all other registries being used by their staff.

The summary results posting performance figures for individual universities do not take into account that some of the trials listed as not having posted results are still ongoing or have been completed less than one year ago. A rapid external audit of a sample of trials from each university shows that due to weak data management practices within universities, registry entries frequently misstate a trial’s status as “ongoing” long after it has been completed and/or contain contradictory information on trial end dates. This makes it impossible for external researchers to precisely and reliably determine which trials have failed to post results 12 months after completion based on the data contained in registries alone. Excluding all trials listed as “ongoing” from the population of unreported trials would thus result in a severe undercounting of trials that have failed to post results. In addition, it would reward weak data management practices by universities and create perverse incentives against performing regular updates of registry entries.

At the same time, a review of registry entries indicates that ongoing trials and trials completed less than one year ago very likely form only a small part of the total number of trials registered by UK universities. Thus, while the resulting figures for trials that have not posted results are imprecise in that they include a minority of trials whose results are not (yet) overdue, this over-counting is more than offset by the under-counting of trials whose results are overdue stemming from the narrow Clinicaltrials.gov search approach and the wholesale exclusion of trials registered on ISRCTN (see above).

Overall, the limitations discussed above mean that the quantitative data presented in this study provides an impressionistic snapshot, rather than a precise measurement, of universities’ performance. It should be noted that this lack of precision is rooted in universities’ own weak data management practices, which make it impossible for external researchers to generate exact numbers based on registry entries alone. Furthermore, as discussed above, the numbers of unreported trials per university stated in this study almost certainly understate the true scale of the problem; a more precise count including ISRCTN trials would paint an even less flattering picture.

Despite the inevitable limitations of this study, TranspariMED is confident that the data presented here are sufficient to demonstrate that medical researchers at all the top 16 UK universities frequently deviate from best practices in the field, and that some universities are more successful than others in ensuring that staff post the summary results of clinical trials on registries. In addition, TranspariMED is confident that the data in this study are sufficient to demonstrate that all 16 universities need to review and update their existing registry entries, and take steps to ensure that in future, all new future registry entries will be comprehensive, correct, and kept up to date.

\(^49\) Personal email communication with Hélène Faure, Database Manager, ISRCTN registry, 24 May 2017