Note: This evidence is being submitted following the inquiry’s verbal evidence session involving Dr Ben Goldacre, Dr Sile Lane, and Dr Simon Kolstoe. This evidence seeks to answer some of the questions raised by Science and Technology Committee members during the session. Specifically, it provides a review of progress achieved since this Committee last issued recommendations on clinical trial transparency in 2013, and clarifies the different options for HRA-led clinical trial audits, including the amount of resources each type of audit would require.

EXECUTIVE SUMMARY

1

• In December 2017, four health integrity groups led by Transparency International called on governments worldwide to ensure that clinical trials are registered and fully reported. The analyses and recommendations in this submission of evidence are fully aligned with transparency standards set out by the World Health Organization, the AllTrials campaign, and Transparency International.

• In 2013, the Science and Technology Committee published a report on clinical trials. The report made several recommendations related to improving clinical trial transparency. Virtually none of these recommendations were subsequently adopted.
  o We recommend that the Committee adopts the 2013 transparency recommendations in its forthcoming report, and requests the HRA, MHRA, NICE, NIHR, and MRC to provide quarterly progress reports to the Committee on the implementation of its recommendations.

• A key recommendation from 2013 the Committee, and one that all experts who testified in 2017 endorsed, was that the Health Research Authority should audit all clinical trials conducted in the UK and impose penalties for non-compliance. While the experts testifying in 2017 concurred that the HRA should conduct audits, they proposed different audit models. This submission outlines the different options proposed, and discusses the approaches and resources their implementation would entail.
  o We recommend that the Committee request the HRA to institute an annual REC-record based audit of all UK trials, covering trial registration, summary results posting onto registries, and best practice academic publication. Such ‘minimalist’ audits would be simple to implement.
ABOUT THE SUBMITTING PARTIES

This is a joint submission by STOPAIDS, HealthWatch UK, UAEM-UK, and TranspariMED.

- **STOPAIDS** is a membership network of 70 UK-based civil society organisations with a thirty year history of engagement on international development and HIV and AIDS. Its members include Oxfam, Save the Children and Doctors Without Borders.
- **HealthWatch UK** is a registered charity that has been promoting evidence and integrity in all forms of medicine and healthcare since 1991.
- **Universities Allied for Essential Medicines (UAEM) UK** is the national branch of a global network of university students that advocate for the maximal public health impact of health products, by promoting access to essential medicines.
- **TranspariMED** is a UK-based initiative that develops and promotes policy solutions to the problem of evidence distortion in medical research.

NEW CALLS FOR CLINICAL TRIAL TRANSPARENCY

In December 2017, four health integrity groups led by Transparency International called on governments worldwide to ensure that clinical trials are registered and fully reported, reflecting an earlier call made by the United Nations. (The other members of the group are Cochrane, CRIT and TranspariMED.) The coalition concurrently published a report detailing the scale, scope and impact of research integrity shortfalls in clinical trials and outlined specific transparency measures that governments should take. The report calls on political decision-makers to:

- Step 1: Ensure that publicly funded clinical trials are transparent
- Step 2: Enforce existing laws, rules and regulations
- Step 3: Strengthen legal and regulatory frameworks.

In November 2017, HealthWatch UK, Universities Allied for Essential Medicines UK, and TranspariMED submitted evidence to the Commons Health Committee detailing how Brexit could either improve or undermine clinical trial transparency in the UK.

The analysis and recommendations in this submission of evidence are fully aligned with transparency standards set out by the World Health Organization, the AllTrials campaign, and Transparency International.

2013 SCIENCE AND TECHNOLOGY COMMITTEE RECOMMENDATIONS IGNORED

In 2013, the House of Commons Science and Technology Committee published a report on clinical trials concluding that “We consider the current lack of trial transparency to be unacceptable and we have not been impressed by the Government’s efforts to resolve this problem to date.” The 2013 report reflected an excellent understanding of the problem and proposed several appropriate, feasible, low-cost measures to resolve it. Four years later, virtually none of the SciTech Committee recommendations has been implemented. Below is a list of key transparency recommendations made by the Committee in 2013 and the progress achieved since then.
7 Trial registration
Recommendation:
“We recommend that the Government take steps to ensure that, in future, all clinical trials conducted in the UK, and all trials related to treatments used by the NHS, are registered in a WHO-listed primary registry.” (page 36)
Action (not) taken:
- The HRA made trial registration compulsory in 2013 but does not systematically monitor or enforce compliance. There are no penalties for non-registration.
- A one-off audit conducted by the HRA in 2015 shows that many trials conducted in the UK are still not being registered.
- The government has not taken any action to get past trials registered.

8 Summary results and academic publication
Recommendation:
“It is also important that summary-level trial results are made public, and we do not accept the argument that it is not possible to publish ‘negative’ results in peer reviewed scientific journals. We recommend that trial registration and publication of summary-level results be made contractual requirements for all publicly-funded trials, including those covered by the Charity Research Support Fund.” (page 3)
Action (not) taken:
- Contractual requirements lack teeth if compliance is not monitored. In 2017, the NIHR and MRC signed up to a new WHO initiative pledging that they will audit grantees’ reporting performance and publish audit results within a year. This is fully in line with a recommendation recently made by Transparency International (see Step 1 above). NIHR and MRC have committed to publicly report the first audit results in 2018.
- The Association of Medical Research Charities (AMRC) has not yet signed up to the WHO initiative.
Note: There is a difference between summary results posted onto trial registries and results reported in journal articles. Clinical trials should report their results in both formats. Please see the 2017 Transparency International study for a detailed explanation and a list of relevant global standards.

9 HRA to screen researchers for past unethical behaviour
In a formal response to the Committee’s 2013 report, the HRA stated that:
“We have also committed to a review of the applicant declaration to RECs so that when new applications are made we seek formal assurances that previous studies have been registered and findings put in the public domain.”
Action (not) taken:
- To the best of our knowledge, the HRA currently does not require researchers submitting ethics applications to RECs to list all past trials they have conducted and to document registration and reporting for each as a precondition for ethics approval.
Note: This measure was explicitly proposed again by Dr Ben Goldacre during the 2017 verbal evidence session.
HRA to monitor and enforce compliance (trial auditing)

Recommendation:
“Research Ethics Committees should have a role in considering and monitoring compliance with transparency policies. We recommend that the HRA... ensure that all trials have been registered and published according to an agreed timeline, rather than performing checks on a sample basis. In addition, there must be penalties for non-compliance.” (page 53)

Action (not) taken:
- The HRA does not systematically monitor compliance with its transparency policies, and does not impose penalties for non-compliance. For more details on this, please see the previous submission of evidence to this Committee by HealthWatch UK, Universities Allied for Essential Medicines UK, and TranspariMED.

Note: All experts providing verbal testimony to the Committee in 2017 explicitly supported HRA-led trial audits based on REC records.

Retrospective audit of public grants

Recommendation:
“We therefore recommend a retrospective audit of all public phase III trial grants awarded since 2000, followed by action to ensure that any failures to register or publish the summary-level results of these trials be rectified within 12 months. Any failures to correct these mistakes should be taken into account when considering future grant applications from principal investigators of previously unregistered or unpublished trials.” (page 49)

Action (not) taken:
- The government never acted on the (excellent) recommendation to conduct a retrospective audit of all large public grants.

Clinical Study Reports

Recommendation:
“CSRs [Clinical Study Reports] can make a useful contribution to the scientific literature. Once a regulatory decision has been reached, there is no compelling reason why CSRs should not be placed in the public domain, with identifiable patient data redacted.” (page 41)

Action (not) taken:
- The UK government has taken no action to get CSRs into the public domain. For example, the NHS continues to pay for drugs whose vendors refuse to grant the scientific community access to the full evidence on those drugs.
- The European Medicines Agency began proactively releasing some CSRs in 2016, but this European policy does not cover CSRs for most drugs currently being prescribed in the UK.
- Post-Brexit, scientists based in the UK may have difficulties accessing even the small sub-set of CSRs released by the EMA.

Note: We strongly agree with this recommendation, which is line with recommendations previously made on various occasions by AllTrials, Transparency International, Cochrane, HealthWatch UK, Universities Allied for Essential Medicines UK, and TranspariMED, and we encourage the Committee to again include it in the 2017 report. More details on CSRs can be found in Transparency International’s 2017 study.
13 The 2013 recommendations listed above all broadly match the recommendations made by Dr Ben Goldacre, Dr Sile Lane (AllTrials) and Dr Simon Kolstoe during the 2017 verbal evidence session.

14 We recommend that the Committee adopt all the 2013 recommendations listed above in its forthcoming report. Post-2013 experience shows that recommendations alone may not be sufficient to change policies and practices, thus we also recommend the following measures.

15 We recommend that the Committee explicitly request the HRA, MHRA, NICE, NIHR, and MRC to provide quarterly progress reports to the Committee on the implementation of its recommendations for the duration of the current Parliament.

16 We recommend that the Committee request the MHRA and NICE to (1) explain to what extent they themselves are currently able to access CSRs, (2) to disclose the number of CSRs they currently hold on file, and (3) to provide a timetable for placing all CSRs they currently hold on file, and that they receive in the future, into the public domain (with identifiable patient data redacted).

OPTIONS FOR CLINICAL TRIAL AUDITS

17 A key recommendation from 2013 the Committee, and one with which all invited experts again concurred in 2017, was that the Health Research Authority should audit all clinical trials conducted in the UK and impose penalties for non-compliance:

“We recommend that the HRA initially retain full responsibility for policing its own policies and ensures that all trials have been registered and published according to an agreed timeline, rather than performing checks on a sample basis. In addition, there must be penalties for non-compliance.” (2013 Committee)

18 While the experts providing verbal testimony to the Committee in 2017 concurred that the HRA should conduct audits, they proposed different audit models. This section outlines the different options proposed, and discusses what implementation of each option would entail in practice.

19 From a transparency perspective, the HRA can audit clinical trials to answer a range of questions. Some of these questions can be answered very easily, while answering others would require significant staff input and hence necessitate additional resources to be allocated to the HRA.
The table below provides an overview of HRA audit options and related methodologies, together with an estimate of the level of input required to perform each audit type.

<table>
<thead>
<tr>
<th>Audit question</th>
<th>Audit methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EASY TO AUDIT</strong></td>
<td></td>
</tr>
<tr>
<td>Was this clinical trial prospectively registered?</td>
<td>Easy to audit. There are only 16 WHO-recognized primary registries that HRA needs to search for each trial.</td>
</tr>
<tr>
<td>Were the summary results of this clinical trial published on all the registries where it is registered within 12 months of study completion?</td>
<td>Very easy to audit. The HRA can quickly check the already identified registry entries (see above) for trial results.</td>
</tr>
<tr>
<td>Has this clinical trial published results in an academic journal following global best practices?</td>
<td>Very easy to audit. The HRA can quickly search journal databases for the trial number.</td>
</tr>
<tr>
<td><strong>MEDIUM LEVEL AUDIT EFFORT</strong></td>
<td></td>
</tr>
<tr>
<td>Are the registration and results data for this trial consistent across different registry entries?</td>
<td>For trials registered in more than one registry HRA can check whether key trial data is consistent across different registries. This requires no specialist skills, but does require manual comparison.</td>
</tr>
<tr>
<td><strong>HIGH LEVEL AUDIT EFFORT</strong></td>
<td></td>
</tr>
<tr>
<td>Has this trial ever reported its results anywhere?</td>
<td>Time intensive to audit. HRA would need to follow a lengthy search protocol for every trial. No specialist skills required.</td>
</tr>
<tr>
<td>Has this trial accurately reported its results?</td>
<td>Time intensive and difficult to audit. HRA would need to conduct a trial-by-trial analysis. This requires specialist skills.</td>
</tr>
</tbody>
</table>

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11 Best practice is for the unique ID number of a clinical trial (issued by a trial registry upon registration) to be included in the abstract of its corresponding journal article. If best practice is followed, publications can be located rapidly and easily. However, many researchers and publishers neglect to follow best practices. Thus, this audit function would detect every best practice trial publication but not be able to distinguish between trials that were published badly and trials that were not published at all. (The existing US-focused “TrialsTracker” transparency platform has the same weakness.)

2 A 2017 TranspariMED study found frequent and substantial inconsistencies in the data on UK university-sponsored trials that had been registered multiple times in different trial registries. Such inconsistencies can make it impossible for scientists to evaluate a trial’s findings and importance (for example, when different registry entries cite different participant numbers or outcome measures).

3 Cochrane reviews often involve time-consuming searches that seek to capture every publication, so appropriate search protocols already exist. HRA would need to define up front what “reported” means in this context, for example, if a trial’s results have only been reported in a Korean-language poster presentation at a conference in Guatemala, does that count as “published”?

4 An alternative model would be for the HRA to require individual researchers themselves to proactively notify the HRA when trial results were published, similar to the mechanism outlined in paragraph 9 above.

5 Dr Simon Kolstoe’s pioneering REC-based trial audit captured not only at registration and reporting status, but also assessed whether results has been reported accurately against pre-defined outcome measures. Thus, his audit was able to detect “outcome switching” in journal articles, a very widespread form of research integrity misconduct with significant negative consequences for doctors and patients (see Transparency International’s 2017 study for details on “outcome switching” and further references.).
We recommend that the Committee request the HRA to institute an annual REC-record based audit covering all clinical trials (as defined by the World Health Organization) conducted in the UK, and publish the results in a machine-readable format line-by-line for each trial, including the names of each trial’s sponsor and principal investigator.

At a minimum, the audit should answer the following questions:

- Was this clinical trial prospectively registered?
- Were the summary results of this clinical trial published on all the registries where it is registered within 12 months of study completion?
- Has this clinical trial published results in an academic journal following global best practices?

A trial should only be marked as having reported results in a satisfactory manner if it has posted its summary results on every registry where it was registered and reported its outcomes in an academic journal.

Such a minimalist audit poses no technical challenges and can be performed by unskilled staff following a simple audit protocol. There is considerable scope for completely automating this audit function; for example, commercial banks worldwide use off-the-shelf automated reporting solutions (“Management Information Systems”) to track the status of millions of outstanding loans every day.

We recommend that the Committee request that the HRA make REC approval records accessible to external researchers.

This will allow third parties to answer the following questions:

- Are the registration and results data for this trial consistent across different registry entries?
- Has this trial ever reported its results anywhere?
- Has this trial accurately reported its results?

The HRA should not place any restrictions on the publication of the results of such third party audits. (For example, witness Dr Simon Kolstoe told the Committee in 2017 that the HRA had not permitted him to publish the line-by-line results of his own audit based on REC files held by the HRA; the HRA had cited confidentiality agreements with trial sponsors.)

We recommend that the Committee request the HRA to publish a binding timetable for phasing in sanctions on trial sponsors, including details on those sanctions and the related enforcement mechanisms. (Note that the Committee itself already recommended in 2013 that the HRA impose sanctions. Note also that some clinical trials [CTIMPs] conducted in the UK are already required to post summary results on the EU trial registry within 6-12 months under an EU regulation that has been in force since July 2014.)

HRA sanctions should be applied to trial sponsors who fail to register trials and/or post their summary results onto registries within 12 months of study completion. Sanctions should incentivize trial sponsors to post overdue summary results for past trials as well as ensuring future compliance with regulations and best practices. A transition period of one year would permit trial sponsors
(companies, universities, charities and public institutions) to clear their current backlogs of unreported trials by posting their summary results before the first sanctions are imposed.

28

In the medium term, the HRA should expand the scope of its audits to include the more challenging audit items in its annual public audits.

29

Initially, the HRA would require additional resources to conduct the more challenging audit types as these are comparatively time-intensive to implement, though as the WHO has noted, the wider benefits of such audits greatly outweigh the costs of the audits themselves. However, ultimately, the cost of auditing could (and should) be fully recovered by the HRA by imposing financial penalties on non-compliant trial sponsors.

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