A National Clinical Trial Audit System to Improve Clinical Trials Reporting

Submission to the Science and Technology Committee's inquiry into research integrity

Written evidence submitted by Dr Till Bruckner on behalf of HealthWatch UK, Universities Allied for Essential Medicines UK, TranspariMED, and Dr Simon Kolstoe.

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Note: Please disregard the earlier submission of evidence by TranspariMED. TranspariMED's current understanding of the issue and position are set out in the submission below.

EXECUTIVE SUMMARY

1

- The incomplete and inaccurate reporting of clinical trials is a well-documented research integrity problem. Major factors contributing to this problem are the failure of trial sponsors and principal investigators to prospectively register all trials, post the summary results of all trials, and publish the outcomes of all trials in academic journals.
- This has negative consequences for UK patients, UK taxpayers, and UK investors, which are also well documented.
- Successive UK governments have failed to monitor compliance with, or sanction the violation of, national and European Union regulations intended to partially resolve the issue. As a result, compliance is weak.
- The persistence of the problem more than two decades after it was first recognized shows that individual action by stakeholders and unmonitored and unenforced regulations are insufficient to resolve it.
- A national clinical trial audit system would substantially strengthen research integrity in this field by monitoring the registration, summary results posting and academic publication of every trial conducted in the UK, benefiting UK patients, UK taxpayers, and UK investors.
- A pilot has proven the feasibility of setting up such a system in the UK.
- The system would cost little to set up and run. Its work would be based on records that already exist, and thus it would not generate any red tape, costs, or time delays for institutions conducting clinical trials in the UK.
- There is broad support within the UK medical research community for a national clinical trial audit system.
- The system would provide Britain with a competitive advantage as a location for cutting edge clinical research and drug development.

ABOUT THE SUBMITTING PARTIES

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This is a joint submission by HealthWatch UK, Universities Allied for Essential Medicines UK, TranspariMED, and Dr Simon Kolstoe.

- 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.
- Dr Simon Kolstoe is the independent chair of the Hampshire A NHS and MOD research ethics committees, a member of the national research ethics advisory panel (NREAP), and a Senior Lecturer in Research Design & Ethics (University of Portsmouth). Dr Kolstoe led the pilot project referenced in this submission.

RESEARCH INTEGRITY IN CLINICAL TRIALS: INCOMPLETE AND INACCURATE REPORTING

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The incomplete and inaccurate reporting of clinical trials is a well-documented research integrity problem. Major factors contributing to this problem are the failure of trial sponsors and principal investigators to prospectively register all trials, post the summary results of all trials, and publish the outcomes of all trials in academic journals. Numerous submissions already made to this Committee summarize the current state of knowledge on this issue,[1] so this joint submission will focus on the downstream consequences and propose a solution.

THE CONSEQUENCES OF INCOMPLETE AND INACCURATE REPORTING

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As a consequence of incomplete and inaccurate reporting, patients are harmed, public health agencies cannot make informed decisions, public health funds are wasted, medical progress is slowed down, and shareholders are exposed to substantial risks.[2] Examples include Lorcainide, a drug that killed over 100,000 people over the course of a decade, Tamiflu, on which the NHS arguably misspent £424 million, and Vioxx, whose withdrawal led to shareholder losses of $37 billion.[3]

5

Incomplete and inaccurate reporting of clinical trials has negative consequences for UK patients, UK taxpayers, and UK investors. For this reason, medical research stakeholders in the UK, including numerous patient groups, have joined the AllTrials campaign in demanding that all trials are registered and fully reported. A majority of the over 730 groups supporting the global AllTrials campaign are based in the UK.[4]

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[1] See for example the written evidence submitted by Dr Ben Goldacre (RIN0073) http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48700.html

[2] Transparency International and TranspariMED. 2017. Clinical Trials Transparency: A Guide for Policy Makers [forthcoming]

[3] Bruckner, Till and Ellis, Beth. 2017. Clinical Trial Transparency: A Key to Better and Safer Medicines DOI:10.13140/RG.2.2.21249.35686 https://media.wix.com/ugd/01f35d_0f2955eb88e34c02b82d886c528efeb4.pdf [Accessed 26 September 2017]

[4] As of 26 September 2017, 734 organisations had formally lent their support to the AllTrials campaign. Full list:

PROGRESS TO DATE

6
Over the past two decades, there has been slow incremental progress in some areas. This progress has largely been driven by medical research community stakeholders themselves.[5] Successive UK governments have failed to monitor compliance with, or sanction the violation of, national and European Union regulations intended to partially resolve the problem.

7
Due to the slow pace of progress, many clinical trials are still not being pre-registered on trial registries (despite being required to do so by UK regulations), do not post summary results onto registries within 12 months (despite being required to do so for some trials by EU regulations), and/or are misreported in academic journals or not published at all.[6]

RESPONSIBILITY OF THE UK GOVERNMENT

8
The persistence of incomplete and inaccurate reporting of clinical trials more than two decades after the problem was first recognized shows that neither individual action by stakeholders nor unmonitored and unenforced regulations are sufficient to resolve it. For example, a recent study of 16 leading UK universities suggests that none are fully compliant with trial registration and summary results posting standards set out by the World Health Organization, and several appear in to be in breach of relevant UK and/or EU regulations.[7] At the current slow pace of progress, medical research will still suffer from the same research integrity issues two decades from now.

9
The United Nations in late 2016 explicitly put the onus on national governments to resolve the problem.[8] The status quo is harmful to the heath and wealth of UK citizens. As efforts at self-regulation by the sector have not delivered satisfactory results, the UK government has the responsibility to take action to prevent further harm to UK citizens.

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http://www.alltrials.net/supporters/supporters-organisation-list/ [Accessed 26 September 2017]

[5] AllTrials. 2016. The AllTrials Roadmap
http://www.alltrials.net/wp-content/uploads/2017/02/AllTrials-Roadmap.pdf [Accessed 26 September 2017]

[6] Kolstoe, S. and Begum, R. 2015. "Do REC approved studies publish?" Presentation at HRA transparency workshop, London, 05 February 2015
http://www.hra.nhs.uk/documents/2015/08/transparency-rec-approved-studies-publish.pdf [Accessed 29 September 2017]
Health Research Authority. 2015. "Clinical Trial Registration Audit Report"
http://www.hra.nhs.uk/wp-content/uploads/2015/07/09-15-14Iii-Clinical-Trial-Registration-Audit-Report_V1-3.docx [Accessed 19 September 2017]
Schmucker, C. et al. "Extent of Non-Publication in Cohorts of Studies Approved by Research Ethics Committees or Included in Trial Registries" PLoS ONE 9(12): e114023.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0114023 [Accessed 04 October 2017]
Song, F. et al. 2010. "Dissemination and publication of research findings: an updated review of related biases" Health Technol Assess. 2010 Feb;14(8):iii, ix-xi, 1-193.
https://www.ncbi.nlm.nih.gov/pubmed/20181324 [Accessed 04 October 2017]

[7] TranspariMED. 2017. "Medical Research Ethics at Top UK Universities: Performance, Policies and Future Plans"
https://docs.wixstatic.com/ugd/01f35d_15c506da05e4463ca8bd70c2b45bb359.pdf [Accessed 01 October 2017]

[8] United Nations. 2016. "Report of the United Nations Secretary-General's High-Level Panel on Access to Medicines"
http://www.politico.eu/wp-content/uploads/2016/09/HLP-Report-FINAL-Sept-2016.pdf [Accessed 20 September 2017]

10
In 2015, then Prime Minister David Cameron acknowledged that resolving the problem would require government intervention, and promised to take action. At the time, the UK government pledged that "the UK will be the first country in the world to require clinical trials and disease control operations to be fully transparent. From now on any UK-funded research, data or operation will be made openly available…"[9] However, this pledge only applied to clinical trials relevant to fighting global health pandemics. It is doubtful that the government subsequently monitored compliance by those conducting clinical trials.

GLOBAL STANDARDS ON CLINICAL TRIALS REPORTING

11
Global standards set by the World Health Organization call for the pre-registration of all clinical trials, timely posting of summary results for all trials, and publication of accurate results of all trials in the academic literature.[10] Bringing UK practices into line with global best practices as set out by the World Health Organization would improve the reporting of clinical trials and substantially strengthen research integrity in this field.[11]

12
Bringing UK practices into line with global best practices will require monitoring whether trials are pre-registered, post summary results within 12 months, and publish accurate results. At present, the UK has no such system for monitoring compliance with best practices and/or relevant regulations.

A NATIONAL CLINICAL TRIAL AUDIT SYSTEM

13
Every clinical trial conducted in the UK requires approval from one of Britain's 68 regional Research Ethics Committees (RECs). A recent pilot project has demonstrated the feasibility of using documents already held by RECs to monitor retrospectively whether trials have been registered, posted summary results within 12 months, and published accurate results.[12] Scaling up this pilot nationwide would create a comprehensive national clinical trial audit system capable of monitoring every trial conducted in the UK.[13]

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[9] Prime Minister's Office. 2015. "Prime Minister calls for 'wake-up to the threat from disease outbreak'" Press release, 07 June 2015
https://www.gov.uk/government/news/prime-minister-calls-for-wake-up-to-the-threat-from-disease-outbreak [Accessed 03 October 2017]

[10] World Health Organization. 2015. "WHO Statement on Public Disclosure of Clinical Trial Results"
http://www.who.int/ictrp/results/reporting [Accessed 20 September 2017]

[11] Moorthy, V. et al. 2015. "Rationale for WHO's New Position Calling for Prompt Reporting and Public Disclosure of Interventional Clinical Trial Results" PLoS Med 12(4): e1001819.
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001819

[12] Begum, R. and Kolstoe, S. 2015. "Can UK NHS research ethics committees effectively monitor publication and outcome reporting bias?" BMC Med Ethics. 2015 Jul 25;16:51.
https://www.ncbi.nlm.nih.gov/pubmed/26206479
For a similar pilot recently conducted in Finland, see:
Chan, An-Wen et al. 2017. "Association of Trial Registration With Reporting of Primary Outcomes in Protocols and Publications" JAMA Research Letter, 11 September 2017
http://jamanetwork.com/journals/jama/fullarticle/2653434

[13] Written evidence submitted by Dr Simon Kolstoe (RIN0022)
http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48484.html
See also: Kolstoe, S. E., Shanahan, D. R., & Wisely, J. (2017). Should research ethics committees police reporting bias?. BMJ: British Medical Journal (Online), 356

14
A national clinical trial audit system would cost little to set up and run. The pilot project covering all trials approved by an REC over two years was largely conducted by a single graduate student working part-time for one year. A national system would require far less input per REC due to economies of scale and the ability to adjust upstream processes to facilitate the audit function. Within a few years, the system could become self-financing (see further below).

15
Importantly, a national clinical trial audit system would not generate any red tape, costs, or time delays for companies, universities or individuals conducting clinical trials in the UK. It would also not create any additional work for RECs themselves, because the Health Research Authority (HRA) already holds the national archives of the required REC records.[14]

16
Making the audit data publicly available would by itself substantially increase research integrity in the field. Trial sponsors' and principal investigators' track records would suddenly become visible and comparable, creating strong incentives to improve performance.[15] Proactively encouraging non-compliant institutions and researchers to adhere to best practices could further increase the system's positive impact.[16]

17
After a transition period, sanctions should be imposed on non-compliant institutions and individuals. The collection of fines could enable the system to operate on a cost recovery basis or even generate a financial surplus within a short period of time.

BROAD SUPPORT FOR A NATIONAL CLINICAL TRIAL AUDIT SYSTEM

18
There is broad support within the UK medical research community for a national clinical trial audit system. Three previous submissions of evidence to this Committee have explicitly called for a national clinical trial audit system to be set up:

- The AllTrials campaign, representing over 730 supporter groups,[17] including the Health Research Authority (HRA), the National Institute for Health and Care Excellence (NICE), the Medical Research Council (MRC), the Association of Medical Research Charities (AMRC), the British Medical Association (BMA), and numerous patient groups[18]
- Dr Simon Kolstoe (independent chair of the Hampshire A NHS and MOD research ethics committees, member of the national research ethics advisory panel [NREAP], Senior Lecturer

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http://www.bmj.com/content/356/bmj.j1501
[14] Written evidence submitted by Dr Simon Kolstoe (RIN0022)
http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48484.html
[15] Goldacre, B. 2015. "How to Get All Trials Reported: Audit, Better Data, and Individual Accountability" PLoS Med 12(4): e1001821.
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001821
[16] Maruani, A. et al. 2014. "Impact of sending email reminders of the legal requirement for posting results on ClinicalTrials.gov: cohort embedded pragmatic randomized controlled trial"
http://www.bmj.com/content/bmj/349/bmj.g5579.full.pdf
[17] As of 26 September 2017, 734 organisations had formally lent their support to the AllTrials campaign. The full list is available here: http://www.alltrials.net/supporters/supporters-organisation-list/ [Accessed 26 September 2017]
[18] Written evidence submitted by AllTrials campaign (RIN0067)
http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48687.html

in Research Design & Ethics [University of Portsmouth]), Samantha Trace (Hampshire B Research Ethics Committee), and Daniel Shanahan (publisher for Springer Nature's open access health sciences journals)[19]

- Dr Ben Goldacre (head of the Evidence-Based Medicine DataLab at the University of Oxford and co-founder of the AllTrials campaign)[20]

19
The previous submissions of evidence to this Committee contain no proposals for alternative solutions to the research integrity problems in medical research that would reliably cover all clinical trials conducted in the UK. The alternative to a national clinical trial audit system is to continue pursuing the same piecemeal approaches that have shown limited success in the past.

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Failure by the government to set up a national clinical trials audit system would leave UK patients, UK taxpayers, and UK investors indefinitely exposed to the negative consequences of research integrity problems in this field.

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A national clinical trial audit system would provide Britain with a competitive advantage as a location for cutting edge clinical research and drug development. 'Successfully trialled in the UK' would become a global quality hallmark for new drugs, devices and treatments.

[ENDS]

[19] Written evidence submitted by Dr Simon Kolstoe (RIN0022)
http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48484.html
[20] Written evidence submitted by Dr Ben Goldacre (RIN0073)
http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48700.html