Using Brexit to improve clinical trials regulation in the UK: Adopting global best practice standards, setting up a National Clinical Trial Audit System, and ensuring access to Clinical Study Reports

Written evidence submitted jointly by HealthWatch UK, Universities Allied for Essential Medicines UK, and TranspariMED to the House of Commons Health Committee's inquiry into "Brexit – medicines, medical devices and substances of human origin".

London and Bristol, 24 November 2017

EXECUTIVE SUMMARY

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- A post-Brexit regulatory framework that reflects and effectively enforces global best practice standards in clinical trials transparency is in the interests of UK patients, UK taxpayers, UK government agencies and health bodies, and medical progress, and would improve the competitiveness of the UK as a location for life sciences research.
- Brexit could strengthen or weaken existing transparency provisions in the regulation of clinical trials in the UK.
- The current regulatory framework pertaining to clinical trial transparency consists of a mixture of UK and EU regulations and rules governing (a) trial registration, (b) summary results posting, and (c) the release of Clinical Study Reports. The current framework includes some positive features, but falls short of global best practice standards on all three dimensions.
- Successive UK governments have failed to monitor compliance with, or sanction the violation of, UK and EU regulations governing (a) trial registration and (b) summary results posting.
- Brexit provides an opportunity for the UK to adopt global best practice standards in clinical trials transparency and patient safety, and ensure compliance with these standards through:
    - The setup of a National Clinical Trial Audit System
    - Ensuring that UK government agencies and the UK scientific community have access to all Clinical Study Reports relevant to drugs being marketed in the UK
    - Making post-marketing surveillance data publicly available

ABOUT THE SUBMITTING PARTIES

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

- 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.

3
The submitting parties share the view that there is a strong public interest in clinical trials being registered, properly conducted and fully reported, irrespective of who funds, sponsors or conducts them. Healthcare should be evidence based, but if the evidence generated by trials is not made fully available, then this degrades the possibility of adequately evidence based decisions. Any regulatory system should go as far as possible to ensure that this is the case.

LACK OF TRANSPARENCY IN THE REPORTING OF CLINICAL TRIALS

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The incomplete and inaccurate reporting of clinical trials is a well-documented problem and has become a cause célèbre through Ben Goldacre's best-selling book *Bad Pharma* and through the widely publicised AllTrials campaign. Major factors contributing to this problem are the failure of trial sponsors and principal investigators to register all trials prospectively, to adhere to design protocols including end dates, to post the summary results of all trials, and to publish the outcomes of all trials in academic journals.[1] An additional problem is the refusal of most pharmaceutical companies and regulatory agencies to release Clinical Study Reports (CSRs), very lengthy and detailed documents that pharmaceutical companies submit to regulatory agencies when seeking marketing approval for a new drug.

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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 unnecessary risks. Examples include Lorcainide, a drug that killed over 100,000 people over the course of a decade, Tamiflu, on which the NHS seems to have misspent £424 million, and Vioxx, whose withdrawal after concealed safety concerns led to shareholder losses of $37 billion. The underlying dynamics and their negative consequences are well documented.[2]

CURRENT REGULATORY FRAMEWORK PERTAINING TO CLINICAL TRIAL TRANSPARENCY

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The current regulatory framework pertaining to clinical trial transparency consists of a mixture of UK and EU regulations and rules governing (a) trial registration, (b) summary results posting, and (c) the release of Clinical Study Reports.[3]

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[1] Written evidence submitted by Dr Ben Goldacre to the ongoing Commons Science and Technology Committee's inquiry into Research Integrity (RIN0073):
http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/48700.html

[2] 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]

[3] For more background on these elements of clinical trial transparency and global best practice standards related to each element, please see:
Cochrane, CRIT, Transparency International UK, and TranspariMED. 2017. Clinical Trials Transparency: A Guide for Decision Makers. Forthcoming study, to be published in London on 12 December 2017.

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Trial registration:

UK regulations require all interventional clinical trials to be registered within six weeks of the recruitment of the first participant.[4] This regulation is a step in the right direction, but falls short of global best practice standards, according to which all trials should be registered before the recruitment of the first participant; doing so would neither slow down research nor increase costs. The current regulation is national in nature and seems unlikely to be affected by Brexit.

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Summary results posting (I):

EU regulations require the summary results of certain types of drug trials to be posted onto the European trial registry within 12 months (6 months for paediatric trials).[5] Summary results posting is important for several reasons. First, summary results make the headline results of trials accessible more rapidly than academic publication, which can take several years. Second, summary results typically provide far more information on the negative side effects of drugs than journal articles do.[6] Third, posting summary results ensures that even if a trial's results never find their way into the academic literature, their findings do not become part of the estimated $170 billion-worth of global health research that goes to waste each year.[7] Finally, while journal articles are often placed behind paywalls, summary results can be viewed free of charge by doctors and patients worldwide.

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Summary results posting (II):

The EU approach falls short of global best practice standards, according to which the summary results of all interventional trials should be posted within 12 months maximum. At very least, existing EU regulations should be adopted by the UK to avoid a regulatory vacuum. Beyond that, Brexit provides an opportunity to adopt best practices. Otherwise, the pace of scientific progress will be slowed down, harms will continue to go unrecognized, UK research funds (including public funds) will be wasted, and patients in the UK and elsewhere will be denied access to information on the benefits and harms of drugs.

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Clinical Study Reports (I):

In 2016, the European Medicines Agency (EMA) became the first regulator worldwide proactively to release some Clinical Study Reports. This is a positive move, but it is far from ideal because it does not cover all CSRs. In particular, the CSRs for virtually all drugs on the market in the UK today typically remain inaccessible to independent researchers and even to UK government agencies. Under the current terms of use set by the EMA, researchers wanting to access the CSRs it has released must provide a place of address within the European Union.[8]

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[4] Health Research Authority. "Research registration and research project identifiers", 2017 https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-and-research-project-identifiers/ [Accessed 23 November 2017]

[5] European Medicines Agency. 2014. "Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014" http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002127.jsp [Accessed 20 September 2017]

[6] Tang, Eve et al. 2015. "Comparison of serious adverse events posted at ClinicalTrials.gov and published in corresponding journal articles", BMC Medicine 2015, 13:189 https://doi.org/10.1186/s12916-015-0430-4 [Accessed 23 November 2017]

[7] Glasziou, Paul et al. 2016. "Is 85% of health research really 'wasted'?", BMJ blog, 14 January 2016 http://blogs.bmj.com/bmj/2016/01/14/paul-glasziou-and-iain-chalmers-is-85-of-health-research-really-wasted/ [Accessed 23 November 2017]

[8] AllTrials campaign. 2016. "European Medicines Agency today releases first Clinical Study Reports" http://www.alltrials.net/news/european-medicines-agency-csr-transparency-policy-0070/ [Accessed 20 October 2017]

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Clinical Study Reports (II):

Clinical Study Reports, which are typically over a thousand pages in length, are a treasure trove of valuable information about the benefits and harms of drugs that cannot be found elsewhere. As noted above, the present situation is clearly unsatisfactory since Clinical Study Reports for trials of most drugs currently being marketed in the UK cannot be accessed by UK government agencies and health bodies, let alone by the wider UK scientific community. This makes it difficult for NICE to accurately assess the cost-effectiveness of medicines, is not in the interests of UK patients or UK taxpayers, and acts as a brake on the development of new and better medicines. To put it bluntly, UK citizens are routinely paying for and using potentially hazardous products while the suppliers of those products refuse to share product safety information they already hold on file. Brexit provides an opportunity to put an end to this remarkable information asymmetry.

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Clinical Study Reports (III):

If the current terms of use are not rewritten, NICE and other UK government agencies, or any other public health bodies which lack an EU address, may not even be able to access the small minority of CSRs that *are* released by the EMA. This will limit their ability to reach sound conclusions on the benefits, harms, and cost-effectiveness of newly developed medicines. To make matters worse, UK-based researchers may find it difficult or even impossible to access these CSRs, placing life sciences research in the UK at a competitive disadvantage.

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Clinical Study Reports (IV):

Conversely, a post-Brexit regulatory framework that ensures that all UK government agencies (including, but not limited to, the MHRA and NICE) as well as all UK-based academic and private sector researchers can access all Clinical Study Reports relevant to all drugs currently in use in the UK would provide a substantial competitive advantage to life sciences research in the UK by giving UK-based researchers unique access to vast amounts of medical research data that so far has remained locked away in company and regulator archives.

WEAK ENFORCEMENT OF THE CURRENT REGULATORY FRAMEWORK

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Successive UK governments have failed to monitor compliance with, or sanction the violation of, the national and European Union regulations discussed above. Many clinical trials conducted in the UK 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.[9]

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[9] 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.

OPPORTUNITIES TO IMPROVE TRANSPARENCY POST-BREXIT

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Brexit provides an opportunity for the UK to adopt global best practice standards in clinical trials transparency. These standards are as follows:

- All clinical trials as defined by the World Health Organisation (WHO) should be required to be registered before the recruitment of the first participant.
- All clinical trials as defined by the WHO should be required to post their summary results onto a WHO-approved trial registry within a maximum of 12 months.
- The Clinical Study Reports for all drugs licensed for marketing in the UK, including for drugs licensed in the past, should be made available to all UK government agencies and health bodies (notably including NICE) and the wider scientific community in the UK.

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Adherence to trial registration and summary results posting provisions should be actively monitored through a National Clinical Trial Audit System. A pilot has proven the feasibility of setting up such a system in the UK. It would cause no delays for institutions conducting clinical trials in the UK and, since its work would be based on records that already exist, it would cost little to set up and run.[10]

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Any post-Brexit institutional and regulatory framework should make access to all relevant Clinical Study Reports a pre-condition for permission to market any drug in the UK, including continued permission to market any and all drugs that are currently in use in the UK. Access to these Clinical Study Reports should be given to all UK government agencies (including, but not limited to, the MHRA and NICE) as well as all UK-based academic and private sector researchers.

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While Clinical Study Reports provide better safety data than journal articles do, clinical trials are not powered to detect less frequent adverse events. To better protect patients based on the full extent of available data, post-marketing surveillance (PMS) data should also be publicly available. Examples of PMS data sources are:

- Sponsors' own voluntary PMS programmes.
- PMS carried out as a condition of a product licence. These data will usually be held by a regulator.
- Academic monitoring centres, such as the Drug Safety Research Unit, Southampton.
- Adverse event reports submitted to a regulator, such as the MHRA `yellow card' system.

Methods to verify and aggregate these sources will be needed, as there is a high risk of data duplication if multiple sources are used.

[ENDS.]

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https://www.ncbi.nlm.nih.gov/pubmed/20181324 [Accessed 04 October 2017
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]

[10] Written evidence submitted by by HealthWatch UK, Universities Allied for Essential Medicines UK, TranspariMED, and Dr Simon Kolstoe to the ongoing Commons Science and Technology Committee's inquiry into Research Integrity (RES0008): http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/research-integrity/written/70815.html