<u>**Clinical trial transparency: Clarifications and additional information**</u>

**Submission to the Science and Technology Committee's inquiry into clinical trial transparency**

*Written evidence submitted by Dr Till Bruckner on behalf of TranspariMED*

> **Bristol, UK, 06 November 2019**
> **Contact:** tillbruckner@gmail.com
> www.TranspariMED.org

*Note: This evidence is being submitted following the session "Oral evidence: Clinical trials transparency: follow-up", HC 139, held on Tuesday 29 October 2019. The purpose is to clarify some of the issues raised, and provide the Committee with information requested during that session.*

**EXECUTIVE SUMMARY**

**1**

- **Drug trials.** Many UK universities and NHS Trusts have made significant progress in uploading the results of drug trials onto clinical trial registries. However, some institutions have failed to put into place appropriate systems and processes.
- **Non-drug trials.** The registration and reporting performance for non-drug trials remains weak. Many UK institutions still seem unaware of the importance of uploading results of non-drug trials onto registries.
- **UK trial funders** have made significant progress over the past year.
- **National Clinical Trial Monitoring System.** A national clinical trial monitoring [or 'audit'] system is necessary but not sufficient for ensuring that every clinical trial conducted in the UK is registered and posts its results. A national monitoring system would be highly cost-effective.
- **Options for sanctions outlined by the Health Research Authority.** The sanctions suggested by the Health Research Authority will not ensure that all future UK clinical trials are registered and reported. The Health Research Authority's resistance to seeking legal powers to impose financial penalties is deeply disappointing.
- **100% trial registration and reporting is achievable without legal changes.** It can be attained by making permission to sponsor new clinical trials contingent on the sponsoring organisations putting into place systems and processes that ensure that all new clinical trials are consistently registered and reported in a timely manner.
- **Problems with the European trial registry.** The current lack of user friendliness of EudraCT makes compliance onerous, but not impossible. The European Medicines Agency recently announced plans to make results reporting easier on EudraCT.

**2**
**Recommendations:**
- The Committee should publicly clarify its expectations for clinical trial results reporting on Clinicaltrials.gov and ISRCTN.
- The Committee should remain engaged in the process of developing the proposed national clinical trial monitoring system and 'league table' to ensure that these highly cost-effective innovations receive funding and meet transparency benchmarks.
- The Committee should ask the Health Research Authority to explain whether and how it will prevent organisations with insufficient safeguards from running more clinical trials in future.
- The Committee should maintain its dialogue with the European Medicines Agency.

**ABOUT THE SUBMITTING PARTY**

**3**
TranspariMED is a UK-based initiative that develops and promotes policy solutions to the problem of evidence distortion in medical research.

**PROGRESS AND GAPS IN THE REPORTING OF DRUG TRIALS**

**4**
**Strong progress.** As a whole, UK universities and NHS Trusts have made strong progress on uploading the results of drug trials onto the European trial registry EudraCT. Non-commercial trial sponsors across the UK have already uploaded more than twice as many trial results onto the European trial registry in 2019 than during the preceding four years combined. This progress is largely due to the letters sent out by the Committee.

**4**
**Missing results.** According to the report submitted to the Committee by AllTrials, 487 due trials run by UK universities (180 trials) and NHS Trusts (307 trials) are still missing results on EudraCT.

**5**
**Non-commercial trial sponsors.** Non-commercial trial sponsors that have already begun systematically addressing the problem can be expected to upload their missing trial results over the coming months. However, the AllTrials report also states that "33 NHS Trusts and six university sponsors have 0% of their due trials reported". This indicates that some institutions have failed to put into place appropriate systems and processes, in some cases despite receiving a letter from the Committee.

**6**
**Commercial trial sponsors.** Large pharmaceutical companies typically have near-perfect EudraCT reporting compliance rates. However, non-reporting by industry remains a concern. Across Europe, 66% of due trials run by small companies are missing results, as are 23% of trials run by medium-sized companies. While aggregate reporting rates for UK companies, or for foreign companies conducting trials in the UK, are not available, it is highly likely that compliance by industry remains suboptimal in the UK.

**PROGRESS AND GAPS IN THE REPORTING OF NON-DRUG TRIALS**

**7**
**Background.** The Committee's recent follow-up session repeatedly touched on the issue of clinical trials that are not listed on EudraCT (which only accepts drug trials), but are instead listed on Clinicaltrials.gov and ISRCTN. This includes all trials of medical devices and non-drug treatments such as surgery.

**8**
**Salience of non-drug trials.** From a patient, public health and scientific point of view, non-drug clinical trials are equally important as drug trials. According to the Vice President of the Royal College of Surgeons of England, "we need to focus more attention on improving the transparency of non-drug trials, especially since EU law will not address this… the evidence base for non-drug interventions has huge implications for public health." In addition, as witness Professor Pearse recently told the Committee: "Some of those clinical trials are much higher risk for patients taking part than some of the drug trials we are focused on reporting today."

**9**

**Large gaps in registration and reporting.** A 2019 audit by the Health Research Authority found that over 30% of non-drug clinical trials conducted in the UK are not being registered in the first place, despite this having been mandatory in the UK since 2013. Clinicaltrials.gov alone includes six times as many UK university sponsored trials as EudraCT does, and 97% of these trials remained unreported there as of January 2019.
*(Note: One witness told the Committee that the Clinicaltrials.gov figures cited above include observational studies. That is incorrect. The figures refer exclusively to interventional clinical trials.)*

**10**
**Large gaps in institutional systems and policies.** Some UK institutions have put into place systems and policies to ensure that in future, all clinical trials will report results in a timely manner, irrespective of registry. However, other institutions are only tackling trials listed on EudraCT, and report no plans for adopting systems that ensure consistent reporting on the other two registries. Unless corrective action is taken, these institutions will continue to fail to report all clinical trial results in a timely manner, and are highly likely to leave some trials entirely unreported, creating further research waste and leaving important evidence gaps. Note that global ethics rules do not distinguish between drug trials and non-drug trials: both have to make their results public.

**11**
**The Medical Device Regulation.** The forthcoming EU Medical Device Regulation does not require clinical trials of medical devices to be registered in trial registries, or their results to be uploaded onto trial registries. Thus, these problems will not be resolved when the Regulation comes into force.

**12**
**Global standards.** Going forward, all UK trial sponsors should routinely and consistently post the results of each and every clinical trial onto all registries where it is listed within 12 months of trial completion, in line with World Health Organisation best practices and global ethics rules. Due to the large volume of missing results on Clinicaltrials.gov and ISRCTN, trial sponsors cannot realistically be expected to retrospectively upload all missing results there. However, at a minimum, institutions should identify those trials listed there that have never reported results anywhere, and post their results onto registries before they become irretrievably lost.

**13**
**Lack of clear UK standards.** While World Health Organisation best practices clearly state that all clinical trials have to make their results public on trial registries within 12 months of completion, many UK institutions still seem unaware of the ethical, scientific and fiduciary importance of uploading results of non-drug trials onto registries.

- **The Committee should publicly clarify its expectations for clinical trial results reporting on Clinicaltrials.gov and ISRCTN.**

**PROGRESS BY UK TRIAL FUNDERS**

**14**
**Strong progress.** Both the MRC and the Wellcome Trust have set up monitoring systems to track whether clinical trials they fund are registered and publish trial results. Their monitoring covers both drug and non-drug trials. Both have made their monitoring results public. NIHR is working on a similar system. Over the past year, UK trial funders have thereby cemented their deserved reputation for leadership in clinical trial transparency. The impact of their efforts will be limited to trials directly funded by them.

**NATIONAL CLINICAL TRIAL MONITORING SYSTEM**

**15**
**Rationale.** A national clinical trial monitoring [or 'audit'] system based on Research Ethics Committee documentation is necessary but not sufficient for ensuring that every clinical trial conducted in the UK is registered and posts its results. No other conceivable mechanism could capture all trials, across all types of trial (non-drug or drug) and across all sponsor types (industry and non-commercial). All documentation required for monitoring is already centrally held by the Health Research Authority. The 'league table of performance' suggested by the Health Research Authority (see below) would rely on data from such a system.

**16**
**Cost-effectiveness.** A national monitoring system would be highly cost-effective. As of May 2019, an estimated 500 clinical trial sponsored by NHS Trusts alone, representing over £250 million in research funding, were at risk of becoming research waste. A national monitoring system would help to prevent future research waste.

- **The Committee should remain engaged in the process of developing the proposed national clinical trial monitoring system and 'league table' to ensure that these highly cost-effective innovations receive funding and meet transparency benchmarks.**

**OPTIONS FOR SANCTIONS OUTLINED BY THE HEALTH RESEARCH AUTHORITY**

**17**
**Three options.** The Health Research Authority's long-standing efforts to promote compliance on a voluntary basis have failed to ensure that all clinical trials conducted in the UK are registered and report their results. Health Research Authority representatives recently told the Committee that they had developed three options for sanctions:
>     (1) publishing a 'league table of performance'
>     (2) examining applicants' past transparency performance when reviewing new grant applications, and
>     (3) "ask[ing] Government for the power to fine in the case of non-compliance" (Q192).

**18**
**Option 1: League table.** TranspariMED strongly supports the creation of a public annual league table that covers all interventional clinical trials and meets key transparency benchmarks. Such a league table would help to drive improvements in performance by flagging shortcomings, and provide patients and taxpayers with important information about the performance of public bodies and pharmaceutical companies. However, experience shows that a league table by itself will not result in 100% compliance. A public league table for drug trials has been in existence in the form of the EU Trials Tracker since September 2018, but according to AllTrials, one year later, "33 NHS Trusts and six university sponsors have 0% of their due trials reported" (see above). Note that in other sectors, it would be unthinkable to propose a public league table as an alternative to sanctions for health and safety violations that put public health at risk.

**19**
**Option 2: Reviewing individuals' performance.** Examining individual applicants' past performance may in some cases help to drive positive behaviour at the individual level. However, this measure would fail to act as an incentive for researchers who are approaching retirement or are about to move abroad; such individuals could neglect to register and report trials without suffering adverse consequences. Furthermore, this measure targets individuals rather than institutions. Under both

European Union regulations and United States law, it is institutions are the 'sponsors' of clinical trials and thus responsible for posting summary results onto registries. Examining the track record of individuals may be helpful, but it cannot substitute for holding institutions to account for their compliance with regulatory requirements, stewardship of public funds, and organisational adherence to scientific good practices.

**20**
**Option 3: Financial penalties.** In August 2019, twelve patient and integrity groups [wrote an open letter](#) asking the Chair of the Committee to encourage the Health Research Authority to "set out a clear timetable for the phasing in of sanctions". Health Research Authority representatives told the Committee that "financial penalties require legislation, which does not seem very likely in the present climate", and suggested that this was a valid reason for the Health Research Authority not to seek such legislation in the first place (Q201). This is deeply disappointing.

**ATTAINING FULL TRIAL REGISTRATION AND REPORTING WITHOUT LEGAL CHANGES**

**21**
**100% trial registration and reporting is achievable without legal changes.** It can be attained by making permission to sponsor new clinical trials contingent on the sponsoring organisations putting into place systems and processes that ensure that all new clinical trials are consistently registered and reported in a timely manner (irrespective of individual employees' priorities and actions).

**22**
**Full compliance could be achieved by 2022 without financial penalties:**

> (1) As a first step, the Health Research Authority should use the first iteration of its league table (presumably in 2020) to identify all trial sponsors who have failed to register a clinical trial, and/or upload its results to a trial registry within 12 months of trial completion.

> (2) The Health Research Authority should then inform such sponsors that their system and processes require strengthening, and give them a one year deadline for doing so.

> (3) After one year, in 2021, the Health Research Authority should use the second iteration of its annual league table to again identify sponsors with unregistered and/or unreported trials. Any organisation that has still failed to adopt adequate systems and processes at that point, and is thus demonstrably not able to ensure consistent compliance, should not be allowed to sponsor any more clinical trials. Such organisations would henceforth need to contract another legal entity to assume the sponsorship function for them.

- **The Committee should ask the Health Research Authority to explain whether and how it will prevent organisations with insufficient safeguards from running more clinical trials in future.**

**ROLE AND PERFORMANCE OF THE MHRA**

**23**
**MHRA role.** The MHRA is responsible for regulating drug trials, but not for regulating trials of medical devices, surgery, or other non-drug interventions.

**24**
**MHRA helpline.** The MHRA operates a helpline to assist trial sponsors in reporting drug trials. TranspariMED has not received any negative feedback from trial sponsors regarding the MHRA's

helpline. In contrast, feedback from trial sponsors on the European Medicines Agency's helpdesk has consistently been negative (see below).

**25**

**Outdated trial data.** Many clinical trials on EudraCT that were completed long ago are falsely listed as 'ongoing'. While this does not prevent results from being uploaded, it makes it difficult for patients to find trials to participate in, and difficult for public health agencies and researchers to gain an overview of the complete scientific evidence base on a medicine. The responsibility for updating the status of drug trials rests with National Competent Authorities (national regulators) in EU Member States, i.e. the MHRA in the UK. Trial sponsors must go through National Competent Authorities to get the status of any trial updated. Available data suggests that all national regulators across Europe have failed to consistently perform this task. The European Medicines Agency has no power to compel national bodies to meet their obligations in this regard.

**26**

**MHRA updates of trial data.** The MHRA is responsible for ensuring that the completion status of UK clinical trials listed on EudraCT is accurate. It is regrettable that the Committee focused on MHRA's past lapses in this regard, rather than on MHRA's rapid progress in clearing its legacy backlog. To the best of TranspariMED's knowledge, MHRA is the only regulator in Europe that has tackled this problem. MHRA has assisted TranspariMED in producing a policy brief aimed at encouraging other regulators in Europe to follow MHRA's positive example.

**MAKING CLINICAL TRIAL REPORTING ON THE EUROPEAN REGISTRY EASIER**

**27**

**Problems with EudraCT.** The Committee heard evidence that uploading the results of clinical trials onto the European registry EudraCT is unnecessarily difficult and time consuming. In theory, uploading the results for a trial should take a few hours at most, but due to various problems, first time users can spend days uploading the required data. (Highly experienced users report being able to upload a trial's results within just 1-2 hours.) Making EudraCT more user friendly would save trial sponsors in the UK and beyond – including industry sponsors – valuable time and resources.

**28**

**Full compliance is possible.** The current lack of EudraCT user friendliness makes compliance onerous, but not impossible. For example, as of early November 2019, King's College London has uploaded 59 clinical trial results, achieving a compliance rate of 100%, demonstrating that full compliance is possible within the existing framework. Also, uploading results onto Clinicaltrials.gov is far easier and less time consuming that with EudraCT, but even so, UK universities had only posted 9% of due trial results there by January 2019 (see above). Note that trial registration – as opposed to results reporting – is comparatively easy on all trial registries.

**29**

**Recent steps taken by the European Medicines Agency.** In its dual role as medicines regulator and EudraCT platform manager, the European Medicines Agency has the mandate, the power and the obligation to facilitate compliance by making the registry more user friendly. In February 2019, TranspariMED and Health Action International published a report urging the European Medicines Agency to take action on these issues. Since then, TranspariMED has met Agency representatives on three occasions to discuss these issues. A list of problems that require addressing has been compiled by TranspariMED (reproduced in the Annex, below) and shared with the Agency. In response, in October 2019, the Agency announced plans to make results reporting easier on EudraCT.

**30**

**Additional steps required.** The [letter](#) that the Chair of the Committee sent to the European Medicines Agency on 31 October 2019 raised highly salient questions. It would be excellent if the Committee published the Agency's response and maintained this dialogue in 2020. In particular, the Committee could encourage the Agency to allocate the resources required to make its helpdesk functional, and to publish performance benchmarks (such as average response time and user satisfaction data). A positive role model in this regard is the 'PRS support team' within the American trial registry Clinicaltrials.gov, which runs an excellent helpdesk that rapidly responds to email enquiries by trial sponsors and provides useful and actionable advice.

- **The Committee should maintain its dialogue with the European Medicines Agency.**

**ANNEX: PROBLEMS WITH UPLOADING RESULTS TO THE EUROPEAN CLINICAL TRIAL REGISTRY**

| MAJOR PROBLEMS |
| --- |
| **Lack of a functional helpdesk** |
| The existing helpdesk takes 2-3 weeks to respond to emails. It typically responds by citing excerpts of regulatory texts, which does not help registry managers to solve the problem in question. |
| **Delays in obtaining 'results user' status** |
| When the original 'sponsor contact' no longer works at an institution, it can take up to 3 months to obtain the status of 'results user', which is a precondition for uploading a trial's results. |
| **Excessive data requirements** |
| The level of detail required by the registry is extremely high, and the registry does not provide the option of simplified reporting for categories of trials where less granularity would be more appropriate. Note that this may lead to incorrect data being entered. |
| **Problems logging into the registry** |
| If the original login details have been lost, sponsors cannot contact the helpline to request a new login and password. |
| **Frequent platform crashes** |
| The registry platform typically crashes several times a day. If this happens during trial results uploading, several hours' worth of work can be lost. |
| **Insufficient save-as-you-go functionality** |
| Saving data during SAE entry is impossible on a rolling basis. This means that if the platform crashes, all data entered up to that point is lost. |
| **Some trials are not publicly visible** |
| Some trials registered on the registry are not visible on its public interface, for reasons unknown to the trial sponsor. |
| **Posting 'results' for trials that never recruited participants** |
| Trials that never recruited participants have no results to report, but it is impossible to progress through the system if participant recruitment is entered as "0". |
| **Workflow interruptions** |
| It is not possible to progress through the system if any fields are left blank. This means that all other data entry must come to a halt until the missing data point has been located. |
| **Lack of useful guidance materials** |
| Existing guidance and manuals on how to post clinical trial results are too long winded and complicated, and fail to meet the needs of trial sponsors. Existing guidance is not sufficiently hands-on and does not permit novice results users to learn from more experienced peers. Furthermore, there are no useful examples for how best to report the results of certain types of trials, for example for parallel and cross over studies. |

| OTHER PROBLEMS |
| --- |
| **Incorrect trial status** |
| National regulators often fail to update trials to 'complete' even after being notified by trial sponsors. (Exception: MHRA) |
| **Lack of a peer-to-peer support network** |
| There is no network or platform through which non-commercial trial sponsors can share experiences, tips and tricks. |
| **Problems transferring trial sponsorship to a different sponsor** |
| When sponsorship of a trial changes during the course of the trial, it is difficult and time-consuming to have the trial re-assigned to a new sponsor. |
| **Delays in making results visible** |
| It typically takes EMA over two weeks to make uploaded results publicly visible. |

*Note on methodology: A draft list of items was compiled by TranspariMED based on interviews with UK registry managers, a previous policy paper on the topic, a guest blog for TranspariMED, presentations and conversations at a recent trial reporting workshop in Berlin convened by the BIH QUEST Center, and workshop slides (available here). Two experienced trial registry managers from UK universities then reviewed and expanded the list, and scored the impact of each item based on their personal experiences with uploading trial results.*