Written Evidence Submitted by
Cochrane, Transparency International Global Health Programme, and TranspariMED
(RRE0024)

EXECUTIVE SUMMARY

Status quo

- Lack of clinical trial transparency undermines the integrity and reproducibility of medical research. This harms patients, undermines public health, and wastes public funds.
- Progress on UK trial transparency in recent years has been significant, but considerable gaps remain, especially with trials of medical devices and other non-drug trials.
- Two previous S&T Committee inquiries into this topic have recommended sanctions for the non-reporting of trial results, but to date, these recommendations have not been adopted.
- Past regulatory experience in the UK, European Union and United States shows that effective sanctions are indispensable for ensuring that the results of all clinical trials are reported in a timely manner. Regulators in the US have recently started imposing sanctions, and EU Member States will start doing so from early 2022. The World Health Organisation also recommends the introduction of sanctions.
- The Health Research Authority (HRA) has made very rapid progress on developing and implementing its excellent #MakeItPublic strategy. The single weak point in the strategy is the lack of a credible plan to impose effective sanctions.

Recommendations

1. **Put into place sanctions with teeth for sponsors that fail to make trial results public, supported by a credible sanctions mechanism.**
2. **Publicly set a starting date for sanctions implementation.**
3. **Conduct annual follow-up sessions until the first sanction has been imposed.**

ABOUT THE SUBMITTING PARTIES

Cochrane focuses on producing relevant and timely synthesized evidence and is a global advocate for evidence-informed health and health care. Cochrane works towards a world of improved health where decisions about health and health care are informed by high-quality, relevant and up-to-date synthesized research evidence. Its members and supporters come from more than 130 countries worldwide, including the UK.

The Transparency International Global Health Programme is part of the Transparency International movement. Based in London, it is hosted by Transparency International UK. It acts as a centre of global health expertise for the entire Transparency International movement. Its mission is to ensure effective, accountable and transparent health systems which leave no room for corruption and deliver Universal Health Coverage.

TranspariMED is a UK-based initiative working to promote clinical trial transparency through a combination of research, advocacy and facilitating peer-to-peer capacity building.

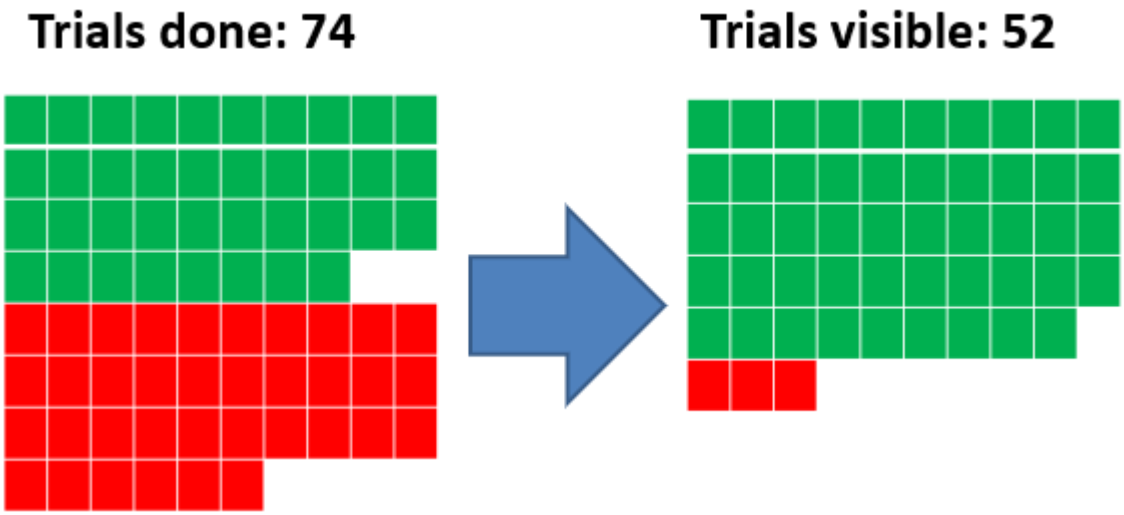
> *Note: Cochrane, the Transparency International Global Health Programme and TranspariMED on several occasions submitted evidence to the S&T Committee's 2018 inquiry on clinical trial transparency, sometimes together with other groups. Some of this material was cited verbatim in the S&T Committee's 2018 report on this issue.*

CLINICAL TRIAL (NON-)REPORTING, RESEARCH INTEGRITY AND REPRODUCIBILITY

Complete non-reporting of results. Failure to make the results of clinical trials public in any form is a violation of global medical research ethics (Article 36 of the Declaration of Helsinki), and therefore clearly a ***research integrity*** issue.

Partial publication of results and misleading reporting. This submission of evidence will use the term "partial publication of results" to refer to instances in which results are made public exclusively in academic journals, but not in trial registries. Partial publication limits ***reproducibility*** because journal articles often do not fully report trial outcomes. It heightens the risk of ***research integrity*** violations because trial outcomes are frequently **reported misleadingly** in journals. A widely cited study of 67 journal articles discussing clinical trial outcomes found that 58/67 articles either did not report all pre-specified outcomes, or silently added outcomes post hoc, only 9/67 journal articles fully met integrity standards. Another widely cited study of 74 clinical trials of antidepressant drugs. It found that 11/74 trials with a 'negative' outcome, i.e. trials that found that patients did not benefit from the medicines being investigated or experienced more harms than benefits, were misleading reported as having had positive outcomes in journal articles. A further 22/74 'negative' trials had not been published in journals at all, rendering them invisible. The image below illustrates the impact this combination of misleading reporting and non-reporting on the publicly available evidence base regarding the efficacy and safety of antidepressant drugs.

Image: *Impact of non-publication and partial publication of results on the medical evidence base on antidepressant drugs, based on Turner et al 2008. On the left side are all 74 clinical and their actual outcomes. Green squares represent trials with positive outcomes, red squares trials with negative outcomes. On the right side is the picture of trial outcomes presented in the scientific literature.*



Negative impacts. That such non-reporting and misleading reporting harms patients, undermines public health, and wastes public funds is universally accepted. These harms were outlined in numerous submissions of evidence to the S&T Committee's 2018 inquiry into clinical trial transparency, are exhaustively documented in the academic literature, and acknowledged in the S&T Committee's 2018 inquiry report. A 2017 report by Transparency International, Cochrane and TranspariMED summarises the academic literature on harms, discusses existing standards and best practices, and provides relevant policy recommendations. Therefore, this submission will not restate the evidence on harms.

Strategic value of transparency. The UK is currently setting out to become the first country worldwide in which all clinical trials are registered and reported. The RECOVERY trial and other Covid research efforts showcased the value added by the UK's strong commitment to clinical trial transparency, regulatory excellence and close cooperation between MHRA, NIHR, MRC and HRA. If fully implemented, the current transparency plans could become a further showcase highlighting the UK's attractiveness as a global hub for cutting-edge biomedical research.

GLOBAL STANDARDS

Global standards. World Health Organisation standards set out in 2017 state that all clinical trials should make their results public in two formats: (1) ***on a trial registry within one year of trial completion***, and (2) ***in a peer-reviewed journal*** ideally within two years of trial completion. According to the WHO, responsibility for ensuring timely and full reporting lies with the ***trial sponsor***, i.e. the institution or company running the trial. The WHO also recommends that "Legislation or supporting regulations [should include] ***sanctions*** if a clinical trial is not registered and/or results are not reported." The Declaration of Helsinki (Article 36) also requires the results of all trials to be made public, but does not specify a format, timeline, or single responsible party.

LEGAL AND REGULATORY FRAMEWORKS

UK framework. The UK legal and regulatory framework governing clinical trial reporting differs between ***drug trials***[1] and ***non-drug*** trials; the latter category includes trials of medical devices and surgical techniques, and constitutes the large majority of trials run in the UK.

- **Drug trials.** Since Brexit, the former EU Guideline mandating drug reporting – which was never legally enforceable in the UK – no longer applies in the UK. MHRA unilateral guidance continues to require UK trial ***sponsors*** (i.e. the commercial or non-commercial entities running trials, rather than individual researchers) to post the results of drugs trials onto the ***European trial registry within one year of trial completion*** until longer-term national solution is found. In practice, MHRA in September 2020 explained that there is "no legislation that would allow us to issue sanctions on sponsors." ***MHRA has no legal powers to sanction trial sponsors*** or compel them to make drug trial results public. There is no requirement to make drug trial results public in academic journals.

- **Non-drug trials.** There are currently ***no legal requirements*** to make the results of non-drug trials public.

[1] This submission somewhat simplistically refers to Clinical Trials of Investigative Medicinal Products (CTIMPs) as "drug trials", and refers to all other trials as "non-drug trials", reflecting current UK regulatory practice. In reality, a minority of drug trials are not regulated as CTIMPs, and a minority of device trials are CTIMPs.

- **All trials.** The Health Research Authority now requires the results of all clinical trials (drug and non-drug) to be made public on trial registries, and plans to soon start monitoring compliance. However, there are ***no sanctions*** for failing report results.

Frameworks in other jurisdictions. Legal and regulatory frameworks in other jurisdictions focus on the publication of results in ***trial registries***. This is because (a) the relevant registries themselves are publicly managed, (b) registry reporting timelines – in contrast to journal publication timelines – are fully under the control of the entity conducting the trial, and (c) reporting trial results on clinical trial registries in tabular form ***strengthens reproducibility*** because the trial design must be set out in detail during the initial registration, and ***strengthens research integrity*** because registries require the uploading of results data conforming to a trial's original parameters, making the misleading reporting common in academic journals (see further above) impossible. The legal responsibility for reporting results typically rests with a trial's institutional ***sponsor*** and not with the individual researcher who ran the trial. This ensures that results are submitted even if an individual researcher moves to a different institution, retires, or dies. ***Sanctions*** are increasingly being introduced to improve compliance.

- **European Union**
  - **Drug trials.** The ***EU Clinical Trial Regulation*** fully comes into force at the end of January 2022. From then on, making the results of ***drug trials*** public on the European registry within a year of trial completion (reduced to 6 months for paediatric trials) will be a national legal requirement for ***sponsors*** in all 27 member states. Each member state will independently define and implement ***sanctions*** for non-reporting. In some countries (for example France and Demark), possible sanctions comprise not only financial penalties, but also prison terms for persistent offenders. The Danish regulator has publicly announced that it will make full use of its new powers in future.
  - **Medical device trials.** In 2024, the ***Eudamed*** database for ***medical devices*** will be launched within the framework of the ***EU Medical Device Regulation***, introducing new reporting requirements for certain medical device trials on the European level.
  - **Trials of other medical interventions**, such as trials of surgical techniques and physiotherapy, are not regulated at the European level. In some member states (for example Germany and Spain) here are long-standing ***national legal requirements*** to report the results of such trials onto ***national databases***, but these databases are not WHO-affiliated trial registries. In practice, national regulators seem not to impose ***sanctions*** when these laws are violated.

- **United States**
  - **Drug and medical device trials.** The 2007 FDA Amendments Act (FDAAA) mandates the reporting of results for certain – but not all – clinical trials of drugs and medical devices on the American trial registry. Legal responsibility for compliance typically lies with the ***sponsor***, but in the case of academic trials, an individual researcher may be designated as the 'responsible party' for uploading results. ***Sanctions*** set out by the law include, but are not limited to, a $10,000 fine for every day that a trial's results are late. The FDA has recently started enforcing this law, sending warning letters to responsible parties that give them 30 days to upload missing results or else face a fine. To date, in every single case, the parties contacted ***have uploaded the missing trial result before expiry of the deadline***, illustrating the potential of enforcement measures to improve compliance.

- **Other trials.** There is no legal requirement to report the results of clinical trials that are not covered by FDAAA, in any form. The majority of trials fall outside the scope of FDAAA.

IMPACT OF PAST S&T COMMITTEE ATTEMPTS TO IMPROVE TRIAL REPORTING

Significant impact but problems persist. The S&T Committee's 2013 and 2018 inquiries generated a lot of policy and public interest in clinical trial transparency, and positively impacted the reproducibility and research integrity of clinical trials, but have failed to solve the problem of complete non-reporting of trial results due to a lack of monitoring and sanctions.

- **The 2013 inquiry's recommendation that sanctions should be imposed was never implemented.** The HRA in 2013 required researchers to register their clinical trials, but did not monitor compliance or threaten sanctions. HRA later found that researchers had failed to register 30% of trials as required. MRC and NIHR adopted stronger policies on trial registration and reporting.
- **The 2018 inquiry was surprised and dismayed to discover that large numbers of clinical trial results were still not being made public.** The inquiry itself, combined with the then Chairman's strong personal engagement, sparked substantial progress on improving the reproducibility and research integrity of clinical trials run in the UK, particularly for drug trials. However, ***the inquiry's recommendation that sanctions should be imposed has not been implemented***.

Recent efforts to improve trial reporting in the UK. In the wake of the 2018 inquiry, MHRA, MRC, NIHR and HRA all invested considerable effort into improving clinical trial registration and reporting:

- **MHRA** pioneered a trial registry data clean-up that has since been emulated by some other regulators in Europe, and has done its utmost to promote voluntary compliance among drug trial sponsors.
- **MRC and NIHR** have put into place systems that monitor whether their grantees register and report trials, and may refuse to award future grants to researchers that break the rules. This approach places MRC and NIHR (together with the Wellcome Trust) among the best-performing funders in terms of promoting reproducibility and research integrity in clinical trials in Europe,[2] and probably worldwide.
- **HRA** has set up the world's first national clinical trial registration monitoring system[3] (and will soon also begin to monitor trial reporting), developed the world's first national transparency strategy for clinical trials (***#MakeItPublic***, see below), reaffirmed a formal requirement to make trial results public, and has energetically promoted best practices within the research community.

RECENT DATA ON MISSING DRUG TRIAL RESULTS IN THE UK

Violations of MHRA reporting requirements. During the 2018 inquiry, the previous Committee's attention almost exclusively focused on drug trials and the reporting of their results on the European trial registry, as the then applicable European regulatory framework already mandated this (as the MHRA does today), and the newly launched EU Trials Tracker provided clear institutional performance data. MHRA continues to expect UK trial sponsors to upload the results of drug trials onto the registry.

The previous Committee's attention and active engagement pushed many – but not all – universities and NHS Trusts to significantly improve their reporting performance on the registry. Example:[4]

- The University of Nottingham was singled out for criticism by the Committee in 2018 for its reporting performance of 6%; today it has a perfect compliance rate of 100%.

[2] Ongoing academic study, publication expected in late 2021.
[3] This submission does not discuss clinical trial registration in detail because the submitters trust that the HRA will implement its plan to centrally register all trials and thereby resolve the problem once and for all.
[4] Based on data extracted from the EU Trials Tracker on 15 September 2021.

However, many institutions still fail to report drug trial results as required. Examples:[5]

- University Hospitals Birmingham NHS Foundation Trust has failed to report 68% of its due results on the registry; fifteen of its trials are missing results.
- University Hospital Southampton NHS Foundation Trust has failed to report 55% of its due results on the registry; eleven of its trials are missing results there, including six cancer trials and one trial that enrolled children.
- Great Ormond Street Hospital for Children NHS Foundation Trust has failed to report 83% of its due results on the registry. Out of six due trials, only one trial has results available.

Complete non-reporting of drug trial results. Some UK drug trials that do not have results available in the European registry have published results in a scientific journal. This violates of MHRA reporting requirements, raises concerns about reproducibility and heightens the risk of research integrity issues, but is still better than complete non-reporting.

TranspariMED combined registry and literature searches to identify completely non-reported drug trials sponsored by NHS Trusts, and published an analysis estimating that as of May 2019, ***NHS Trusts alone had run around 500 UK drug trials costing £250 million that had not made their results public in any form*** one year or more after trial completion. This is a rough estimate only, based on conservative assumptions; actual figures might be higher. Comparable estimates for UK drug trials run by universities and pharmaceutical companies are not available.

RECENT DATA ON MISSING NON-DRUG TRIAL RESULTS IN THE UK

Widespread failure to report results of non-drug trials on trial registries. Global ethics requirements (Declaration of Helsinki, Article 35) and HRA rules adopted in 2013 require all clinical trials to be registered on a trial registry. Non-drug trials cannot be registered on the European registry. UK researchers tend to register such trials either on the London-based ISRCTN registry or on the US-based ClinicalTrials.gov registry.

While WHO standards set out that all trials should make their results public on registries within one year of completion, UK researchers in practice rarely upload the results of non-drug trials onto registries. A 2021 study reviewing 3,034 completed UK university trials listed on ClinicalTrials.gov found that ***nearly 90% of UK university trials did not have tabular summary results on the registry***. Only 1.6% of all trials had uploaded results within the WHO's one-year timeframe. Comparable figures for trials run by NHS Trusts and industry are not available.

The findings strongly suggest that while many UK universities significantly improved their reporting of drug trials on the European registry ***in the wake of the 2018 S&T Committee inquiry, transparency efforts were not extended to non-drug trials on other registries***, presumably because performance data for other registries was not readily available at the time and the 2018 inquiry had overwhelmingly focused on European registry data. As noted above, such ***partial publication*** has negative effects on reproducibility and research integrity.

Complete non-reporting of non-drug trial results. It is unknown how many UK non-drug trials never make their results public in any form, i.e. not on registries and not in journals. Responses to Freedom of Information requests filed by TranspariMED indicate that most UK universities and NHS Trusts have historically not tracked whether the non-drug trials they sponsored made their results public or not; however, several institutions have started doing this in recent years.

[5] Based on data extracted from the EU Trials Tracker on 15 September 2021.

A 2019 peer-reviewed study of 1,509 trials sponsored by Germany universities found that 26% had never made their results public in any form. A comparable study, which has yet to be published, found a similar non-reporting rate for Dutch universities. Based on these figures, it seems reasonable to assume that in the past, ***around a quarter of UK non-drug trials never made their results public***. TranspariMED is currently conducting research to generate more precise figures.

RECENT DATA ON MISSING TRIAL RESULTS FROM OTHER JURISDICTIONS

Compliance with US law and EU regulations. Over a quarter of applicable trials in both jurisdictions are still missing results in violation of the rules (US: 2,928 trials total, 26%; EU: 3,763 trials total, 26%).[6] Overall, reporting rates are measurably improving in both jurisdictions, but this is largely driven by improved performance of large pharmaceutical companies and some of the largest universities, in part because their reporting performance is sometimes scrutinised and publicised by advocacy groups.

Compliance with national laws. Recent studies of national databases (technically not trial registries, but with a similar function) in Germany and Spain, for which national legal reporting requirements exist but where compliance is neither monitored nor enforced with sanctions, have shown extremely low compliance rates.

Lessons learnt from other jurisdictions. International regulatory experience shows that even in the presence of clear-cut legal and/or regulatory requirements to make trial results public, ***both monitoring and sanctions are required to ensure consistent compliance by sponsors***. Two trial trackers developed by the University of Oxford have for years enabled regulators and the public to monitor whether sponsors are violating laws (US) and regulatory guidelines (EU) on trial reporting.[7] Despite the long-standing availability of such monitoring data, over a quarter of trials in both jurisdictions are still missing results today. In the European Union, the European Medicines Agency is additionally prompting negligent researchers with reminder emails, but these messages do not include a threat of sanctions and are evidently having limited impact.

THE *#MAKEITPUBLIC* STRATEGY FOR CLINICAL TRIAL TRANSPARENCY

Background to the strategy. The development of the #MakeItPublic strategy was the direct result of the 2018 S&T Committee inquiry into clinical trial transparency. The development of the strategy was led by the Health Research Authority (HRA), reflecting its role as the only gatekeeper through which every single clinical trial must pass before it can recruit UK patients, and its institutional mandate to promote transparency in medical research. The strategy was developed pre-Brexit, when it was unclear whether the UK would become subject to two incoming European Union regulations that would have affected the regulation of drug and medical device trials, including whether and how the European trial registry would continue to be used by UK sponsors. Due to the pandemic, the strategy was published with considerable delay, in July 2020.

[6] Figures extracted from the FDAAA Trials Tracker and the EU Trials Tracker on 15 September 2021. Due to conservative counting methodologies and technical reasons, the numbers of unreported trials stated by both trackers significantly understate the number of trials actually in violation of transparency requirements. For the same reasons, actual non-reporting rates are almost certainly higher than 26%.

[7] See the FDAAA Trials Tracker and EU Trials Tracker websites.

The strategy outlines measures that, if fully implemented, will significantly and lastingly improve the reproducibility and research integrity of clinical trials.

- **Clinical trial registration.** The strategy envisions putting HRA directly in charge of trial registration following ethics approval, which would guarantee that in future every single clinical trial is registered. This innovative solution would make the UK the ***first country in the world to ensure universal trial registration***, fixing a persistent and severe reproducibility and research integrity problem once and for all.[8] (HRA already monitors trial registration.)
- **Results publication.** The HRA will require trial results to be made public within one year of trial completion, including on trial registries. These requirements fully meet the 'gold standard' WHO benchmarks for clinical trial transparency. HRA formally introduced these requirements in September 2021, with immediate effect, which is a big step forward and arguably makes the UK the ***first country in the world to require reporting of all clinical trial results***.
- **Monitoring compliance.** In future, the HRA will monitor compliance with reporting requirements, actively prompt researchers who fail to submit results on time, and publish monitoring reports. These elements are vital because in the past, many researchers have overlooked, forgotten or ignored HRA transparency requirements.
- **Making transparency easy.** The strategy avoids imposing additional red tape on medical researchers and seeks to align transparency requirements and related processes across major UK stakeholders such as MRC, NIHR and MHRA.

The strategy has a single weakness: Lack of sanctions.

- **Lack of sanctions.** The strategy does not include any sanctions with teeth for pharmaceutical companies and research institutions that neglect – or refuse – to make clinical trial results public. ***The 2013 and 2018 S&T Committee inquiry reports both explicitly called for the adoption of sanctions, a recommendation that was never adopted*** (see the annex, further below). Meanwhile, the 'voluntary compliance' and 'gradual culture change' approach preferred by the HRA has consistently failed to bring about an acceptable level of reproducibility and research integrity in terms of ensuring that all clinical trial results are reported. The #MakeItPublic strategy merely envisages to "introduce research transparency performance assessment into review of new studies," meaning that in theory, ethics approval for future trials could be refused for individual researchers who have broken rules in the past. In practice, this approach cannot and will not ensure that all trial results are reported (see further below). ***The HRA's proposed approach is flawed because it lacks teeth, targets individuals rather than sponsors, and lacks a credible sanctions mechanism.***

[8] This submission does not discuss clinical trial registration in detail because the submitters trust that the HRA will implement its plan to centrally register all trials and thereby resolve the problem once and for all.

RECOMMENDATIONS

The following section provides three recommendations:

1. **Put into place sanctions with teeth for sponsors that fail to make trial results public, supported by a credible sanctions mechanism.**
2. **Publicly set a starting date for sanctions implementation.**
3. **Conduct annual follow-up sessions until the first sanction has been imposed.**

RECOMMENDATION 1: Put into place sanctions with teeth for sponsors that fail to make trial results public, supported by a credible sanctions mechanism.

(1a) Adopt sanctions with teeth

Global regulatory experience consistently shows that sponsors will not consistently make trial results public in a timely manner unless there is a threat of sanctions. As the limited impact of two existing trial trackers and EMA reminder emails have shown, publicly monitoring sponsors' performance and sending voluntary compliance prompts will not ensure compliance.

In the United States, the 2007 FDA Amendments Act (FDAAA) sets a fine of $10,000 for every day a clinical trial result is overdue. For over a decade, the FDA did not enforce that law, and over a quarter of clinical trials remained unreported. The FDA has recently started sending out warning letters threatening steep fines, and to date, every sponsor that has received such a warning letter has uploaded the missing trial result within the 30 day deadline.

While there is no comprehensive overview of the range of sanctions that the 27 national regulators in the European Union will have at their disposal from the end of January 2022, Denmark and France have already adopted national legislation that could result in prison sentences for persistent offenders, in addition to financial penalties. Denmark's regulator has already publicly emphasised that it plans to make full use of its powers. WHO recommends the introduction of sanctions,[9] and there is a global regulatory trend towards imposing sanctions with teeth.

In 2019, twelve patient and integrity groups including Transparency International, Cochrane, the International Alliance of Patients' Organizations and TranspariMED wrote an open letter[10] to the then Chair of the S&T Committee, urging the adoption of sanctions and asking for "a clear timetable for the phasing in of sanctions". The Chair publicly responded that "The Health Research Authority (HRA) must follow my Committee's recommendation from last Autumn to introduce a system of sanctions for those who do not comply with reporting results requirements for clinical trials. ***For too long there has been little consequence to non-compliance with current requirements and it's time action was taken.***" The open letter and response are reproduced in full in the annex at the end of this submission.

[9] "Legislation or supporting regulations [should include] sanctions if a clinical trial is not registered and/or results are not reported."

[10] Permanent link here: https://web.archive.org/web/20191221062618/https://docs.wixstatic.com/ugd/01f35d_e9427c06b7134f9b81ddf58c39b5d4ff.pdf

(1b) Target sanctions at sponsors, not at individuals

The HRA's current plan to target measures at individuals – rather than at the pharmaceutical companies and institutions sponsoring trials – is ineffective. In academic research, clinical trial results often remain unreported because lead investigators retire or leave for other positions, including non-research positions such as clinical work, and positions abroad. These researchers will never again submit an ethics application in the UK, and thus the HRA's proposed mechanism will have no leverage over them. Furthermore, common reasons for late reporting in academia include personal factors such as illness or pregnancy. In such cases, the HRA does have leverage, but it would be inappropriate to use it. In the commercial sector, a pharmaceutical company could choose not to report a trial result, and then assign different employees to run future trials, easily circumventing the mechanism proposed by the HRA. Sanctioning individuals would also run counter to WHO standards and be misaligned with regulatory approaches in other jurisdictions, including the European Union and the United States, which for good reason focus on sponsors and not on individuals.

Placing the onus for compliance with reporting requirements on sponsors has four advantages.

- ***It is effective***, avoiding the pitfalls associated with attempting to secure individual compliance (see above).
- ***It is efficient***, as regulating a few hundred sponsors is easier than attempting to secure the compliance of thousands of medical researchers whose contact details regularly change.
- ***It ensures consistent timely results publication*** even when individual researchers change jobs, become ill or pregnant, because it forces institutions themselves to put into place policies, systems and safeguards that ensure compliance irrespective of individual personal circumstances. (Many UK universities have already done this for drug trials in the wake of the 2018 inquiry.) Trial participants and patients should be able to expect timely reporting of trial results irrespective of personal factors.
- ***It promotes institutions' responsibility for upholding reproducibility and research integrity standards*** in medical research conducted with human volunteers under their roofs.

(1c) Put into place a credible sanctions mechanism

MHRA may be better positioned to manage the sanctioning process. While HRA's senior management is very strongly committed to clinical trial transparency, and HRA has done outstanding work in developing the strategy and implementing its first stages, HRA's institutional culture is non-confrontational and HRA's main points of contact (via ethics committees) are individual researchers rather than sponsoring institutions. Under the HRA's current plan, research ethics committees – which are comprised of unpaid volunteers – would be given discretionary powers over whether or not to refuse new approvals due to past non-reporting. The HRA's then Chair told the 2018 inquiry that "there was quite strong resistance" among research ethics committee members to refusing ethics approvals:

> *"There was a group that simply told us it did not think it should happen; a group that thought it would not be possible to deliver on it; and a group that thought it was too ambiguous… I am not convinced that the ethics committee is the right bit of the system to do that."*
> (see Paragraph 40)

Against this backdrop, MHRA may be better positioned to impose sanctions, as it already regulates drug trials, frequently interacts with both commercial and non-commercial trial sponsors in that capacity, and has strong experience in using legal enforcement powers. One option might be for HRA to manage the initial stages of monitoring compliance and sending out 'soft' reminders to individual

researchers (as it already plans to do), and in case of – clearly defined and inflexible – deadlines not being met, for HRA to turn case management over to MHRA to initiate the sanctioning process.

The sanctions mechanism must be efficient in order to be effective. A key lesson learnt from various European countries and the United States is that regulators are reluctant to impose sanctions if they have to go through the courts every time to impose a fine, which can be very time consuming. An ideal sanctions mechanism would combine clear-cut rules, fixed deadlines, and efficient processes, akin to the issuing of a speeding ticket. The Committee could explore whether an appropriate sanctions process could be put into place under the auspices of the MHRA within the scope of the 2021 Medicines and Medical Devices Act without requiring new legislation.

RECOMMENDATION 2: Publicly set a starting date for sanctions implementation

Publicly set a starting date for sanctions implementation. The 2018 inquiry "recommend[ed] that the Government explicitly re-commit to tackling clinical trials transparency, perhaps through a focused ministerial speech on this issue. This should set a clear time limit for institutions to fully comply with clinical trials transparency requirements and make clear what the consequences will be of failing to meet that deadline" (Paragraph 26).
That recommendation has not been implemented.
HRA's current strategy implementation plan lists two items under 'Sanctions implementation':

- *"Develop a policy for how we will assess performance against research transparency requirements and how that will be used when reviewing new studies for approval."*
- *"Introduce Research Transparency performance assessment into review of new studies."*

The stated timeframe for both of these items is "March 2022 ***onwards***" [emphasis added]. This open-ended timeline inspires little confidence, does not meet patient expectations, and does not send a clear signal to researchers or sponsors.
The Committee should revisit its predecessor's recommendation.

RECOMMENDATION 3: Conduct annual follow-up sessions until the first sanction has been imposed.

Continued parliamentary oversight required. After the last election, the departing S&T Committee Chair wrote an open letter to the incoming Science and Technology Committee stating that:

> *"We know the consequences of non-compliance with reporting requirements: wasted money and research, publication bias and risks to human health… The Committee's work has led to a real momentum in this area, but there is a risk of this diminishing if scrutiny of relevant bodies and organisations is not maintained. This is particularly crucial as the Health Research Authority's new Research Transparency Strategy (as recommended by the Committee) is expected in 2020 and will require further scrutiny by the Committee"*

Since then, HRA (as well as MRC, NIHR and MHRA) have fully met, and in some cases exceeded, expectations in terms of improving the reproducibility and research integrity of clinical trials, and HRA is maintaining strong positive momentum overall.
However, despite calls by the S&T Committee in 2013 and again in 2018 to introduce sanctions, to date no progress has been made on developing or implementing a credible sanctioning mechanism.
The current S&T Committee has the opportunity to decisively contribute towards ending the long-standing problem of non-reported and incompletely reported clinical trials once and for all.
In order to provide assurance that patient expectations will be met, the Committee should consider briefly revisiting this issue every year until the first sanction has been imposed.

ANNEX 1: OPEN LETTER BY 12 GROUPS TO THE THEN HEAD OF THE S&T COMMITTEE

Letter sent to Norman Lamb MP, 20 August 2019

Dear Mr Lamb,

Every year, 870,000 UK patients volunteer to participate in clinical trials[11] in the hope of making a contribution to medical progress. However, these hopes are betrayed when the institutions sponsoring clinical trials fail to ensure that research results are made publicly available.

In recent months, many UK universities and NHS Trusts in particular have significantly strengthened their clinical trial registration and reporting policies and performance. However, while the progress of the non-commercial research sector as a whole is impressive, it is also uneven.[12] Meanwhile, the reporting performance of smaller commercial trial sponsors also remains a concern.

The Science and Technology Committee's 2018 report on Clinical Trial Transparency identified the need to review and strengthen the current framework to ensure that in future, all clinical trials are registered and their results reported.[13] In response, the HRA set up a Research Transparency Strategy Group to explore possible options. A key question is whether or not the revised framework should include sanctions.

Minutes from a recent meeting of the HRA's Research Transparency Strategy Group state that:

> *"The Group agreed that we need to tighten up the requirement here as it is crucial that registered studies report their results. However,* ***the Group felt that discussing firmer [sic] sanctions was premature*** *and that before that it explored we should do much more to facilitate compliance through better systems, collaboration with funders, data sharing and making information public."*[14] [emphasis added]

We do not share the HRA Group's perspective that discussing sanctions is "premature". The HRA itself has held a mandate to promote transparency in health research since 2011,[15] and reporting clinical trial results has been a global medical research ethics requirement since 2013.[16]

Also in 2013, a Science and Technology Committee report stated that:

> *"We recommend that the HRA… ensures that all trials have been registered and published according to an agreed timeline... In addition,* ***there must be penalties for non-compliance****."*[17] (Paragraph 110) [emphasis added]

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[11] NIHR. 2019. "Record number of patients take part in clinical research" https://www.nihr.ac.uk/news/record-number-of-patients-take-part-in-clinical-research/11460 (accessed 09 July 2019)
[12] TranspariMED. 2019. Clinical Trial Reporting by UK Universities: Progress Report June 2019 https://docs.wixstatic.com/ugd/01f35d_915fb4e5aab048afb5cf89f2a369d8f0.pdf?index=true (accessed 09 July 2019)
[13] UK House of Commons Science and Technology Committee. 2018. "Research integrity: clinical trials transparency" https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/1480/148002.htm (accessed 09 July 2019)
[14] Minutes of the second meeting of the Research Transparency Strategy Group, London, 08 May 2019. HRA website. https://www.hra.nhs.uk/about-us/what-we-do/our-transparency-agenda/research-transparency-strategy-group/research-transparency-strategy-group-minutes/ (accessed 09 July 2019)
[15] HRA website. https://www.hra.nhs.uk/about-us/ (accessed 09 July 2019)
[16] World Medical Association. 2013. Declaration of Helsinki (2013 amended version) https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (accessed 09 July 2019)
[17] UK House of Commons Science and Technology Committee. 2013. "Clinical trials" https://publications.parliament.uk/pa/cm201314/cmselect/cmsctech/104/104.pdf (accessed 09 July 2019)

Subsequently, the HRA did not adopt the Parliamentary recommendation to impose penalties. It continued to promote compliance on a purely voluntary basis.

This approach failed to bring about an acceptable level of trial registration and reporting. When the Science and Technology Committee revisited the issue five years later, it stated that:

> *"Echoing our predecessor Committee's conclusions from 2013,* ***we recommend that the HRA introduce a system of sanctions*** *to drive improvements in clinical trials transparency, such as withdrawing favourable ethical opinion or preventing further trials from taking place. The Government should consult specifically on whether to provide the HRA with the statutory power to* ***fine sponsors for non-compliance***." [18] (Paragraph 41) [emphasis added]

Based on the groundwork laid by its Research Transparency Strategy Group, the HRA is currently holding a public consultation on its future transparency strategy, which will close on September 6th, 2019.[19]

Noting your strong past engagement for greater clinical trial transparency, we ask you to seize this opportunity to write a public letter to the HRA to remind it of Parliament's expectations, and encourage it to set out a clear timetable for the phasing in of sanctions.

Thank you for your time, best wishes,

/signed/

Action against Medical Accidents	(Peter Walsh, Chief Executive)
Cochrane	(Mark Wilson, CEO)
HealthWatch	(Susan Bewley, Chair)
International Alliance of Patients' Organizations	(Kawaldip Sehmi, Chief Executive Officer)
JustTreatment	(Diarmaid McDonald, Lead Organiser)
Sling the Mesh	(Kath Samson, Coordinator)
STOPAIDS	(James Cole, Advocacy Officer)
T1International	(Fiona Conner, Trustee)
Transparency International Health Initiative	(Rachel Cooper, Director)
TranspariMED	(Till Bruckner, Founder)
Universities Allied for Essential Medicines UK	(Sarai Keestra, National Coordinator)
Universities Allied for Essential Medicines Europe	(Priscilla Li Ying, Executive Director)

[ENDS]

[18] UK House of Commons Science and Technology Committee. 2018. "Research integrity: clinical trials transparency" https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/1480/148002.htm (accessed 09 July 2019)
[19] HRA. 2019. "Make it Public" https://www.hra.nhs.uk/about-us/consultations/make-it-public/ (accessed 09 July 2019)

ANNEX 2: PUBLIC STATEMENT IN RESPONSE TO THE LETTER

Statement posted on the S&T Committee's website, 23 August 2019

Earlier this week (20 August 2019) TranspariMED, along with eleven patient and integrity groups, published an open letter to the Chair of the Science and Technology Committee, Rt Hon Norman Lamb MP, regarding clinical trials.

In their letter they called on the Chair to write a public letter to the Health Research Authority (HRA) to remind it of Parliament's expectations with regard to sanctions for non-compliance with reporting requirements for clinical trials and to encourage the HRA to set out a clear timetable for the phasing in of sanctions.

Chair's comments

In response to the open letter, Rt Hon Norman Lamb MP, Chair of the Science and Technology Committee, said:

"The Health Research Authority (HRA) must follow my Committee's recommendation from last Autumn to introduce a system of sanctions for those who do not comply with reporting results requirements for clinical trials. For too long there has been little consequence to non-compliance with current requirements and it's time action was taken.

"I will be writing to the HRA to encourage them to propose a system of sanctions in their response to their consultation on the HRA's draft transparency strategy, which closes next month.

"My Committee is committed to ensuring improvements in clinical trials transparency and we will continue to push for change in this area. This year we have already written to NHS Trusts in England and universities across the UK reminding them of their responsibilities and put them on notice that if they didn't get their houses in order, we would be asking them to come before us to explain themselves. We will be holding this follow-up session in the Autumn and will announce details in due course."

(September 2021)