REPORT

COVID-19 **CLINICAL TRIAL** INTEGRITY

Impact on global health and the future European regulatory agenda

TranspariMED

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COVID-19 **CLINICAL TRIAL** INTEGRITY

Impact on global health and the future European regulatory agenda

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This report reviews the integrity of clinical trials for COVID-19 vaccines, repurposed drugs and non-pharmaceutical interventions, discusses the factors driving research successes and failures and their impacts on global health, and explores the implications for the future European and global regulatory agendas.

WHAT IS CLINICAL TRIAL INTEGRITY?

Why Clinical Trial Integrity is Important

Clinical trials are the cornerstone of modern medicine, providing gold standard scientific evidence on whether and how well medical treatments work and how safe they are. The World Health Organization (WHO) defines a clinical trial as "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes."

Drug regulators depend and rely on data from clinical trials to decide which medicines, medical devices and vaccines to allow onto the market. Public health bodies rely on trial data to decide which treatments to procure and make widely available. Medical professionals rely on trial data to recommend treatment choices to their patients.

Therefore, ensuring the integrity of clinical trials and the data they generate is paramount. Clinical trial integrity is composed of two elements:

1. Scientifically sound and clinically relevant trial design.
2. Transparency of trial design and outcome data.

Clinical Trial Design

The design of a clinical trial must be methodologically sound and clinically relevant to ensure that a trial has the potential to contribute towards advancing medical knowledge and/or improving healthcare practices. Thus, a trial must ask a medically relevant question, and be designed in a manner that enables it to answer (or at a minimum contribute to answering) that question. Any trial that fails to meet these basic criteria cannot deliver useful evidence and does more harm than good because futile trials reduce the finite pool of resources available to other research programmes, including money, qualified staff and patients.

Numerous trial features are salient in this regard. For example, a trial that sets out to answer a question that has already been answered, or that will have been answered by other trials by the time the trial has been completed, is futile. Equally, an underpowered trial that cannot conclusively answer a question by itself because the number of participants is too low can only make a valuable contribution if it has comparable outcome measures to other trials, enabling their results to later be combined in a wider meta-analysis. Which other trial features are salient depends on context. For example, a trial that only includes healthy young people may not deliver useful evidence on how to treat a condition that overwhelmingly affects old people with multiple co-morbidities.

Clinical Trial Transparency

Clinical trial transparency refers to the degree to which the design and outcomes of a trial are publicly accessible. Cochrane, Transparency International and TranspariMED have previously identified five pillars of clinical trial transparency:[1]

- **Registration on a trial registry** before a trial is launched enables researchers to avoid duplicating previous research and helps them to identify legitimate knowledge gaps. Registration also reduces the potential for bias and evidence distortion during the later reporting of results.
- **Publication in a scientific journal** makes the results of a trial accessible to medical practitioners.
- **Posting of summary results** onto a trial registry allows scientists to rapidly and systematically share new discoveries without having to wait for publication in a medical journal, which usually takes several years. Registry reporting also reduces the potential for bias and evidence distortion.
- **Clinical Study Reports (CSRs)** are lengthy documents that allow experts to determine how significant and reliable a trial's findings are, and reduce the potential for evidence distortion and fraud. Pharmaceutical companies are required to provide regulators with CSRs when they apply for a license to market a drug.
- **Individual Patient Data (IPD)** are the raw data generated by a trial and provide insight into the benefits and harms experienced by each individual trial participant. IPD sharing can shed light on whether a treatment has different effects on different types of patients and reduces the scope for evidence distortion and fraud.

This report additionally discusses the transparency of trial protocols, which provide far more detail on the design of clinical trials than registrations in trial registries do, and the publication of trial results using alternative channels, such as press releases.

The Role of Regulatory Agencies

Regulatory agencies have some powers to strengthen trial designs and improve the transparency of clinical trials.

However, regulators typically only have authority over some types of trials. For example, the European Medicines Agency (EMA) exclusively deals with clinical trials of investigative medicinal products, but other trials—including trials of medical devices and non-pharmaceutical interventions—are outside its mandate. Within the European Union (EU), the mandates of the various national regulatory agencies vary significantly from one country to the next. In some jurisdictions, such as the United Kingdom (UK), central ethics regulators oversee research ethics committees; these committees can require changes to trial protocols or block the launch of trials by withholding ethics approval.

Below are the key mechanisms that regulatory agencies can use to improve trial integrity:

- **Refusing trial approval.** Some types of trials, such as investigative drug trials run in the EU, require approval from national drug regulators to go ahead. These drug regulators could refuse to approve trials that needlessly duplicate existing research or that are weakly designed. Globally, all interventional trials additionally require ethics approval, but ethics approval systems and their centralisation vary strongly between countries.
- **Setting evidence criteria.** Drug regulators can—and often do—substantially shape the design of pivotal drug trials run by pharmaceutical companies by detailing what kind of evidence they will require before and after letting a new drug onto the market. This means that regulators can effectively mandate that companies run trials that are sufficiently large, use meaningful outcome measures, and include patients from specific sub-groups, such as children or pregnant women. In some countries, health technology assessment agencies' expectations for evidence influence commercial trial designs in similar ways.

1. These five basic pillars are non-exhaustive. Other experts have proposed a far larger number of constituent elements of clinical trial transparency.

- **Promoting clinical trial transparency.** Regulators can promote clinical trial registration and reporting on a voluntary basis, by conducting trainings, actively encouraging best practices, monitoring performance, and sending out regular reminders (including via trial registries). In some jurisdictions, including EU Member States and the United States (US), regulators additionally have legal powers to sanction sponsors who violate these basic transparency requirements for some types of trials. Regulators can also make the Clinical Study Reports in their archives accessible to the scientific community, either proactively or on demand. However, regulators currently have no power to influence whether and how trial results are published in scientific journals, or to release–or compel trial sponsors to release–IPD.Monitoring trial conduct and conducting post-marketing surveillance also support trial integrity but are beyond the scope of this report.

COVID-19 CLINICAL TRIAL DESIGN

Design of COVID-19 Vaccine Trials

Successes - COVID-19 vaccine trials run in Europe and the US were well-designed overall. This was partly because those trials were designed and managed by pharmaceutical companies that typically had substantial expertise and strong commercial incentives for generating sufficient quantity and quality of evidence to meet regulatory benchmarks. (This also applied to non-Western companies, as securing a WHO Emergency Use Listing would broaden their access to global markets). In addition, the pool of potential trial participants was virtually unlimited as seven billion people worldwide were at risk of contracting COVID-19, permitting rapid large-scale recruitment. However, regulatory quality also played a role (see below).

Ongoing controversies - Some aspects of the COVID-19 vaccine research agenda are still being debated. Contentious issues include whether vaccine development and rollout could have been significantly accelerated through challenge trials (in which vaccinated volunteers would be deliberately exposed to the virus), and whether and when some subgroups—notably pregnant women and children—should have been included in trials. In addition, the launch of head-to-head trials directly comparing multiple vaccines at an early stage could have reduced uncertainties about comparative efficacy. Similarly, when the Delta variant began rapidly spreading in the UK, lack of trial data on different dosing intervals created considerable uncertainty about whether to shorten the timespan between the first and second vaccine shots.

Role of regulators - Regulators set clear success benchmarks for potential COVID-19 vaccines at an early stage, contributing to the overall high quality of vaccine trials. Early in the pandemic, the EMA and other major regulators, including the US Food and Drug Administration, defined the evidence and efficacy bars that new vaccines would have to clear to be allowed onto their markets.

Global health impacts - The strong design and implementation of COVID-19 vaccine trials—at least those run in Europe and the US—supported the extremely rapid development of vaccines that substantially reduced deaths and hospitalisations, saved countless lives, and eventually enabled normal life to resume in many countries in the Global North. However, the benefits of vaccination were very unevenly distributed because of limited production capabilities and supply chain related difficulties. This resulted in severe inequity in access to vaccines, with countries in the Global South typically trailing far behind.

Design of COVID-19 Drug Trials

Early warnings - Experts have long warned that very many clinical trials fail to meet basic quality standards and are therefore doomed to become research waste before they even begin. These warnings were fully borne out during the 'research chaos' that erupted in the early months of the pandemic when hundreds of trials were hastily launched to evaluate whether existing drugs might be effective at treating patients with COVID-19, often by non-commercial sponsors with no prior experience of running trials of investigative medicinal products. Experts warned at an early stage that rampant duplication of research efforts and weak trial designs doomed the overwhelming majority of these trials to end up as research waste before they had even started. Drug regulators and the wider medical research community now concur that this proliferation of uncoordinated, unaligned, underpowered, and often badly designed trials of repurposed drugs constitutes a major collective failure of the global medical research enterprise during the pandemic.

Global research chaos - The most notorious failure in this regard involved the drug hydroxychloroquine (HCQ). Early research (later criticised as flawed) indicated that HCQ might be an effective COVID-19 treatment. HCQ was already widely used for other indications, so many clinicians had access to the drug and promptly started administering it. During the first hundred days of the pandemic, 84 separate HCQ trials were registered worldwide. Long before most of those small trials had been completed, strong evidence from two large high-quality trials showed that HCQ provided no benefit to COVID-19 patients. These HCQ trials were not an isolated case. Overall, most COVID-19 drug trials focused on only a small number of treatment options, and many eventually ground to a standstill. By October 2020, nearly a third of the 516 trials registered during the first hundred days of the pandemic had not recruited a single patient, and only 10% had made their results public. The limited outcome data that small single-center trials did generate could not easily be pooled for meta-analyses because of widely divergent standards of care, inclusion criteria, dosages, and outcome measures.

Clinical trial registries - A key benefit of trial registries is their potential to prevent exactly the kind of research chaos that ensued during the pandemic. There is a long-standing global ethical obligation to register all trials, including trials of non-pharmaceutical interventions (NPIs) before they start, shored up by regulatory requirements in some jurisdictions to register some types of trials. Data from 18 registries worldwide feed into the WHO-managed International Clinical Trials Registry Platform (ICTRP), in theory providing a continuously updated overview of who is researching what, when, where and how. If that infrastructure had worked and been used as intended, much of the COVID-19 research chaos would have been avoided. For example, researchers considering launching an HCQ trial could have searched ICTRP and discovered that HCQ was already being investigated by numerous other trials and could accordingly have focused on investigating other treatment options instead, or aligned their outcome measures with existing trials. Trial registries also offer the option of rapidly uploading summary results once a trial has been completed, offering the opportunity to make outcome data public at speed, open access and easy to find. However, registries failed to deliver on their considerable promise during the pandemic, as the box below explains.

Neglect of trial registries contributed to research chaos The global registry infrastructure has long been inadequately supported by legislators and regulators and is woefully underfunded. This persistent neglect of the world's only comprehensive directory of medical research led to costly research waste on an incredible scale during the COVID-19 pandemic.	
Legislative and regulatory neglect	The WHO recommends that Member States should by law require every interventional trial to be registered and reported. In addition, WHO recommends that all trial results should be made public specifically on a registry within 12 months, and that registry data should be kept up to date. By enforcing these three simple rules, regulators would ensure that there is a comprehensive, up-to-date global database of all trials and their results. In reality, existing laws in the EU and the US only cover a small minority of trials and are not being effectively enforced, while many other jurisdictions have no relevant laws at all. (The UK is the only country worldwide that currently has comprehensive legislation in the pipeline.) Much registry data continues to be entered by untrained individual researchers with no effective institutional or regulatory oversight. Due to this long-standing legislative and regulatory neglect, many trials are never registered, around half of all trials never make their results public in any form (let alone on a trial registry), and registry data are often incomplete, inconsistent and out of date. Gaining a comprehensive, reliable, and up-to-date overview of all clinical trials and their results is thus impossible. For example, out of 3,754 pre-pandemic trials of 19 potential COVID-19 (repurposed) drugs, 40% had never made their results public in any form when the pandemic hit.
Underfunding of the global ICTRP hub	At the very moment when real-time access to the only available map of global research efforts was most important, during the early days of the pandemic, the WHO's perennially underfunded ICTRP registry hub crashed due to its inability to handle the massive increase in traffic. ICTRP for several months was unable to provide users with real-time access to its data, instead making weekly updates available for download. More broadly, the world's only global trial registry hub should be expected to contain a management information system and dashboard that synthesises actionable 'big picture' information that is vital to aligning global research efforts. For example, such a dashboard should have included breakdowns of the status, outcome measures, and inclusion—and exclusion criteria used by every HCQ trial involving COVID-19 patients. In reality, ICTRP only has basic search and filter functions, making it necessary to aggregate such data manually, which cannot be done in real time. It required the combined efforts of 19 researchers just to compile a basic overview of the key features of all trials launched during the first hundred days of the pandemic because the process was so laborious and time-consuming.
Underfunding of contributing registries	ICTRP can only be as good as the data it receives from its 18 contributing registries. Some of those registries are perennially underfunded, have a dismal infrastructure and extremely limited IT support, and appear to lack even basic quality control mechanisms. For example, the Dutch registry's design is extremely basic, the Indian registry reportedly only receives IT support once a year, and the European EudraCT and CTIS registries and the German DRKS registry sometimes include entries that are not in English, making systematic searches using key terms difficult. Frequently, these registries feed incomplete registrations into the global system that lack even basic data, such as the identity of a trial's sponsor or the treatment being investigated. Research has repeatedly documented widespread inconsistencies between data for identical trials listed in two or more different registries. The American ClinicalTrials.gov registry alone seems to meet high quality standards, combining a structured tabular summary result function with quality assurance through manual expert review of results submitted. The adoption of simple features such as automated emails to remind researchers to upload their trial results could significantly improve the global medical evidence base.

Underuse of registry reporting	Due to lack of legal requirements and regulatory engagement and enforcement (see above), researchers still do not habitually upload or link all trial results on registries. Thus, locating the results of all relevant clinical trials requires time-consuming manual literature searches that sometimes miss relevant publications, undermining rapid evidence syntheses. In some cases, researchers, apparently unaware of the option of sharing results through trial registries, complained about difficulties in rapidly getting their results published in journals and instead took to social media.

Role of regulators - Regulators worldwide failed to ensure that trials of potential repurposed drugs for the treatment of COVID-19 were adequately coordinated and well designed. Notably, in some EU Member States, national drug regulators appear to have uncritically greenlighted multiple small COVID-19 drug trials without considering their potential to add scientific value. During the first three months of the pandemic alone, 118 separate investigative drug trials testing potential COVID-19 treatments were registered across 14 EU Member States, each of them authorised by the national drug regulator of that country. A third of those trials were run by sponsors that had never before run an investigative drug trial, and nearly all of the remainder were run by sponsors with a track record of violating European trial reporting guidelines. It appears likely that most investigative COVID-19 drug trials registered in the EU (and in virtually all other jurisdictions) eventually ended up as research waste. Research into repurposed drugs appears to have been highly successful only in the UK.

Regulatory success in the UK versus widespread failures elsewhere	
UK success	All key stakeholders in the UK–the medicines regulator, the ethics regulator, and the two major public research funders–worked together from the outset of the pandemic to coordinate and align clinical trial efforts on a national level. These factors speeded up the funding and regulatory approval of strong trials, while also preventing the launch of futile trials that could divert potential participants. The flagship of the UK's successful approach was the RECOVERY trial, a low-cost pragmatic platform trial that by April 2020 had already enrolled over 39,000 patients from 178 hospital sites in the UK. By the end of June 2020, RECOVERY had already delivered strong evidence on the efficacy of five widely investigated repurposed drugs (dexamethasone, hydroxychloroquine, azithromycin, lopinavir and ritonavir), probably saving hundreds of thousands of lives worldwide–and making hundreds of smaller, slower trials launched in other countries clinically irrelevant. However, strong regulatory leadership alone would not have enabled other populous countries with high infection rates to successfully run a comparable trial. The trial's ultra-rapid recruitment would have been impossible without the UK's centralised health system and pre-existing strong clinical trial infrastructure, both of which had been built up over many years and simply do not exist in many other countries.
Spanish failure	Spain provides a clear example of the uncoordinated proliferation of futile COVID-19 trials. By June 2020, the national drug regulator AEMPS had given the green light to 48 separate investigative drug trials. A subsequent analysis found that by October 2020, a total of 123 COVID-19 trials had been registered in Spain (including both drug and non-drug trials), over half of which were funded with public money. Twenty of those trials were investigating a single drug, hydroxychloroquine. It appears that only one of these 20 Spanish HCQ trials was completed and published rapidly enough to contribute clinically salient evidence, suggesting that the other 19 HCQ trials may have ended up as research waste.

Failures in other large countries	Other populous countries also failed to produce much useful evidence on repurposed drugs. Research efforts in the US were largely unproductive due to the country's uncoordinated research agenda and decentralised health system. In addition, the widespread haphazard administration to US patients of experimental treatments (including HCQ and convalescent plasma) in non-trial settings reduced the pool of patients eligible for participation in trials. Researchers in China initially registered a large number of trials (apparently in an uncoordinated manner) but these never gained traction as infection rates there rapidly dropped to virtually zero. Researchers in India seem to have produced no notable drug breakthroughs despite the country's high infection rates. Research efforts in Germany were also disappointing despite ample funding. Trial startup was reportedly slow due to systemic weaknesses and bureaucratic holdups, and the effects of very weak patient recruitment were further compounded by the fragmentation of the pool of participants between multiple trials.
Failures of multinational trials	Meanwhile, two multinational trials whose design was similar to RECOVERY, the WHO's Solidarity trial and French INSERM's Discovery trial, were reportedly slow to get off the ground due to the need to secure multiple regulatory approvals and funding commitments. However, Solidarity does appear to eventually have made some clinically relevant contributions.

Global health impacts - The uncoordinated 'research chaos' surrounding potential COVID-19 treatments had a substantial negative impact on global health. Many patients died because of delays in identifying effective treatments; only the UK's RECOVERY trial (and to a lesser degree WHO's Solidarity trial) prevented that death toll from becoming far worse. Also, considerable resources were wasted on ineffective treatments, and millions of patients were exposed to treatments whose benefit-harm balance was unclear. For example, convalescent plasma, a treatment whose administration requires substantial human resources and entails significant costs, was given to an estimated 500,000 US patients during the first year of the pandemic based on weak evidence. Due to lack of robust evidence from large trials, it long remained unclear to regulators and clinicians whether the treatment on balance benefited or harmed patients. In December 2021, the WHO recommended against giving plasma to patients in standard care, while calling for plasma trials involving patients with severe Covid to continue. As of April 2022, more than two years since the start of the pandemic, plasma trials have still not delivered sufficient evidence for the WHO to come to a definite conclusion on the treatment's merits for severely ill patients.

Design of Trials of Non-pharmaceutical Interventions

Early warnings - At the start of the pandemic, governments worldwide imposed various combinations of NPIs, such as stay-at-home orders and closures of schools or businesses, which directly affected the lives and livelihoods of billions of people worldwide. Concerns over the weak evidence base for the public health benefits of some NPIs were raised very early in the pandemic, coupled with urgent pleas for more and better research.

Research gaps - Nonetheless, two years into the pandemic, only 57 randomised trials assessing NPIs had been registered. Around half of NPI trials were focused on just two interventions: protective equipment and information or education programmes. Only 11 NPI trials had published their results by February 2022. A Cochrane review of interventions to reduce the risk of COVID-19 infection outside of healthcare settings published in May 2022 found only one relevant completed trial. In contrast, over 300 trials for the drug hydroxychloroquine alone, and more than 4,000 COVID-19-related clinical trials overall, had been registered by that time. (Note that interventional studies of "behavioural treatments" are explicitly included the WHO definition of clinical trials.) According to one calculation, only 4% of global COVID-19 research funding was allocated to researching public health measures.

Role of regulators - The scarcity of trials of NPIs was outside the control of regulators. Responsibility for this research gap lies primarily with governments, which typically implemented NPIs across the board instead of running cluster randomised trials to generate robust evidence before further rollout. In addition, research funders–many of which are public bodies–appear to have neglected to encourage and fund relevant research.

Global health impacts - The failure to generate robust evidence on NPIs probably had a major negative impact on global health. The WHO has argued that "evidence-informed decision-making is essential to ensure that the intervention burden of [NPIs] does not outweigh their benefits," but has concluded that there is still a lack of "studies disentangling the relative effects of various measures, their intervention burden and risk–benefit ratios." Similarly, a recent OECD review of 67 government evaluations concluded that "issues relating to policies' proportionality and coherence are still largely under-explored". Policy makers reviewing lessons learned from COVID-19 during the outbreak of the next pandemic may struggle to rely on actionable evidence to demonstrate that NPIs had a positive benefit-harm balance, for what population, in what settings, unless empirical data currently available is carefully processed, synthetized and made public.

COVID-19 CLINICAL TRIAL TRANSPARENCY

Transparency of vaccine trials - The transparency of vaccine trials appears to have varied considerably. In the EU and US, the transparency of landmark pivotal trials was high overall. This was largely due to pre-existing regulatory requirements, combined with strong political, public and scientific community pressure for transparency. For example, after Moderna and Pfizer voluntarily publish their trial protocols, AstraZeneca followed suit two days later. The outcomes of their landmark trials were rapidly published in academic journals, and EMA released the relevant Clinical Study Reports (CSRs). However, a report by Transparency International that reviewed 86 clinical trials of 20 COVID-19 vaccines in development or on the market found significant transparency gaps in many trials as of March 2021. Full protocols were available for only 12% of all trials. Transparency levels appeared to be low overall outside the North Atlantic region. A subsequent academic study that assessed a wider range of transparency elements also found "varied transparency" at the level of individual trials, pharmaceutical companies, and regulatory agencies.

It warned that the Chinese Sinovac and Sinopharm vaccines accounted for the majority of vaccines administered in Asia, South America, and Africa, but that disclosures of their trial results had "largely been limited to government media reports and press releases". The study also noted that only EMA, Health Canada and the Japanese regulator had disclosed CSRs, and flagged strong variations in companies' stated willingness to share Individual Participant Data (IPD). As of May 2022, a total of 38 different vaccines are on the market of worldwide; most of these have been approved by a very small number of countries only.

Access to clinical trial protocols and results (including CSRs) constitutes a critical element for effective technology transfer and a fundamental component in initiatives such as the WHO's COVID-19 Technologies Access Pool (C-TAP) and mRNA Tech Transfer hub. Such access should be planned for by funders and sponsors, and embraced by researchers and other stakeholders involved in the design, development and management of clinical trials. Platforms like ICTRP and the European Union's new CTIS registry should be adequately supported and given an explicit role in technology transfer processes by granting access to test data and CSRs to researchers involved in replicating or reverse engineering authorised and/or patented products.

EMA exceptional transparency measures

The European Medicines Agency early in the pandemic adopted 'exceptional' transparency measures covering both COVID-19 vaccines and new licensed COVID-19 drugs. Key elements included:

- Accelerated publication of European Public Assessment Reports (EPARs)
- Proactive release of Clinical Study Reports (CSRs)
- Publication of full Risk Management Plans and monthly vaccine safety updates

The recent Regulation 2022/123 sets out that the same transparency standards will also be applied during future public health emergencies.

Transparency of drug trials - In the case of repurposed drugs, the results from large trials conclusively proving or disproving the efficacy of widely studied repurposed drugs were rapidly made public (see box below). At that point, most small trials were still far from completion, and their transparency—or lack thereof—had arguably become clinically irrelevant.

Challenges for evidence-based medicine

Proponents of evidence-based medicine have long argued that interventions should be based on 'robust' evidence generated by large and well-designed clinical trials whose results have been peer reviewed prior to publication in a scientific journal. (Journal publication processes, including peer review, typically takes at least several months.) In the absence of such 'robust' evidence, health professionals should take a 'first, do no harm' approach and avoid exposing patients to unproven interventions. The pandemic has challenged this conventional wisdom in three ways:

Preprints	First, during the pandemic trial results and other evidence were frequently shared through preprints, academic papers that are directly uploaded onto online platforms without the quality control ostensibly provided by peer review. Overall, preprints probably considerably accelerated pandemic science by enabling researchers to rapidly share and build upon new insights, but in some cases, hastily published flawed research did more harm than good.

Press releases	Second—and more controversially—both industry and academic players often rapidly announced clinical trial results through press releases that lacked the detailed data that scientists require to be able to fully evaluate trial outcomes. For example, on 16 June 2020, the RECOVERY trial team announced via press release that the repurposed drug dexamethasone significantly reduced mortality in hospitalised patients. On the same day, the UK government 'authorised' its use as a COVID-19 treatment across the country's National Health Service. Also on the same day, the WHO, in a press release, "welcomed" the "preliminary results" from the trial, with its Director General lauding dexamethasone as "the first treatment to be shown to reduce mortality" and therefore de facto encouraging clinical use of the drug. (The strong reputations of the trial and its team, combined with impressive recruitment numbers and treatment effects, presumably played a role in UK government and WHO decision-making.) The preprint containing the results was published six days after the press release. A preliminary version of the peer-reviewed journal article was only published on 17 July, one month after the press release, followed by the final version more than half a year later. Meanwhile, EMA appears to have been more cautious than the WHO, and only officially 'endorsed' the use of the drug on 18 September after a protracted review of the trial's results. In hindsight, the almost immediate responses of the UK government and the WHO may have saved many lives. (EMA's more cautious approach probably did no harm, and is unlikely to have influenced clinical practice.) In contrast, company press releases announcing trial results for COVID-19 vaccines or newly developed drugs added absolutely no value to clinical decision-making because such compounds would not become available until regulators had reviewed them in depth and greenlighted them. While critics charged that companies were shortcutting the usual scientific publication process for marketing purposes, they sometimes overlooked that publicly traded companies can be legally obliged to immediately disclose headline clinical trial results (but not interim trial results) if these are expected to 'materially' affect their shares price.
Evidence for NPIs	Third, due to the lack of salient randomised controlled trials (see above), there was no 'robust' evidence base on many NPIs, such as face masks or school closures, forcing policy makers to decide whether to impose measures whose benefit-harm profiles were highly uncertain and hotly contested.

Transparency and trust - Some decision-makers in Western democracies appear to have concluded during the pandemic that placing limitations on public debate may reduce vaccine hesitancy and/or improve compliance with NPIs. Many governments seemed to quietly accept–if not tacitly endorse–social media companies' muting or silencing of voices and content questioning the current scientific consensus on some hot topics. However, these efforts to shape public discourse, ostensibly narrowly targeted at nefarious state-sponsored disinformation and 'anti-vaxxers', also led to the muting of valid concerns raised by highly credentialled experts and negatively affected scientific discussions about the origin of the virus or about the comparative benefits and harms of vaccinating children. It is unclear to what extent efforts to frame public and scientific debates have reduced vaccine hesitancy or NPI compliance in the short term, or will improve public health outcomes in the long term. Meanwhile, the EMA's exceptional transparency measures (see below) and some companies' disclosures of their trial protocols do not seem to have registered much on the public radar.

Global health impacts - The pandemic highlighted significant differences between regulatory transparency standards and corporate transparency practices between countries, and the consequences of global regulatory fragmentation. While there are no signs that opaque vaccine development and

licensing processes in some countries have led to ineffective or excessively harmful COVID-19 vaccines being administered on a large scale, this may (or may not) simply be due to luck. The accelerated speed at which some high-profile COVID-19 trial results were made public, including through unconventional publication channels, appears to have benefited patients worldwide overall, though not without exceptions. The long-standing neglect and underfunding of the global trial registry infrastructure led to large-scale research waste and significant opportunity costs. The relationship between clinical trial transparency and public trust in medical products and public health measures is not clear.

IMPLICATIONS FOR THE EUROPEAN REGULATORY AGENDA

Strengthening Clinical Trial Coordination and Design

Impact on policy agenda - A journal article written by European regulatory staff in October 2021 illustrates that regulators are highly aware of the problems caused by "the fragmented nature of clinical trials [of repurposed drugs, which were] often small, underpowered or with suboptimal design". The paper concludes that:

"There is a need to support and enable rapid advice and approval of large, well-designed trials, including platform trials, that can provide the robust data needed to support decision making and demonstrate that new or repurposed medicines are safe and effective, whilst also refuting as early as possible those which are ineffective and or unsafe. It is also key to establish the research investigator networks on a large, pan European scale with effective infrastructural support, to enable such large trials, whether private or publicly sponsored."

Policy initiatives - There is now positive momentum towards strengthening the coordination of clinical research efforts and improving the quality of trials. Relevant global initiatives include the 2021 G7 'Clinical Trials Charter', and a recent Global Health Assembly draft proposal (see box below). Within the EU, the recently launched multiyear ACT-EU initiative aims to improve trial coordination, promote better and larger multinational trials, streamline trial approval processes, and support academia with training. On a national level, the UK is currently reviewing its entire national trial portfolio to winnow out studies that are "struggling to deliver" and refocus resources on trials that are likely to add value.

Joint UK-Argentinian World Heath Assembly proposal

A draft proposal recently put forward by the UK and Argentina ahead of the 75th Global Heath Assembly urges United Nations Member States to improve the coordination of clinical trials, strengthen trial quality, avoid duplication of research, and take steps to promote trial registration and rapid results reporting. The proposal also requests the Director-General of the WHO to develop a corresponding draft action plan by 2023.

RECOMMENDATION 1 – to the European Commission
Set up a working group to develop actionable recommendations for improving clinical trial coordination and design and curbing research waste for interventional clinical trials that fall outside the purview of the EU Clinical Trial Regulation.

RECOMMENDATION 2 – to the European Medicines Agency
Clearly and publicly identify which gatekeeper will be made responsible and accountable[2] for preventing futile trials of investigative medicinal products from being launched.

Clinical trials of non-pharmaceutical interventions

Impact on policy agenda. During 2020-2022, many heated political debates revolved around which NPIs to impose at what points in time. However, there was often little to no 'robust' evidence from randomised controlled trials on which decision-makers (or their critics) could draw. Now that NPIs are being discontinued in most countries, there is an acute danger of this highly consequential research failure of the pandemic being forgotten–until the next pandemic strikes.

Policy initiatives - While a low profile WHO working group is currently attempting to strengthen the evidence base on NPIs, there currently appear to be no high-level policy initiatives promoting the generation of robust evidence on NPIs.

RECOMMENDATION 3 – to the European Commission
Form a working group to develop actionable recommendations for European bodies and national governments on how to generate and synthesize robust evidence on NPIs.

Clinical Trial Transparency

Impact on policy agenda. There were few political debates about clinical trial transparency in Europe and North America during the pandemic largely because vaccine trials–which received most attention–were largely transparent in those countries. Furthermore, the results of clinically relevant vaccine and drug trials in those countries were typically made public very rapidly. These highly visible transparency successes distracted attention from widespread opacity in other areas.

- First, over half of COVID-19 vaccine doses administered worldwide originate from regions outside Europe and North America, where there appear to have been instances of considerable opacity in both regulatory decision-making and clinical trial reporting. If the pandemic is 'not over anywhere until it is over everywhere', as has frequently been claimed, then lack of clinical trial transparency anywhere now threatens the health of patients everywhere. Beyond COVID-19, there is a clear danger that in future very large numbers of patients in the Global South could in future be exposed to vaccines and drugs with opaque efficacy and safety profiles.
- Second, around half of all clinical trials worldwide never make their results public and thus end up as research waste. Furthermore, for the trails that do get made public, the typical publication timeline for results is far longer than the 12 months recommended by WHO.

2. A key reason why decades of efforts to curb research waste have failed to deliver much progress is perpetual buck-passing on this issue between regulators, funders, industry, ethics committees, research institutions, and investigators.

COVID-19 research inequality

The pandemic created a strong sense of urgency around COVID-19-related research, and many of the most important vaccine and drug trials made their results public within weeks of trial completion. This contrasts with 'medical research as usual,' where a comparable sense of urgency seems to be lacking, even though many patients' health and survival hinges on rapid medical progress. A recent study of 4,657 pediatric clinical trials worldwide found that only 52% had made their results public within three years of trial completion. A different recent study of 1,658 trials run by German universities found that only 43% had made their results public within two years. In both cases, most of the remaining trials will probably never make their results public. Note that the WHO recommends a maximum reporting timeframe of 12 months for all interventional trials.

Policy initiatives - On a global level, the Joint UK-Argentinian World Heath Assembly proposal contains elements that address the late and non-reporting of clinical trial results (see above). Within the EU, Regulation 2022/123 shortens the reporting timeframe for clinical trials of drugs and vaccines to a non-specified time period of less than 12 months, and extends the EMA 'extraordinary transparency measures' (see further above). However, this accelerated reporting timeframe and enhanced measures will only apply during future global health emergencies.

RECOMMENDATION 4 – for the European Commission

Ensure that the HorizonEurope research programme immediately signs up to and fully implements the WHO Joint Statement to ensure that the results of all clinical trials funded are made public within 12 months.

RECOMMENDATION 5 – for the European Medicines Agency

Open a dialogue on developing common minimum transparency standards both for regulatory documents and for pivotal clinical trial data within the International Coalition of Medicines Regulatory Authorities (ICRMA), while seeking to widen ICRMA's membership to include all emerging medical research and export hubs. In addition, form a working group within ICRMA to exchange experiences on regulatory actions to promote or enforce clinical trial registration and reporting.

RECOMMENDATION 6 – for the European Medicines Agency

Set a date for the resumption of releasing Clinical Study Reports under Policy 0070, which has been suspended since 2018.

Clinical Trial Registries

Impact on policy agenda – The long-standing neglect and underfunding of the global clinical trial registry infrastructure significantly undermined efforts to coordinate COVID-19 research and prevent duplication of trials, and continues to do so for all other disease areas. For example, the global ICTRP registry hub lacks a management information system and dashboard that would allow users to generate rapid and detailed 'at a glance' overviews of ongoing and completed research. Many of the 18 separate trial registries that feed data into ICTRP, including the EU's EudraCT registry (see below), have large data gaps and severe data quality issues. However, the urgent need to strengthen the global registry system and its 18 constituent registries has so far not made it onto the wider policy agenda.

Policy initiatives – There are currently several developments within EU that will influence the completeness and robustness of medical evidence on trial registries for many years to come.

- **EudraCT registry –** The Heads of Medicines Agencies appear to have walked back on a 2021 commitment to encourage and support the reporting of over 3,400 overdue trial results on EudraCT. While the EMA itself and several National Competent Authorities (NCAs) have made significant efforts to address this issue, often with considerable success, some NCAs have yet to take action. Unless action on these data gaps is taken soon, the results of many clinical trials will be lost forever.
- **Clinical Trial Information System (CTIS) registry –** The new EU trial registry CTIS, launched in February 2022, has additional functionalities and transparency features. The EU Clinical Trial Regulation, which also became applicable in February 2022, gives legal force to a maximum 12 month reporting timeframe for all new clinical trials of investigative medicinal products registered on CTIS. In the runup to the launch, the EMA put considerable effort into preparing trial sponsors for the new registry, which will hopefully improve voluntary compliance. However, if and when violations occur, it remains to be seen whether EU Member States will enforce their national laws effectively.
- **The EU Medical Device Regulation**, incoming in May 2022, does not require clinical trials of medical devices to be registered on an ICTRP-linked registry, and does not require the results of all medical device trials to be made public on an ICTRP-linked registry. While some medical device trials will have to be entered into the new EUDAMED database, EUDAMED is not linked to the WHO's global trial registry network; this could lead to a fragmentation of the global evidence base for medical devices.

RECOMMENDATION 7 – for the European Commission

Clearly communicate to the Heads of Medicines Agencies and governments of EU Member States the expectation that NCAs will initiate efforts to address the backlog of missing drug trial results on EudraCT (as recently demanded by Members of the European Parliament and civil society), and going forward will effectively enforce drug trial reporting timeframes on CTIS.

RECOMMENDATION 8 – for the European Commission

Install automated safeguards in the EUDAMED medical device database to ensure that clinical trials of medical devices can only be entered into EUDAMED once they have obtained a registration number from an ICTRP-linked global trial registry, and explore options for using EUDAMED functionalities to encourage—and ideally de facto necessitate—the reporting of trial results on an ICTRP-linked registry.

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