Written Evidence Submitted by Christopher Marc Taylor, Chair, ISRCTN Registry

(C190077)

I submit the following evidence on a personal basis.

I chair the ISRCTN registry[1]. As a member of the international network of clinical trial registries coordinated by the WHO, ISRCTN is recognised as the primary registry for the UK. ISRCTN is a public registry and curated database which makes public a standard set of data items essential to describe a research study before it commences, and to report its conclusion and link it to published findings. It is owned by a not-for-profit company independent of government, industry, and research institutions.

Registration on the ISRCTN registry meets internationally agreed ethical and legal obligations set out by the World Health Organization (WHO) and the International Committee of Medical Journal Editors (ICMJE). All study records in the ISRCTN database are freely accessible and searchable and have been assigned an ISRCTN ID. The ISRCTN registry was established twenty years ago as an international research registry to promote transparency in clinical trials and related health research. It registers studies of health interventions conducted in any country.

In this evidence, I draw the Committee's attention to

- The history and aims of the international network of clinical trials registries;
- The WHO's unique role in facilitating collaboration in health science;
- The fragile state of the WHO system for pooling knowledge about clinical trials;
- The overwhelming volume of preliminary, unconfirmed reports of research on COVID-19;
- Persistent incentives leading to widespread under-reporting of verified research results;
- The risk that pressures on UK universities may undermine action to redress the failures exposed by your predecessors' inquiry ***Research Integrity: clinical trials transparency*** (HC1480)

This evidence is therefore framed around *the mechanisms for communication of scientific evidence internationally, within national governments and with the public.* It has wide implications for the capacity and capability of the UK research base to rise to the challenge of a worldwide health emergency; the flows of information that underpin the ability of institutions, government departments and public bodies to respond appropriately; and public confidence in the evidence.

The bottom line is: can we trust our leaders and institutions to know the difference between a well-supported body of evidence, and hasty conjecture based on inadequate or selective data?

The history of the international network of clinical trials registries

In the 1990s there was growing concern that health care relied on scientific evidence which was incomplete, selective or in some case undermined by the manipulation of data. In the USA, the Food

[1] I am also a trustee of the UK Research Integrity Office and of the York Blind and Partially Sighted Society "MySight York"; and a member both of a statutory committee advising the Health Research Authority on confidential patient information, and of the HRA's Audit and Risk Committee. This evidence is not related to any of those roles.

and Drug Administration Modernization Act of 1997 required the U.S. Department of Health and Human Services, through the National Institutes for Health, to establish a registry for both federally and privately funded trials of investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions. This led to the establishment of ClinicalTrials.gov at the National Library of Medicine (NLM)[2]. In the UK, the Department of Health sponsored the creation of the ISRCTN registry. Both began registering studies in 2000. From the outset these registries invited the registration of studies in any country.

At the Ministerial Summit on Health Research in 2004, participants called for the WHO to facilitate the establishment of: "*a network of international clinical trials registers to ensure a single point of access and the unambiguous identification of trials*". In 2005, the ICMJE began requiring trial registration as a condition of publication. Its policy was not limited to clinical trials for regulatory purposes. It covered all prospective studies of health interventions. In 2005, the 58th World Health Assembly approved a set of International Health Regulations to manage public health emergencies of international concern. It passed Resolution WHA58.22 calling on the global scientific community, international partners, the private sector, civil society, and other relevant stakeholders to: "*establish a voluntary platform to link clinical trials registers in order to ensure a single point of access and the unambiguous identification of trials with a view to enhancing access to information by patients, families, patient groups and others*". In 2006 to 2007, international experts supported the WHO in defining standards for the operation of recognised clinical trials registers, and an international standard data set. The WHO launched its International Clinical Trials Registry Platform (ICTRP).

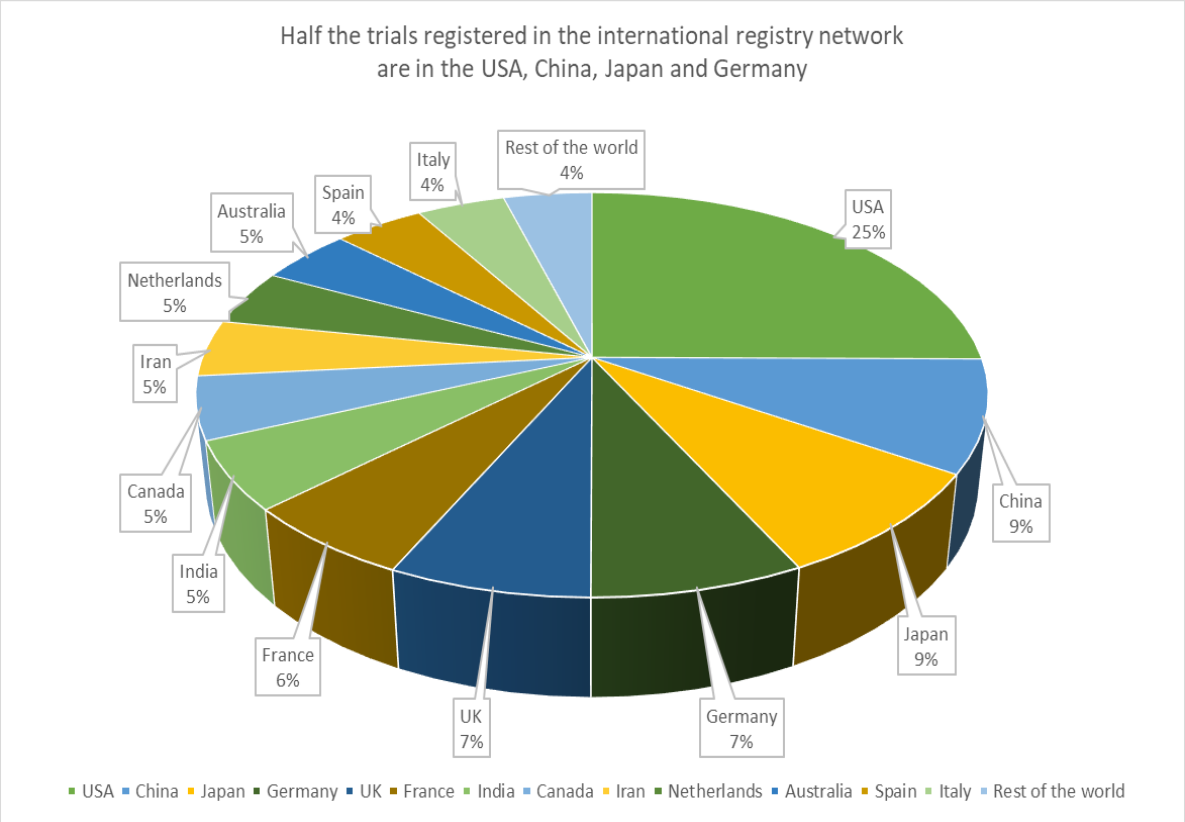
The network of registers coordinated by the WHO now comprises sixteen primary registries and two partner registers. The primary registries (one of which is the UK's ISRCTN registry) meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity, and administration. They also meet the requirements of the ICMJE. They collect, curate, and update a standard data set. They offer open access to the data they hold individually. They contribute to a combined list of study records which is normally searchable via a portal on the website of the WHO's ICTRP. The largest contributor to the portal, the USA, does not formally subscribe to the WHO standards. Its registry is a statutory arm of government.

In 2008, the World Medical Association (WMA) General Assembly amended the *Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects*. Two new principles considered the prospective registration and the public disclosure of study results to be ethical obligations. From 2013, the WMA required prospective registration in these terms: "*Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.*" The *Helsinki Declaration* also now states, "*Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties … should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available*."

[2] A detailed history from a US perspective of the registration of clinical trials can be found on the website of the National Library of Medicine at https://clinicaltrials.gov/ct2/about-site/history#InternationalCommittee

The WHO's unique role in facilitating worldwide collaboration in health science

By July 2020, the number of studies accessible on the WHO's clinical trials portal passed 570,000. It lists trials in some 200 countries and territories. Half of the trials are in four countries: the USA, China, Japan, and Germany. 46% are in another nine countries: the United Kingdom (7%), France (6%), India, Canada, Iran, Netherlands, and Australia (5% each), Spain and Italy (4% each). The rest of the world accounts for the other 4% (including only 45 other countries with over 1,000 trials each).



The mechanisms for open access to the design, conduct and results of clinical trials are well-developed in very few countries. Most of the world relies on international efforts to pool the information needed to avoid duplication and waste of scientific effort. Open access to results enables reviews of evidence across groups of studies that between them have enough data to support reliable conclusions. Access through the WHO's network of regional offices to information about studies and results has a high premium for many countries with an immature research culture, limited resources, and poor access to research that bears on their health and social challenges. The British Government says it aims to be a partner of choice for world-leading research and innovation

Through this Roadmap, we will be testing in detail how we can:

- ***Be a partner of choice for other world-leading research and innovation nations, as well as strengthening R&D partnerships with emerging and developing countries.*** *We will develop a new funding offer for collaboration to ensure the UK can further benefit from the opportunities of international scientific partnerships……*

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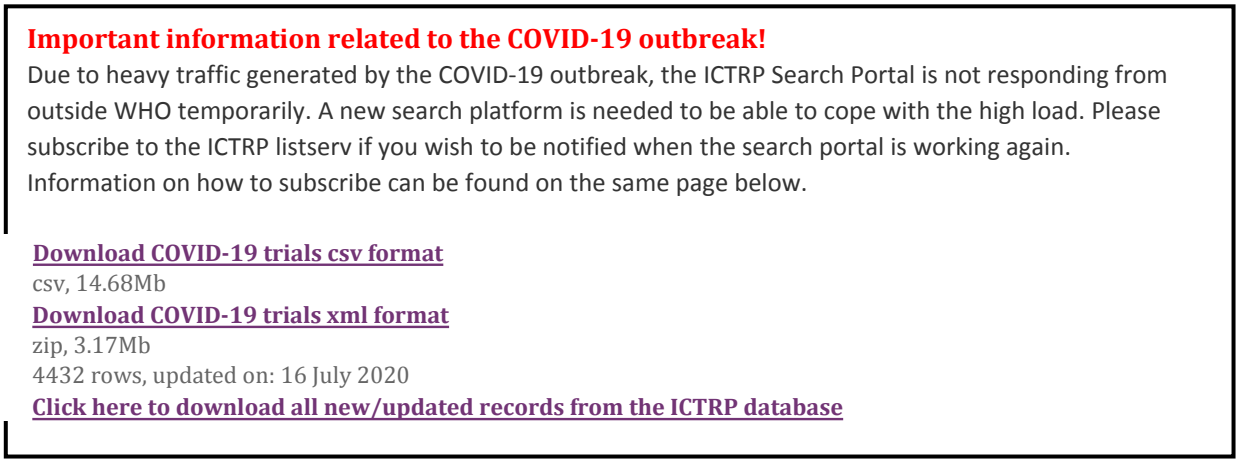
nations as well as a partner for emerging and developing countries.

Fragile state of the WHO clinical trials registry system

Because of concerns about commercial or political influence, the WHO standard for primary registries emphasises independence. But many clinical scientists have a strong preference for registration in the USA. By July 2020, ClinicalTrials.gov listed nearly 350,000 studies in over 200 countries and territories. 38% of them were in the USA, 29% in Europe, and 33% in the rest of the world. In 2019, ClinicalTrials.gov contributed over half the studies listed on the WHO's portal.

A key aim of the WHO's clinical trials portal was to make it possible swiftly to identify relevant clinical trials worldwide in a public health emergency. Since the latest pandemic began, members of the WHO international clinical trials registry network, including ISRCTN, have promptly shared with the WHO the standard data set for over 4,400 registered studies related to COVID-19. The WHO portal has always been underfunded. Its search function is just adequate when it is working. Soon after the pandemic began, it collapsed under the weight of the enormous interest in research on COVID-19. Its website at www.who.int/ictrp carries a notice to say that the search function is available only inside the WHO. For the time being, the details of clinical trials registered in the WHO



network can be searched to a limited extent on ClinicalTrials.gov.

Should we write off the ICTRP as a failed attempt at sharing information to sustain international scientific collaboration? In my view, no. Recent developments make it urgent to give the WHO adequate support for this part of its mission. As recently as 2015 it may have seemed reasonable in for the sponsors of the majority of clinical trials in the world to rely on the altruistic internationalism of the US government. However, the USA has decided to leave and defund the WHO[3]. We need renewed political agreement on the system for pooling scientific information to underpin the international response to future public health emergencies and wider public health challenges.

Overwhelming volume of unconfirmed reports of research on COVID-19

The astonishingly rapid worldwide response to the pandemic draws on unprecedented scientific collaboration. It has enabled the WHO to coordinate studies comparing a range of treatments in patients across many countries. By mid-July, there were only two COVID studies listed with results out of 4,400 studies on the WHO portal related to the pandemic. Meanwhile, the enormous burst of coronavirus research activity has generated an overwhelming number of preliminary reports of

[3] ClinicalTrials.gov has so far continued to register non-US studies and to contribute data to the WHO portal.

studies awaiting verification by peer review. For example, by mid-July there were over 6,500 such reports on the leading preprint websites medRχiv and bioRχiv at https://www.medrxiv.org.

medRχiv carries a prominent warning. *Caution: Preprints are preliminary reports of work that have not been certified by peer review. They should not be relied on to guide clinical practice or health-related behavior and should not be reported in the news media as established information.* Nonetheless, journalists - including those in the UK media with the widest audiences - often cover these reports as if they were definitive This tends to wind up public anxiety about a cacophony of apparently contradictory scientific opinion, adding to well-founded concern about the limits to the actionable scientific evidence that can be relied on to guide responses to the pandemic.

It is enormously valuable, especially in a public health emergency, for scientists promptly to expose their unconfirmed findings to critical examination. That includes many studies that offer pointers to guide future research although they failed to recruit enough people to support statistically reliable conclusions. On the other hand, the tsunami of preliminary reports appears to be overwhelming the expert capacity to review and communicate emerging science in all the university systems of nations we rely on to verify it, with consequences for regulators and governments.

Persistent under-reporting

The previous history of failure to write up and report clinical trials rings alarm bells about the low priority universities give to their responsibility as sponsors for the quality and completeness of their research outputs. That makes the precarious state of the international consensus on providing for the registration and reporting of clinical trials especially concerning. Only 8% of trials on the WHO portal are listed with results.

In 2015 the WHO published a statement on the disclosure of results[4]. It was followed in 2017 by a consensus statement[5] from major research funders, including several from the UK[6], undertaking to adopt policies requiring results to be reported one year after a study concludes. The UK was influential in both these statements, and the NIHR and others have adopted the policies they promised. Official US research funders did not subscribe to the 2017 consensus statement. As the past leader in clinical studies, the USA was a pioneer in legislating to require registration and reporting. Its official registry ClinicalTrials.gov lists nearly 350,000 studies. 54% of those US-registered studies are reported as complete. Of those, 24% are listed with results. That means only 13% of US-registered studies worldwide are listed with results.

45% of the studies on ClinicalTrials.gov are outside the USA. The rate of under-reporting for non-US studies is higher, and this poor showing is no better for trials in Europe: for both Europe and the rest of the world, 18% of completed studies are with results. On ClinicalTrials.gov, the countries demonstrating the highest commitment to reporting are Australia, with results listed for 53% of completed studies, and Japan with 48%. Of completed studies within the USA, under one third are listed with results despite the penalties available under US law for non-reporting of studies done for US regulatory purposes or with US government funding. Weak enforcement has attracted criticism;

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[4] The WHO's statement in 2015 drew attention to the section of the Declaration of Helsinki requiring reporting of results. It said the key outcomes of a study should be reported through an open access mechanism 12 months after study completion. The statement can be downloaded from https://www.who.int/ictrp/results/reporting/en/

[5]The funders' joint statement on public disclosure of results from clinical trials can be downloaded from https://www.who.int/ictrp/results/jointstatement/en/

[6] The UK signatories were the Department for International Development, the Medical Research Council, the National Institute for Health Research and the Wellcome Trust.

and no penalties apply to the large body of US-registered trials which are not subject to US law. The decision of research teams in other countries to register in the USA can look like lip-service to the ethical consensus on transparency: doing just enough to get past the research ethics committee.

Even within a general culture of under-reporting, US-registered studies in the UK set a poor example. By July 2020, ClinicalTrials.gov listed 18,680 UK studies. 56% were reported complete. Of those, 29% were with results. That means UK research teams have reported results to ClinicalTrials.gov for only 16% of the UK studies registered with the US government. The most optimistic gloss one can put on this is that under-reporting is even worse for US-registered studies in Germany, France, and China. Registering with ClinicalTrials.gov is meant to showcase UK research to colleagues and funders in the USA. What the UK, Germany and France are showcasing is a failure of research governance in many of their research institutions.

In 2018 your committee castigated many British research institutions[7] for not having systems to ensure completed studies were written up and reported. The impetus for the registration of clinical trials was originally driven by the suppression of unfavourable research for commercial reasons. HC1480 found under-reporting is now prevalent in many British universities and NHS research centres. Following the amendments to the Helsinki Declaration I mentioned earlier, registration and reporting have for some years been a routine condition of a research ethics committee's approval of a clinical trial. HC1480 recommended among other things that the Health Research Authority should audit compliance. Leading British funders of clinical trials have begun concerted action to question institutions and research teams about under-reporting. In July 2020, the HRA published a transparency strategy[8] following a period of consultation. This strategy takes account not only of the HRA's response to HC1480 but also measures related to its wider statutory functions[9].

> *The strategy sets out our vision for research transparency and our mission in helping to make it happen across the UK. We also outline planned activities in three key areas: registering research studies, reporting results and informing participants.*
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> *Currently, clinical trials of medicines are automatically registered. We expect sponsors themselves to register other types of clinical trials such as those for medical devices, surgery, public health and behavioural interventions. However, despite it being a condition of research approval by the HRA, these clinical trials are not always entered onto a public registry. We want to fix this, so that there is full visibility of all clinical trials from the beginning of the study. In future, the HRA will register clinical trials on behalf of the sponsor using data that applicants submit for their study to be approved, unless a sponsor has been granted permission to defer registration. We will work with stakeholders to determine the most appropriate way to achieve this.*
>
> ***Registering research: 30% of clinical trials are not registered.***
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> Page 5 of Transparency and openness in health and social care research, Health Research Authority

[7] Research integrity: clinical trials transparency (HC1480)

[8] Make It Public: Transparency and openness in health and social care research, Health Research Authority, July 2020

[9] Section 110 (2) of the Care Act 2014:

> *(2) The main objective of the HRA in exercising its functions is—*
>
> > *(a) to protect participants and potential participants in health or social care research and the general public by encouraging research that is safe and ethical, and*
> > *(b) to promote the interests of those participants and potential participants and the general public by facilitating the conduct of research that is safe and ethical (including by promoting transparency in research).*

In future, we will make it clearer to applicants at the time of study approval that they have to submit a final report 12 months after the study has ended.

25% of clinical trials of medicines are not reported

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Research teams have chosen to register far fewer studies with the UK's primary registry ISRCTN than they registered in the USA. ISRCTN depends on fees for individual registrations. The research grants of most UK funders provide for ISRCTN's fees, but in the HRA's consultation on its transparency strategy respondents blamed ISRCTN's fees as an obstacle to registration. For those that do register with ISRCTN, the rate of reporting is much higher than on ClinicalTrials.gov. Nearly 10,500 UK studies are registered with ISRCTN. 82% of them are reported complete. Of those, 61% are with results.

ISRCTN sends reminders to research teams to highlight overdue updating and reporting. Friendly prompting seems to work well alongside the pressure that funders can apply. This raises our ambition for further improvement through a concerted effort engaging research institutions, funders, and regulators as well as registries. ISRCTN's approach seems to work also for studies recruiting outside the UK. Over 45% of the studies registered with ISRCTN are from other countries. 90% of them are reported complete; 49% with results. For the 500 US studies registered with ISRCTN, the reporting rate is higher still: 63% of completed studies are with results!

Following your committee's 2018 report, some universities strengthened their research management systems to ensure that writing up and reporting clinical trials is a routine part of the research cycle. However, the research culture which leaves so many studies unreported is deeply embedded. In its recent policy paper ***UK Research and Development Roadmap***, the government noted the incentives that dominate a research environment driven by constant competition for short-term funding. Insecure employment for members of research teams constantly undermines the capacity to develop and retain skills in research management which are essential if research institutions are to deal competently with the ethical and legal obligations of transparency as well as other processes underpinning the integrity of research.

The factors that can create an insecure and threatening working environment for junior researchers are also bad for their seniors. Tenured research leaders are expected to demonstrate compliance with ethical and legal obligations and to guarantee the quality of an institution's research outputs. The lack of consistent support throws an intolerable burden on them. They know their careers are more likely to progress if they win new grants than if they prioritise keeping faith with the people who took part in or funded their previous clinical trials. These bad incentives harm researchers, and

Careers in research and development are not as attractive as they should be due to lower salaries and an over-dependence on competing for short-term funding.

Page 11 of the British Government's policy paper UK Research and Development Roadmap, published 1 July 2020

We will work with funders to set clear expectations of research organisations in supporting safe and open research cultures that lead to high integrity of research.

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they harm the most important resource for British clinical research: the wonderful altruism of people who volunteer for clinical trials.

Pressures on UK universities may undermine action to redress these failures

The coronavirus pandemic can be expected to have major consequences for UK universities. Your committee has taken evidence about the financial consequences. Deprived of income from overseas students, institutions will have to take urgent measures to reduce spending. They may be tempted to make deep cuts in the posts of people on short contracts starting careers in research or research management. What priority will they give to preserving the systems and processes that underpin scientific integrity and transparency, and the posts of junior staff who learn and run them?

Clinical research on topics other than COVID-19 is already on the back burner. In this context, the Department of Health and Social Care and the National Institute for Health Research have shown active support for the registration and reporting of clinical trials, and for ISRCTN's role as the UK's primary registry in the WHO system: see the box on the next page. The ISRCTN team can fast-track applications and assist research teams in keeping records as complete and up-to-date as possible. With such high volumes of trials being registered worldwide, curation and cleaning of meta data will be crucial. By mid-July 2020 over 90 COVID-19 studies were registered with ISRCTN, 56 of them recruiting in the UK. One was completed. Four incomplete studies had reported results. ClinicalTrials.gov listed over 2500 COVID-19 studies, including over 500 recruiting in the USA and over 120 recruiting in the UK. Eight were reported complete, none with results.

Will the plans announced by the HRA, given active support from the UK's many official and charitable research funders, be sufficient to address the deep-seated issues described in HC1480? In its transparency strategy, the HRA proposes to carry out an options appraisal for a model for the registration of UK clinical trials. The legal basis for the HRA is the Care Act 2014. Section 111 (3) says *The HRA must promote the co-ordination and standardisation of practice* ***in the United Kingdom*** *relating to the regulation of health and social care research…..* The HRA's transparency strategy does not mention the WHO clinical trials registry network or the ISRCTN registry. It is altogether silent on the reasons for international collaboration to promote transparency in research that bears on the capacity to manage public health emergencies of international concern.

Conclusion

The pandemic has highlighted significant weaknesses in the commitment of many research institutions to scientific transparency. It is challenging the world's capacity to translate preliminary findings into settled and reliable evidence. International tensions have thrown into sharp relief the precarious situation of the WHO system for pooling research evidence, already weakened by a failure to invest in and make full use of the international network of clinical trials registries.

I suggest that, in planning how to follow up your committee's current inquiry, it would be helpful to consider when to review three issues.

- **Are post-COVID pressures on the UK's research culture likely to defeat the government's aspiration for the UK to be regarded as a partner of choice and a leader in research integrity?**
- **How much can be expected of the Health Research Authority's plans to embed transparency in health research culture if UK research institutions do not take ownership of their obligations?**
- **Can the mechanisms for international scientific collaboration recover from the impact of bilateral tensions between countries that the UK has regarded as major partners and prospective partners in the research and innovation that are vital for everyone's health?**

Registration with ISRCTN of Urgent Public Health badged studies in the NHS.

Approval letters from the NIHR for COVID-19 studies in the NHS include the following:

It is compulsory for all Urgent Public Health (UPH) badged studies to be entered on the ISRCTN registry. ISRCTN is able to offer same-day registration for UPH badged studies. To access this please contact info@ISRCTN.com before creating or logging into your ISRCTN account and making your ISRCTN application through the ISRCTN online submission portal. Alternatively, you can apply for your ISRCTN registration through our Central Portfolio Management System (CPMS) on receipt of your CPMS ID. Instructions on how to do this will be provided. All non-commercial studies badged as UPH are able to have their registration fee paid by the Department of Health and Social Care. Reimbursement is not possible if you have already applied and received an ISRCTN before confirmation of your UPH badging and inclusion on the NIHR CRN Portfolio.

(July 2020)