Who takes responsibility for our unreported clinical research?

What do we make of the under-reporting of studies registered in the USA on ClinicalTrials.gov but conducted in France, the United Kingdom and Germany?

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Our agenda for today

- Scientific **transparency**: *a reminder of the history behind the ethical consensus on registering and reporting clinical research.*
- The role of **clinical trial registries** since 2000:
  - *The international network coordinated by the World Health Organization;*
  - *The influence of the USA's ClinicalTrials.gov.*
- The scale of **under-reporting** internationally, and from the UK.
- 2020: the enormous volume of **unverified research** on COVID-19.
- **Discussion**:
  - *What does this tell us about the British clinical research environment?*
  - *What would make the UK a world leader in reporting robust findings?*
  - *Can British academics rely on public trust (if they don't do what they promise)?*

Scientific transparency in clinical trials: *international consensus, ethical and legal duty*

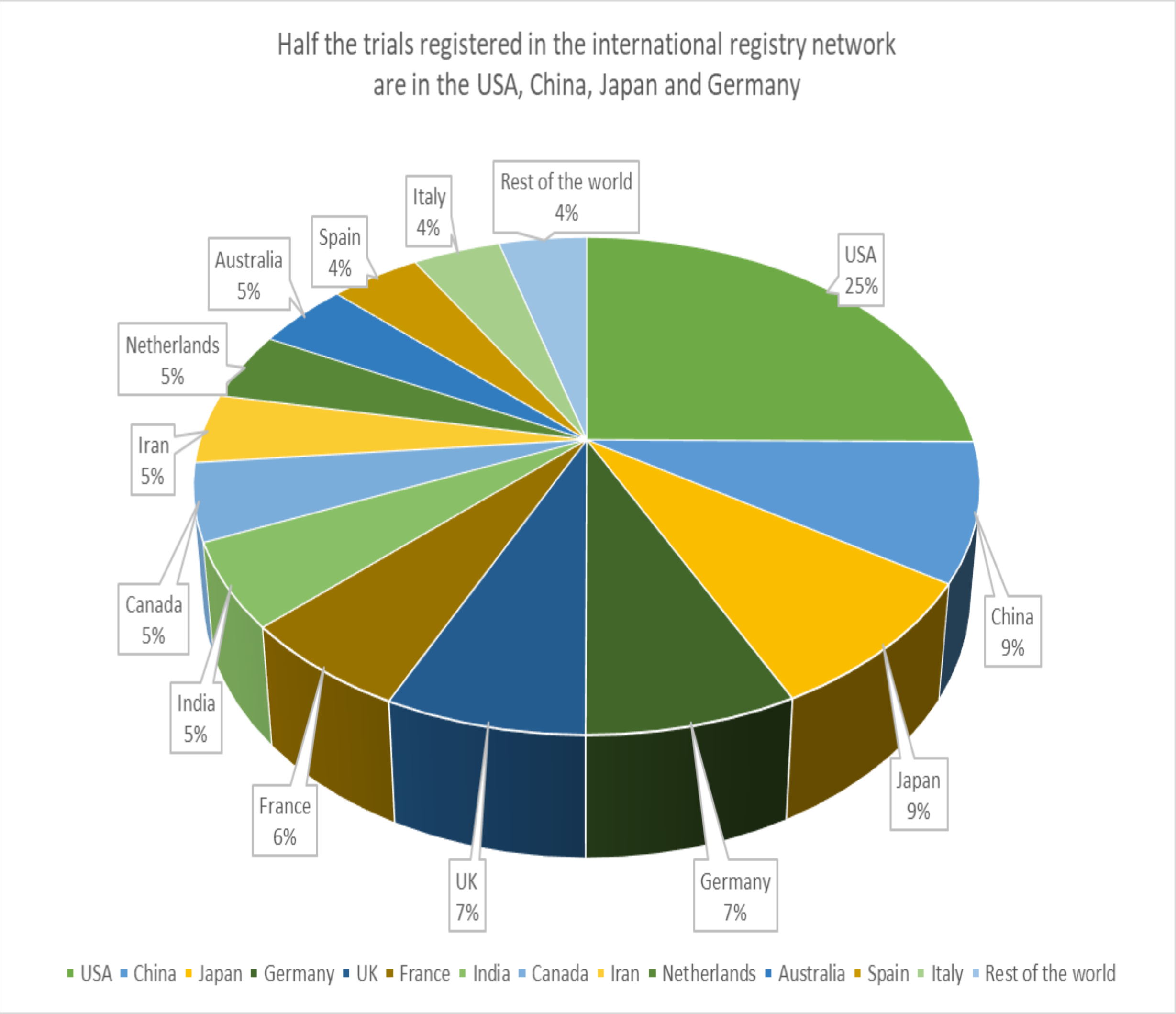
- 1997, Food and Drug Administration Modernization Act
  - *mandated a US registry and required registration of clinical trials by law.*
  - *Amended 2007 requiring registration of more types of trials and more information.*
- 2000, ClinicalTrials.gov and UK's ISRCTN commenced registration.
- 2004, WHO Ministerial Summit called for a registry network.
- 2005, ICMJE made publication conditional on registration.
- 2005, World Health Assembly agreed:
  - *International Health Regulations on public health emergencies, and*
  - *resolution calling for an international platform to link clinical trials registries*.
- 2008, WMA Declaration of Helsinki made prospective registration of clinical trials and the public disclosure of results an ethical obligation.

The WHO promotes scientific transparency and collaboration.

Members of the World Health Organization share scientific information through the **International Clinical Trials Registry Platform**.

You can search standard information from the international registry network via the WHO's clinical trials portal. **Registries on the WHO portal have registered 580,000 studies since 2000**.

350,000 of these studies – including over 130,000 in the USA – **are registered on ClinicalTrials.gov**.


Half the trials registered in the international registry network are in the USA, China, Japan and Germany

ClinicalTrials.gov, the world’s leading registry

- **ClinicalTrials.gov** is the **US Government’s registry** of clinical trials.
- ***38% of studies registered on ClinicalTrials.gov recruited in the USA***.
- US law requires research studies to be registered on ClinicalTrials.gov
  - if they are related to the **licensing of treatments in the USA** and/or
  - if they are **funded by US agencies** of the National Institutes of Health.
- US law requires those trialists to report results on ClinicalTrials.gov
  - *When other trialists choose US registration there is no pressure to report.*
- ***ClinicalTrials.gov registered over half the studies on the WHO portal***
- Nearly 30% of US-registered studies recruited in Europe….
  - Let’s look at studies in France, the UK and Germany **completed in 2014-2018**.

France

- **Out of 5,633 studies**
  - registered on ClinicalTrials.gov,
  - recruiting in France
  - with completion dates in 2014 to 2018,
- **1,077 (19%) were listed with results** by August 2020

France has no primary clinical trials registry.

This record of reporting is barely better than China's. Of over 6,200 studies registered on ClinicalTrials.gov, Chinese researchers reported 2,652 completed, ***17.5%*** *of them with results.*

United Kingdom

- **Out of 4,553 studies**
  - registered on ClinicalTrials.gov,
  - recruiting in the UK
  - with completion dates in 2014 to 2018,
- **1,443 (32%) were listed with results** by August 2020

The UK's primary registry ISRCTN lists over 10,500 studies recruiting in the UK.

- *Of 8,700 listed as complete, nearly 5,400 (62%) are with results.*
- *Of nearly 2,450 UK studies completed in 2014-2018, 1,500 (61%) are with results.*
- *ISRCTN reminds trialists when updates and reports are overdue.*

Germany

- **Out of 4,444 studies**
  - registered on ClinicalTrials.gov,
  - recruiting in Germany
  - with completion dates in 2014 to 2018,
- **1,576 (35%) were listed with results** by August 2020

Germany has its own primary clinical trials registry.

Other countries do better (but not well enough)

Of completed studies registered on ClinicalTrials.gov

- Japan has results reported for **49%** of studies ending in 2014 to 2018
- Australia has results reported for **46%**

- ClinicalTrials.gov lists **over 130,000 studies conducted in the USA**
  - *Nearly 76,000 are listed as complete.*
  - ***Under 24,000*** *(32% of US studies listed complete) are* ***with results***
- The US registry has results reported for **38%** of studies ending in 2014 to 2018.

Reporting of results from studies conducted in France is no better than the world average.
France does not have its own clinical trials registry. It relies on ClinicalTrials.gov.
US law on results reporting has no effect on researchers in France.
French research funding agencies don’t enforce conditions requiring results to be reported promptly.

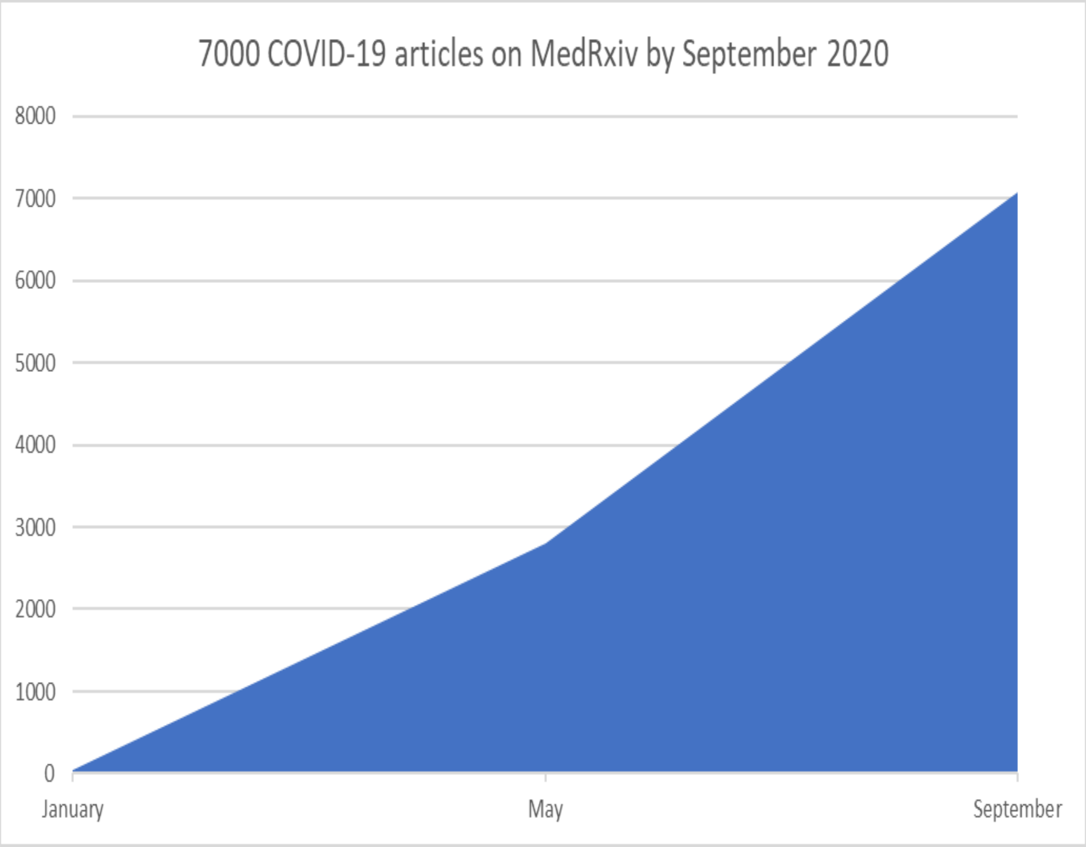
Of studies completed in:		World	USA	UK	France	Germany	Japan	Australia
% with results in 2020	2018	16%	33%	24%	15%	31%	47%	44%
% with results in 2020	2017	18%	38%	30%	18%	35%	46%	52%
% with results in 2020	2016	21%	39%	32%	19%	38%	51%	34%
% with results in 2020	2015	22%	40%	34%	21%	34%	47%	56%
% with results in 2020	2014	25%	42%	39%	25%	40%	55%	52%

Under-reporting clinical trials in the UK

- **When RECs approve clinical trials, it's conditional on registration and reporting.**
  - *Initially, some sponsors of commercial trials opposed this.*
  - *Now the biggest failures of governance are in universities and the NHS.*
- **UK was a leading advocate** in the World Health Organization for:
  - a resolution on **registration & disclosure** (2015)
  - a **funders'** consensus statement **committing to timely reporting** (2017)
- In 2018, the Commons **Science and Technology Committee criticised many UK universities** over registration and reporting of clinical trials.
  - It **criticised the Health Research Authority for inaction**.
- In 2020, the NIHR required all **COVID-19 studies to be registered with ISRCTN**.
- In 2020, the **HRA published its transparency strategy** Make It Public.
  - *It said 25% of clinical trials of medicines are not reported.*
  - *It said participants were not informed of the results of 90% of clinical trials*

COVID-19: a pandemic of unverified research

- medRχiv is the leading preprint server. It publishes preliminary research findings prior to review.
- In January 2020, medRχiv had 37 articles on COVID-19. **By 12 October it had 7,443.**
- By 12 October, ClinicalTrials.gov listed 3,567 COVID-19 studies, **9 with results.** No results from UK.
- *Other WHO registries listed 2,630 more.*
- *Of these, ISRCTN has 152 studies,* ***9 with results*** *including 6 in the UK.*



Treating COVID-19: missing evidence

Dexamethasone

features in **3,224 trials** on ClinicalTrials.gov;

- **1,436** reported complete
- **493 (34%) with results**

- in **261** preliminary findings on **medRχiv since 2019** and
- **27** reports on Elsevier's preprint server SSRN

Remdesivir

features in **62 trials** on ClinicalTrials.gov

- **8** reported complete
- **1 with results**

- in **468** preliminary findings on **medRχiv in 2020** and
- **24** reports on Elsevier's preprint server SSRN

REGN-COV2: miracle cure?

"I went in, I wasn't feeling so hot, and within a very short period of time, they gave me Regeneron. It's called Regeneron. And other things, too, but I think this was the key. But they gave me Regeneron. And it was, like, unbelievable. I felt good immediately“

President Donald J Trump

REGN-COV2

- 1 trial on ClinicalTrials.gov, recruiting
- 1 trial on ISRCTN, recruiting
- 0 reported complete
- 1 with preliminary results
- 1 preliminary finding on medRχiv
- 0 reports on SSRN

Some topics for discussion

- Do **leading countries have the capacity** to verify all these preliminary outputs?
- Do UK universities **value international collaboration** in health research?
  - *The USA is leaving the World Health Organization. The UK will become its largest funder.*
- Is it realistic to present the **UK as a world leader** in biomedical research?
  - *Why does UK research culture leave so many clinical trials unverified and unreported?*
  - *How many UK universities are capable of producing timely high quality results?*
  - *Does it matter if they ignore international standards of scientific transparency?*
- **Whose problem is it** if researchers persistently ignore their commitments?
  - *The Health Research Authority? Research funders? Academic and commercial sponsors?*
- **Would you join a trial if the results are unlikely to be fed back or reported**?

Further information

- Marc Taylor: my note to the Science and Technology Committee's inquiry into UK Science, Research and Technology Capability and Influence in Global Disease Outbreaks is at www.linkedin.com/in/cmarctaylor
- The UK's ISRCTN health research registry is at https://www.isrctn.com
- The US government's health research registry is at www.clinicaltrials.gov
- The WHO clinical trials registry network: www.who.int/ictrp
- The leading preprint server medRχiv is at https://www.medrxiv.org
- The Health Research Authority recently published a new transparency strategy
- The British Government is consulting on a UK Research and Development Roadmap
- In his speech to the UN General Assembly the Prime Minister committed the UK to support the World Health Organization, promote open research and champion a new global approach to health security.
- ISRCTN supports the All Trials campaign to have clinical trials registered and reported.

Of studies on ClinicalTrials.gov completed 2014 to 2018 what % are listed with results?