University of Basel
Department of Clinical Research

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Klinische Studien zu COVID-19

Lars G. Hemkens

Jahrestagung der AKEK
(Arbeitskreis Medizinischer Ethik-Kommissionen in der Bundesrepublik Deutschland e.V.)

online, 11. November 2021

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“Klinische Studien”

- Randomisierte Studien: A vs B
- Jede Intervention / Strategie
- Auch ohne Kliniken.

Never before

have **clinical trials** drawn as much **public attention** as those testing **interventions** for **COVID-19.**

F1000Research F1000Research 2020, 9:1193 Last updated: 15 OCT 2021

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RESEARCH ARTICLE

REVISED The worldwide clinical trial research response to the COVID-19 pandemic - the first 100 days [version 2; peer review: 2 approved]

Perrine Janiaud[1,2], Cathrine Axfors[1,3], Janneke van't Hooft[1,4], Ramon Saccilotto[1], Arnav Agarwal[5], Christian Appenzeller-Herzog[6], Despina G. Contopoulos-Ioannidis[7], Valentin Danchev[1,8], Ulrich Dirnagl[9], Hannah Ewald[6], Gerald Gartlehner[10,11], Steven N. Goodman[1,12,13], Noah A. Haber[1], Angeliki Diotima Ioannidis[14], John P. A. Ioannidis[1,8,12,13,15], Mark P. Lythgoe[16], Wenyan Ma[2], Malcolm Macleod[17], Mario Malički[1], Joerg J. Meerpohl[18,19], Yan Min[1,12], David Moher[20], Blin Nagavci[18], Florian Naudet[21], Christiane Pauli-Magnus[2], Jack W. O'Sullivan[1,22], Nico Riedel[9], Jan A. Roth[2,23], Mandy Sauermann[23], Stefan Schandelmaier[2,24], Andreas M. Schmitt[2,25], Benjamin Speich[2,26], Paula R. Williamson[27], Lars G. Hemkens[1,2,15]

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We aimed to describe the **worldwide COVID-19 clinical research response** and its evolution over the **first 100 days…**

Janiaud et al. F1000. 2020: 9;1193

First 100 days…

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- Descriptive analysis of planned, ongoing or completed trials by **April 9, 2020**
- Testing any intervention to treat or prevent COVID-19
- Systematically identified in trial registries, preprint servers, and literature databases.

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First 100 days…

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689 trials

- Median sample size 120 (IQR 60-300)
- 522 randomized (75.8%)
- 352 China (51.1%)
- 76 USA (11%)
- 607 evaluated treatments (88.1%)
- 78 prevention (11.3%); 14 vaccine trials
- Interventions tested in 11 trials with >5,000 participants were also tested in 169 smaller trials (median sample size 273; IQR 90-700).
- Hydroxychloroquine alone was investigated in 110 trials.
- No trial investigated social distancing.

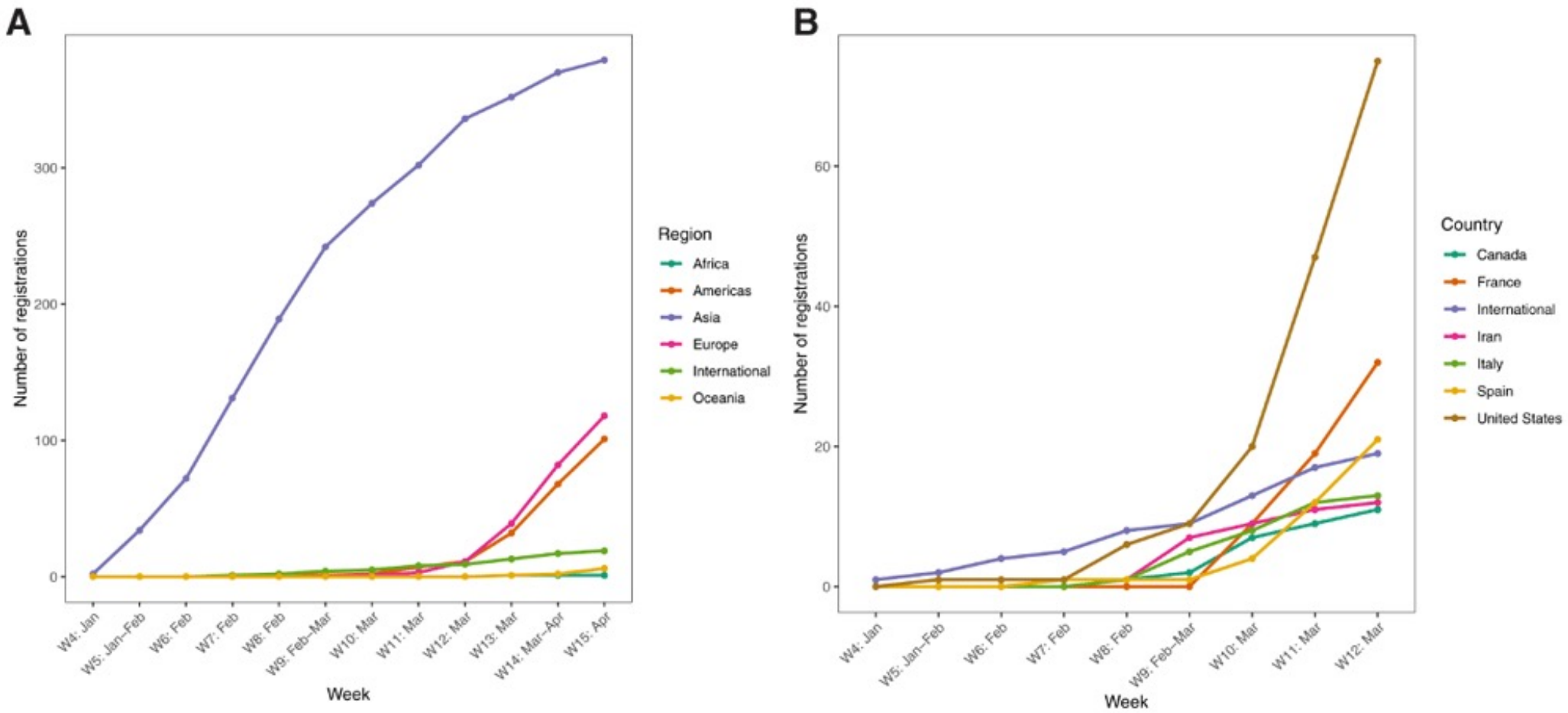
Janiaud et al. F1000. 2020: 9;1193

First 100 days…

Cumulative number of registered trials over time

A by continent

B countries with at least 10 registrations (excluding China)



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First year… (approx.)

2814 RCTs registered as of **Feb 2021**

- 283 publications
- Majority small (18% plan include n > 500)
- Often same interventions:

  > 300 RCTs w. hydroxychloroquine in intervention arm (60 of them registered ***after*** RECOVERY press release)
- Almost all on therapeutics; vaccines: 6.2% RCTs (vs. 10.8% on hydroxychloroquine !)

Review > Can J Cardiol. 2021 Sep;37(9):1353-1364. doi: 10.1016/j.cjca.2021.05.009.
Epub 2021 May 30.

Challenges and Lessons Learned From COVID-19 Trials: Should We Be Doing Clinical Trials Differently?

Perrine Janiaud [1], Lars G Hemkens [2], John P A Ioannidis [3]

Affiliations + expand

PMID: 34077789 PMCID: PMC8164884 DOI: 10.1016/j.cjca.2021.05.009
Free PMC article

Abstract in English, French

The COVID-19 crisis led to a flurry of clinical trials activity. The COVID-evidence database shows 2814 COVID-19 randomized trials registered as of February 16, 2021. Most were small (only 18% have a planned sample size > 500) and the rare completed ones have not provided published results promptly (only 283 trial publications as of February 2021). Small randomized trials and observational, nonrandomized analyses have not had a successful track record and have generated misleading expectations. Different large trials on the same intervention have generally been far more efficient in producing timely and consistent evidence. The rapid generation of evidence and accelerated dissemination of results have led to new challenges for systematic reviews and meta-analyses (eg, rapid, living, and scoping reviews). Pressure to regulatory agencies has also mounted with massive emergency authorizations, but some of them have had to be revoked. Pandemic circumstances have disrupted the way trials are conducted; therefore, new methods have been developed and adopted more widely to facilitate recruitment, consent, and overall trial conduct. On the basis of the COVID-19 experience and its challenges, planning of several large, efficient trials, and wider use of adaptive designs might change the future of clinical research. Pragmatism, integration in clinical care, efficient administration, promotion of collaborative structures, and enhanced integration of existing data and facilities might be several of the legacies of COVID-19 on future randomized trials.

Janiaud et al. Can J Cardiol. 2021

Deutschland 2020…

- We included all planned, ongoing, or completed **RCTs** assessing interventions to treat or prevent COVID-19, registered in 2020, that recruited or planned to recruit at least one participant in Germany

➔ <u>any</u> intervention/strategy (drug, vaccine, device, testing, social, public health, behavioural…)

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RESEARCH ARTICLE

Clinical trial research on COVID-19 in Germany – a systematic analysis [version 1; peer review: awaiting peer review]

Julian Hirt[1,2], Abeelan Rasadurai[3], Matthias Briel[1,4], Pascal Düblin[1], Perrine Janiaud[1*], Lars G. Hemkens[1,5,6*]

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Open Peer Review

Reviewer Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

Abstract

Background: In 2020, the COVID-19 pandemic led to an unprecedented volume of almost 3,000 clinical trials registered worldwide. We aimed to describe the COVID-19 clinical trial research agenda in Germany during the first year of the pandemic. **Methods:** We identified randomized clinical trials assessing interventions to treat or prevent COVID-19 that were registered in 2020 and recruited or planned to recruit participants in Germany. We requested recruitment information from trial investigators as of April 2021. **Results:** In 2020, 65 trials were completely (n=27) or partially (n=38) conducted in Germany. Most trials investigated interventions to treat COVID-19 (86.2%; 56/65), in hospitalized patients (67.7%; 44/65), with industry funding (53.8%; 35/65). Few trials were completed (21.5%; 14/65). Overall, 187,179 participants were planned to be recruited (20,696 in Germany), with a median number of 106 German participants per trial (IQR 40 to 345). From the planned German participants, 13.4% were recruited (median 15 per trial (IQR 0 to 44). **Conclusions:** The overall German contribution to the worldwide COVID-19 clinical trial research agenda was modest. Few trials delivered urgently needed evidence. Most trials did not meet recruitment goals. Evaluation and international comparison of the challenges for conducting clinical trials in Germany is needed.

Hirt et al. F1000. 2021:10;913

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- **Source**
  - ClinicalTrials.gov
  - WHO International Clinical Trials Registry Platform
  - German Clinical Trials Register (DRKS)
- **Publications** (incl. preprints and registry entries)
  - Living OVerview of Evidence platform for COVID-19 (L-OVE)
  - Cochrane COVID-19 Study Register
  - MEDLINE/PubMed
  - Google Scholar using the trial registry number

Last update/search: 1 April 2021

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65 RCTs registered

- 17 published results
- 27 completely, 38 partially conduct in Germany
- 86.2% Treatments
- 67.7% in hospitalized patients
- 53.8% industry funding
- 21.5% completed

Hirt et al. F1000. 2021:10;913

Deutschland 2020…

17 RCTs (26.2%) had published results

- 15 partially conducted in Germany
- 12 industry-funded
- 12 peer-reviewed articles or preprints
- 5 exclusively press release or in registry

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Abstract

Background: In 2020, the COVID-19 pandemic led to an unprecedented volume of almost 3,000 clinical trials registered worldwide. We aimed to describe the COVID-19 clinical trial research agenda in Germany during the first year of the pandemic. **Methods:** We identified randomized clinical trials assessing interventions to treat or prevent COVID-19 that were registered in 2020 and recruited or planned to recruit participants in Germany. We requested recruitment information from trial investigators as of April 2021. **Results:** In 2020, 65 trials were completely (n=27) or partially (n=38) conducted in Germany. Most trials investigated interventions to treat COVID-19 (86.2%; 56/65), in hospitalized patients (67.7%; 44/65), with industry funding (53.8%; 35/65). Few trials were completed (21.5%; 14/65). Overall, 187,179 participants were planned to be recruited (20,696 in Germany), with a median number of 106 German participants per trial (IQR 40 to 345). From the planned German participants, 13.4% were recruited (median 15 per trial (IQR 0 to 44). **Conclusions:** The overall German contribution to the worldwide COVID-19 clinical trial research agenda was modest. Few trials delivered urgently needed evidence. Most trials did not meet recruitment goals. Evaluation and international comparison of the challenges for conducting clinical trials in Germany is needed.

Target (planned) sample size:

- Internationally/Overall: N=300 per trial (IQR, 174 to 830)
  German participants: N=106 per trial (IQR 40 to 345)

Recruited:

- From the planned German participants, **13.4% were recruited** (median **15** per trial (IQR 0 to 44))

Limitation:

Full recruitment data for only 34.3% of the industry-funded trials compared to 80% of the publicly-funded trials

Hirt et al. F1000. 2021:10;913

Deutschland 2020…

F1000Research F1000Research 2021, 10:913 Last updated: 15 OCT 2021

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RESEARCH ARTICLE

Clinical trial research on COVID-19 in Germany – a systematic analysis [version 1; peer review: awaiting peer review]

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No trial was conducted in

- Nursing homes
- Kindergarten
- Childcare
- Schools

No trial was conducted on NPIs:

- Air filters
- Masks, face shields
- Testing strategies
- Hygiene education
- Access restriction
- School closure organization/schedule
- Home office policies

…

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Comments (1)

Randomized trials on non-pharmaceutical interventions for COVID-19 as of August 2021: a meta-epidemiological analysis

Julian Hirt, Perrine Janiaud, Lars G. Hemkens

doi: https://doi.org/10.1101/2021.08.20.21261687

This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

Abstract | Full Text | Info/History | Metrics | Preview PDF

Abstract

Background Numerous non-pharmaceutical interventions (NPIs) were taken worldwide to contain the spread of the COVID-19 pandemic. We aimed at providing an overview of randomized trials assessing NPIs to prevent COVID-19.

Methods We included all randomized trials assessing NPIs to prevent COVID-19 in any country and setting registered in ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform using the COVID-evidence platform (until 17 August 2021). We searched for corresponding publications in MEDLINE/PubMed, Google Scholar, the Living Overview of Evidence platform (L-OVE), and the Cochrane COVID-19 registry as well as for results posted in registries.

Results We identified 41 randomized trials. Of them, 11 were completed (26.8%) including 7 with published results. The 41 trials planned to recruit a median of 1,700 participants (IQR, 588 to 9,500, range 30 to 35,256,399) with a median planned duration of 8 months (IQR, 3 to 14, range 1 to 24). Most came from the United States (n=11, 26.8%). The trials mostly assessed protective equipment (n=11, 26.8%), COVID-19-related information and education programs (n=9, 22.0%), access to mass events under specific safety measures (n=5, 12.2%), testing and screening strategies (n=5, 12.2%), and hygiene management (n=5, 12.2%).

Conclusions Worldwide, 41 randomized trials assessing NPIs have been initiated with published results available to inform policy decisions for only 7 of them. A long-term research agenda including behavioral, environmental, social, and systems level interventions is urgently needed to guide policies and practices in the current and future public health emergencies.

Competing Interest Statement

The authors have declared no competing interest.

Funding Statement

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RCTs on Non-pharmaceutical interventions in RCTs

N=41 as of August 2021

10 trials: USA
3 trials: France, UK
2 trials: Australia, Bangladesh, Canada (±Israel), Norway
1 trial: China, Colombia, Congo, Denmark, Guinea-Bissau, India, Spain, Switzerland
0 trial: …

Hirt et al. medRxiv 2021.08.20.21261687

Conclusion

- Der deutsche Beitrag zur weltweiten klinischen Forschung zu COVID-19 war insgesamt relativ bescheiden
- Sehr wenige Studien lieferten Evidenz für Entscheidungsträger, d.h. publizierte Ergebnisse
- Keine Forschung aus Deutschland, die zuverlässige Evidenz liefert für bessere Entscheidungen bzgl. kritischer NPI
- Es braucht dringend Meta-Forschung zur weiteren Bewertung und zum internationalen Vergleich von Herausforderungen und Hindernissen bei der Durchführung von klinischen Studien in Deutschland
- …

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