COVID-NMA
COVID-19 OPEN LIVING EVIDENCE SYNTHESIS TO INFORM DECISION

The COVID-NMA initiative

An Evidence Ecosystem for the COVID-19 Pandemic

I Boutron

BMG
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Institut national de la santé et de la recherche médicale

Context and objectives

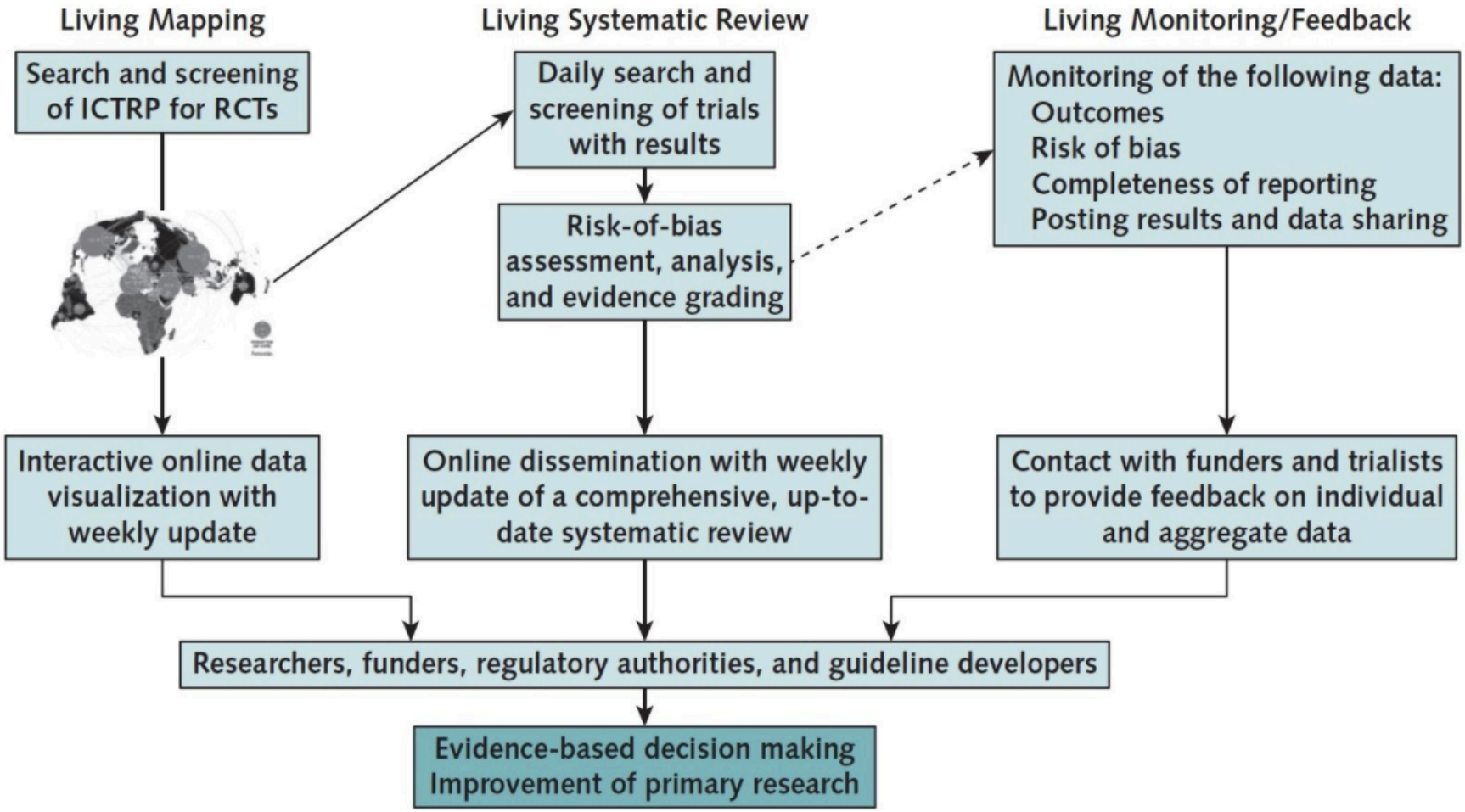
- Stakeholders urgently need up-to-date high quality syntheses of evidence to inform their decisions.

- To provide a living mapping and living synthesis of trial evidence

- Scope: all treatments and preventive interventions for COVID-19

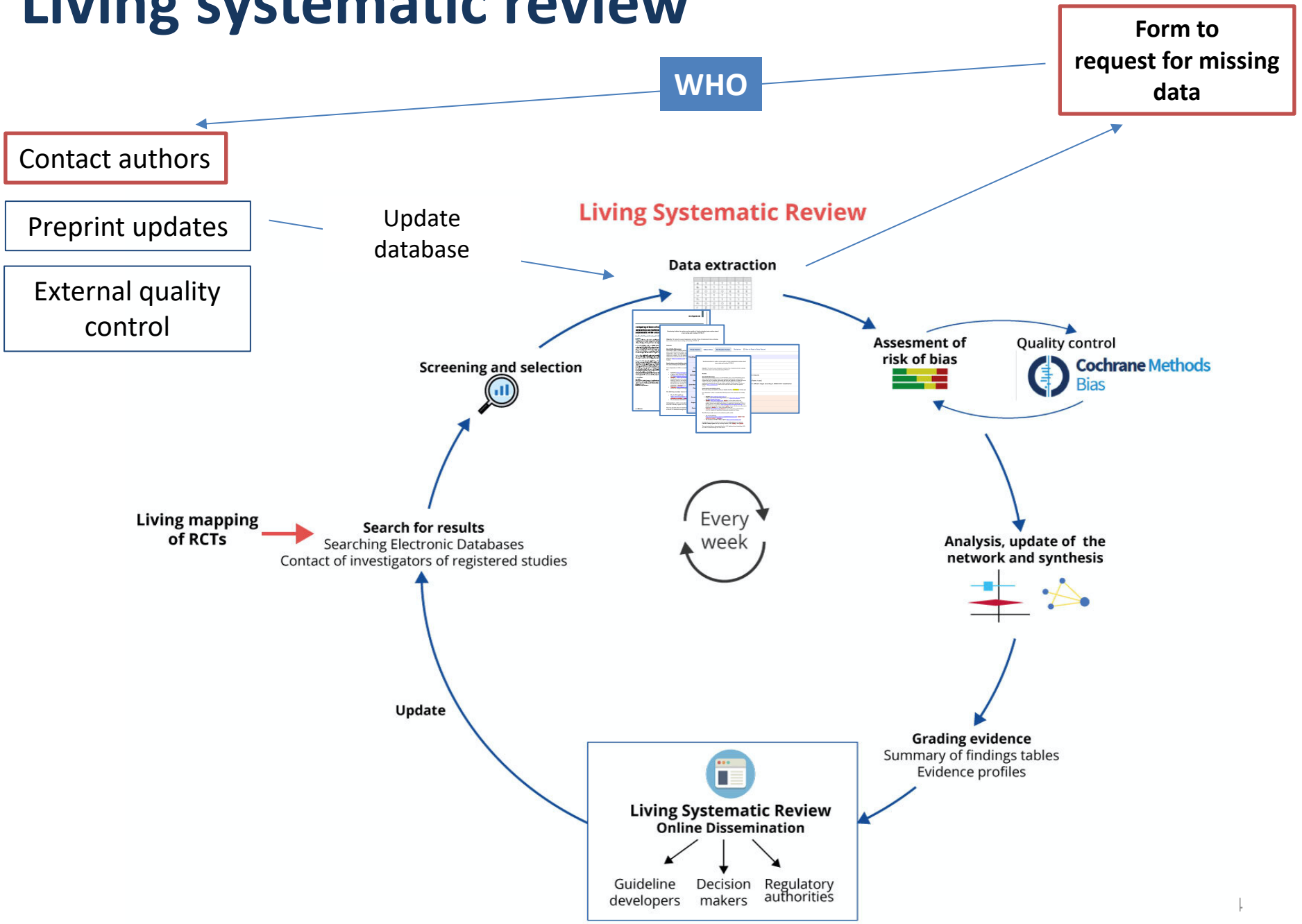
Boutron et al. J Clin Epidemiol 2020
Crequit et al. J Clin Epidemiol 2020
Ravaud et al. J Clin Epidemiol 2020
Ioannidis, Milbank Q. 2016

The model



Boutron et al. Annals Internal Med 2020
Nguyen et al. J Clin Epidemiol 2020

Living systematic review

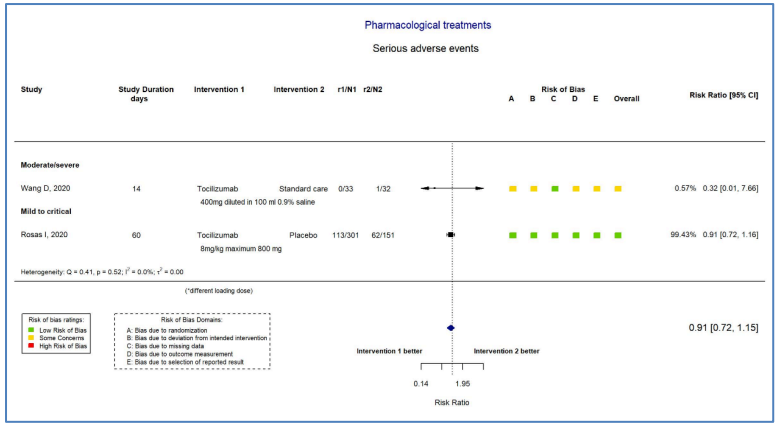


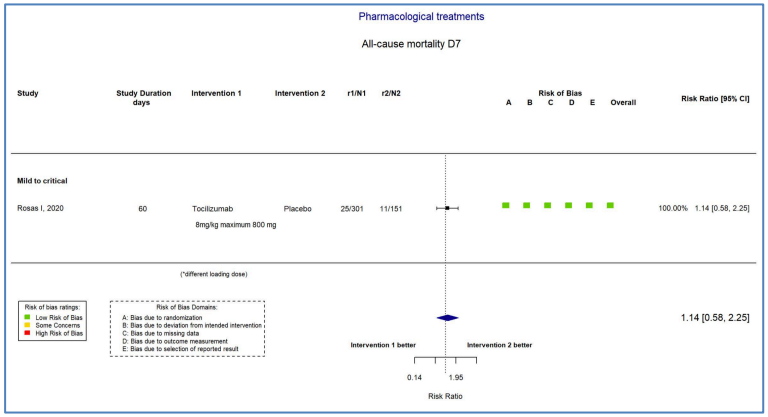
Trial NCT04320615
Publication Rosas I, medRxiv, 2020 (preprint)
Dates: 2020-04-03 to 2020-07-28
Funding: Mixed (F. Hoffmann-La Roche Ltd; Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority)
Conflict of interest: COI

Methods	RCT Blinding: double blinding
	Location : Multicenter / Canada, Denmark, France, Germany, Italy, Netherlands, Spain, UK, USA Follow-up duration (days): 60
Inclusion criteria	Patients 18 years or older with severe COVID-19 pneumonia confirmed by positive polymerase chain reaction test in any body fluid and evidenced by bilateral chest infiltrates on chest x-ray or computed tomography were enrolled. Eligible patients had blood oxygen saturation ≤93% or partial pressure of oxygen/fraction of inspired oxygen <300 mm/Hg. Informed consent was obtained for all enrolled patients.
Exclusion criteria	Report: Patients were excluded if the treating physician determined that death was imminent and inevitable within 24 hours or if they had active tuberculosis or bacterial, fungal, or viral infection other than SARS-CoV-2. Registry: Known severe allergic reactions to TCZ or other monoclonal antibodies Active tuberculosis (TB) infection Suspected active bacterial, fungal, viral, or other infection (besides COVID-19) In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments Have received oral anti-rejection or immunomodulatory drugs (including TCZ) with the past 3 months Participating in other drug clinical trials (participation in COVID-19 anti-viral trials may be permitted if approved by Medical Monitor) Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination Treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization (investigational COVID-19 antivirals may be permitted if approved by Medial Monitor) Any serious medical condition or abnormality of clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 10 x upper limit of normal (ULN) detected within 24 hours at screening (per local lab) Absolute neutrophil count (ANC) < 1000/mL at screening (per local lab) Platelet count < 50,000/mL at screening (per local lab)
Interventions	**Treatment** Tocilizumab (8mg/kg) Co-Intervention: Standard care Duration : 1 day
	Control Placebo Duration : 1 day

Trial NCT04320615
Publication Rosas I, medRxiv, 2020
Primary outcome on the report: Clinical status assessed on a 7-category ordinal scale at day 28

Bias	Author's judgement	Support for judgement
Randomization	Low	Quote: "Eligible patients were randomized (2:1) to receive intravenous tocilizumab (8 mg/kg infusion, maximum 800 mg) or placebo plus standard care using an interactive voice or web-based response system and permuted-block randomization. Randomization was stratified by geographic region (North America, Europe) and mechanical ventilation (yes, no)." Comment: Allocation sequence random. Allocation sequence concealed. Any differences in baseline characteristics appear to be compatible with chance.
Deviations from intervention	Low	Quote: "Masking: Double (Participant, Investigator)" Comment: Blinded study. Appropriate method of analysis was used i.e. modified-intention-to-treat (all randomized patients who received study treatment)
Missing outcome data	Low	Comment: 452 patients randomized; 438 patients analyzed. Missingness in <5% of population. Risk assessed to be low for the outcome: Mortality. Time to clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Adverse events. Serious adverse events.
Measurement of the outcome	Low	Comment: Appropriate method of outcome measurement Measurement of outcome does not differ between groups. Blinded study (outcome assessor) Risk assessed to be low for the outcomes: Mortality. Time to clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Adverse events. Serious adverse events.
Selection of the reported results	Low	Comment: The protocol and statistical analysis plan were not available. The prospective registry was available. Result was not selected from multiple outcome measurements or analyses. Trial analyzed as prespecified. Risk assessed to be low for the outcomes: Mortality. Time to clinical improvement. Incidence of WHO score 6 and above. Incidence of WHO score 7 and above. Adverse events.
Overall risk of bias	Low	





Trial	Comparisons		Design	Participants	Sample size	Overall risk of bias Primary outcome	Full description
	Treatment 1	Treatment 2					
NCT04320615 Rosas I, medRxiv, 2020 Full text Pubpeer	Tocilizumab	Placebo	RCT	Patients with confirmed COVID-19 (mild-critical) admitted to multiple centers across 9 countries	N=452	Low Details	Full description
ChiCTR2000029765 Wang D, SSRN, 2020 Full text Pubpeer	Tocilizumab	Standard care	RCT	Patients with confirmed COVID-19 (moderate-severe) admitted to 6 centers in China	N=65	High Details	Full description

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https://covid-nma.com

LIVING MAPPING OF TRIALS

(i.e., trials registered on the WHO platform)

Updated weekly

1940

Randomized Trials

1107 RCTs recruiting

1649

RCTs on treatments

(957 recruiting)

217

RCTs on prevention

(93 recruiting)

74

RCTs on vaccines

(57 recruiting)

LIVING SYNTHESIS OF PUBLISHED TRIALS

(include both articles and preprints)

Updated daily

110

RCTs with results

included in our evidence synthesis

97

RCTs on treatments

7

RCTs on prevention

4

RCTs on vaccines

Challenges

- Flexibility
- To achieve rapidity and quality
- Living evidence
  - 64% evidence is reported in a preprint
  - Of the studies reported as preprint
    - 14 (25%) preprint and publication
    - 30% >1 preprint version
- Transparency
- Sustainability of the model
- Reward model for researchers involved

Oikonomidi T, BMC Med, in revision

Acknowledgements:

- **Large international consortium**
- **Members of the COVID-NMA steering committee**: Isabelle Boutron,, Anna Chaimani, Declan Devane, Giacomo Grasselli, Asbjørn Hróbjartsson, Joerg J. Meerpohl, Gabriel Rada, David Tovey, Philippe Ravaud.
- **Members of the COVID-NMA consortium**: Solaf Alawadhi, Sihem Amer-Yahia, Chiara Arienti, David Auber, Camila Ávila, Aïda Bafeta, Fulvia Baldassarre, Rita Banzi, Julien Barnier, Julia Baudry, Hanna Bergman, Claudia Bollig, Hillary Bonnet, Marinette Bouet, Mohand Boughanem, Brian Buckley, Guillaume Cabanac, Sarah Charpy, David Chavalarias, Yaolong Chen, Astrid Chevance, Sarah Cohen-Boulakia, Elise Cogo, Françoise Conil, Emmanuel Coquery, Mauricia Davidson, Laura De Nale, Elise Diard, Taoufiq Dkaki, Bastien Doreau, Merwan El Asri, Theodoros Evrenoglou, Alice Fabbri, Robin Featherstone, Gilles Feron, Gabriel Ferrand, Leopold Fezeu, Mathilde Fouet, Joly Ghanawi, Lina Ghosn El Chall, Carolina Graña, François Grolleau, Benoit Groz, Mohand-Saïd Hacid, Candyce Hamel, Camilla Hansen, Nicholas Henschke, Ameer Hohlfeld, Chantal Julia, Dimitris Mavridis, Brice Meyer, Silvia Minozzi, Jose G. Moreno, Nivantha Naidoo, Van Thu Nguyen, Theodora Oikonomidi, Matthew Page, Jennifer Petkovic, Elizabeth Pienaar, Olivier Pierre, Katrin Probyn, Fiona Quirke, Pierre Ripoll, Carolina Riveros, Philippe Rivière, Marie Sauvant, Jelena Savovic, Christine Schmucker, Yanina Sguassero, Jonathan Sterne, Farouk Toumani, Gemma Villanueva, Romain Vuillemot, Jun Xia, Xuan Yu, Emina Zoletic, and Pierre Zweigenbaum.

- **Funding and support**
  - Agence Nationale de la Recherche
  - the World Health Organization
  - Cochrane France, Centre of Research in Epidemiology and Statistics, Centre d'Epidémiologie Clinique (GHU Cochin, Hôtel Dieu, Assistance Publique Hôpitaux de Paris, and Université de Paris)
  - Centre National de la Recherche Scientifique.

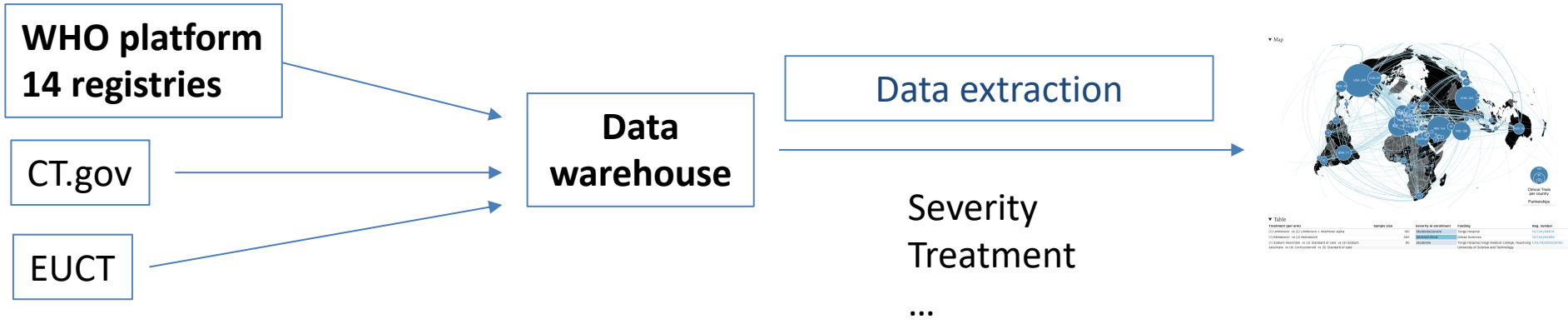
Conclusion

- A new model to fulfil stakeholders needs (WHO)

- Next steps
  - Request and management of IPD

The living mapping

- 1/semaine



Laboratoire de Recherche en Informatique (LRI), University Paris-Saclay, CNRS, France
LIRIS, université Lyon 1, CNRS
LIMOS, CNRS
LIMSI, CNRS

▼ Map

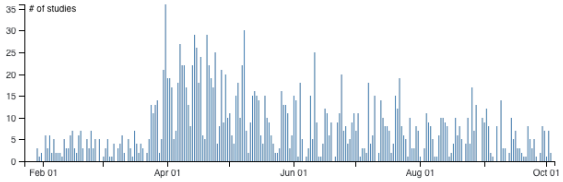
Filters

All trials selected **(1905)** | Reset all

Search...

Ex: Interferon, antiviral, Spain, Assistance Publique, EUCTR2020…

▼ Registration date

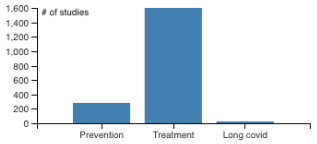


To filter by Registration dates, click and drag to create a range.

▼ Recruitment status

- [x] Recruiting (1,086 studies)
- [x] Not recruiting (746 studies)
- [x] Completed (61 studies)
- [x] Terminated (6 studies)
- [x] Suspended (5 studies)
- [x] Withdrawn (1 study)

▼ Study aim

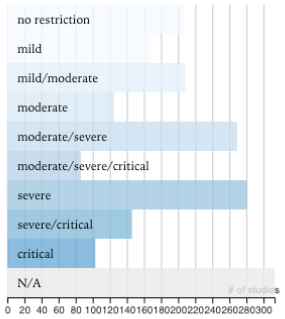


▼ Table

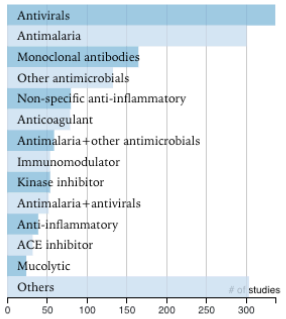
- [x] Show full table

Treatment (per arm)	Sample size	Severity at enrollment	Funding	Reg. number
(1) Umifenovir *vs* (2) Umifenovir + interferon alpha	100	Moderate/severe	Tongji Hospital	NCT04254874
(1) Remdesivir *vs* (2) Remdesivir	400	Severe/critical	Gilead Sciences	NCT04292899
(1) Sodium Aescinate *vs* (2) Standard of care *vs* (3) Sodium Aescinate *vs* (4) Corticosteroid *vs* (5) Standard of care	90	Moderate	Tongji Hospital,Tongji Medical College, Huazhong University of Science and Technology	ChiCTR2000029742
(1) Chloroquine *vs* (2) Doxycycline + ivermectin	40	No restriction on type of patients	Tanta University	NCT04403555
(1) Tocilizumab *vs* (2) Standard of care	150	Severe/critical	Benefic©ncia Portuguesa de S©o Paulo	NCT04403685
(1) Pacritinib *vs* (2) Placebo	358	Severe	CTI BioPharma	NCT04404361
(1) L-citrulline *vs* (2) Placebo	100	Critical	Rennes University Hospital	NCT04404426
(1) mRNA-1273 *vs* (2) mRNA-1273	600	Healthy volunteers	ModernaTX, Inc.	NCT04405076
(1) Ozanimod *vs* (2) Standard of care	48	Moderate/severe	Fran©ois Lellouche	NCT04405102
(1) Emtricitabine + tenofovir *vs* (2) Placebo	1378	Health workers	Hospital Italiano de Buenos Aires	NCT04405271
(1) Budesonide + formoterol *vs* (2) Placebo	600	Severe	Stanford University	NCT04193878
(1) Enoxaparin *vs* (2) Standard of care	1000	Moderate	University of Zurich	NCT04400799
(1) ChAdOx1 nCoV-19 vaccine *vs* (2) MenACWY vaccine	10260	Healthy volunteers	University of Oxford	NCT04400838
(1) Chloroquine *vs* (2) Lopinavir + ritonavir	112	No restriction on type of patients	The Fifth Affiliated Hospital Sun Yat-Sen University	ChiCTR2000029741
(1) Resveratrol + Vitamin D3 *vs* (2) Vitamin D3	200	Mild/moderate	Marvin McCreary, MD	NCT04400890
(1) Sargramostim *vs* (2) Placebo	30	Moderate/severe	Singapore General Hospital	NCT04400929
(1) Vitamin C *vs* (2) Placebo	800	Moderate/severe/critical	Universit© de Sherbrooke	NCT04401150
(1) Enoxaparin *vs* (2) Enoxaparin	308	Moderate/severe	Northwell Health	NCT04401293
(1) Angiotensin 1-7 *vs* (2) Placebo	100	Moderate/severe	Columbia University	NCT04401423
(1) EB05 *vs* (2) Placebo	865	Severe/critical	Edesa Biotech Inc.	NCT04401475
(1) Sodium Nitrite *vs* (2) Placebo	200	Critical	Hope Pharmaceuticals	NCT04401527
(1) Remdesivir + baricitinib *vs* (2) Remdesivir	1032	Moderate/severe/critical	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04401579
(1) APL-9 *vs* (2) Placebo	66	Severe/critical	Apellis Pharmaceuticals, Inc.	NCT04402060
(1) Favipiravir *vs* (2) Standard of care	50	Mild/moderate	Bangladesh Medical Research Council (BMRC)	NCT04402203
(1) Hydroxychloroquine *vs* (2) Standard of care	78	Mild/moderate	The First Hospital of Peking University	ChiCTR2000029740
(1) TD-0903 *vs* (2) Placebo	159	Moderate/severe	Theravance Biopharma	NCT04402866
(1) Prone positioning *vs* (2) Standard of care	596	Moderate/severe	University of Calgary	NCT04402879
(1) Dornase alfa *vs* (2) Placebo	60	Critical	Boston Children©s Hospital	NCT04402944
(1) Brensocatib *vs* (2) Placebo	300	Moderate/severe	University of Dundee	ISRCTN30564012
(1) Ivermectin *vs* (2) Ivermectin *vs* (3) Placebo	45	No restriction on type of patients	Lagos University Teaching Hospital	ISRCTN40302986
(1) CIGB 300 *vs* (2) Standard of care	20	Severe/critical	Center for Genetic Engineering and	RPCEC00000317

▼ Disease severity



▼ Type of pharmacological treatment

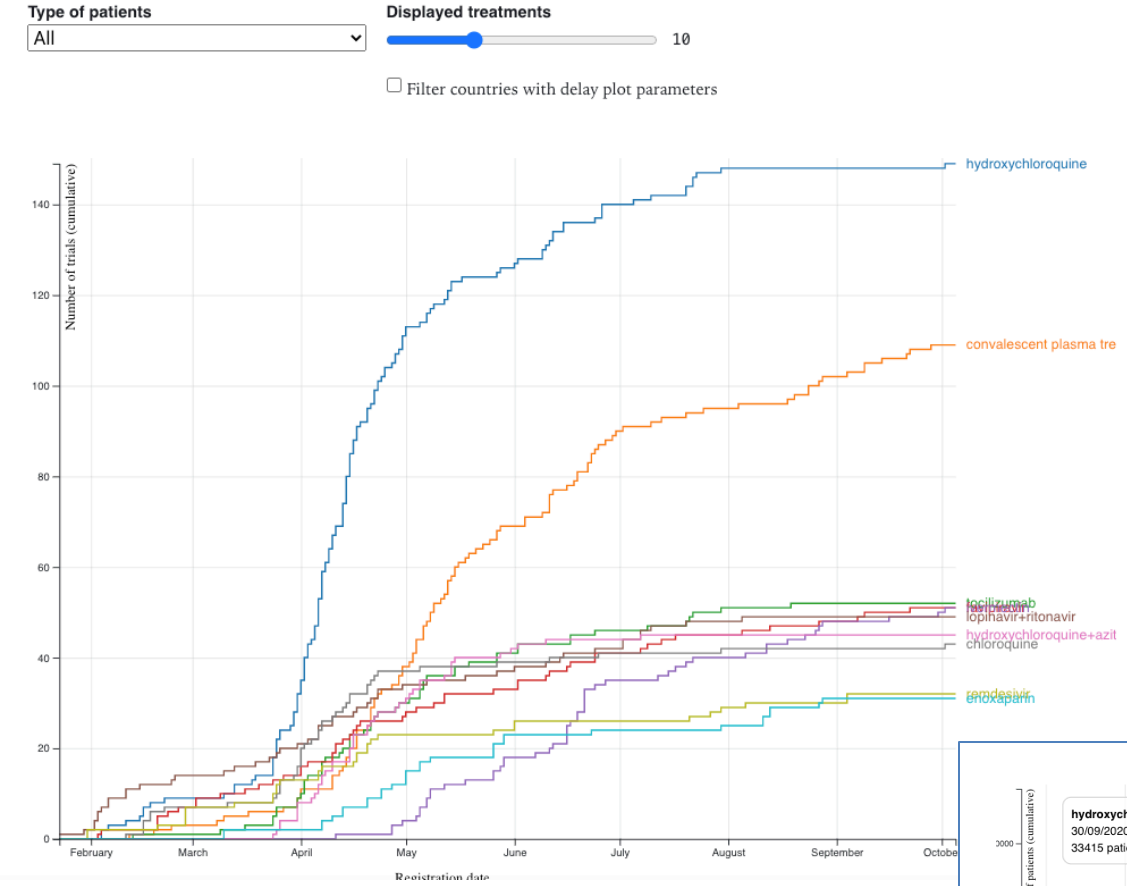


▼ Publication status

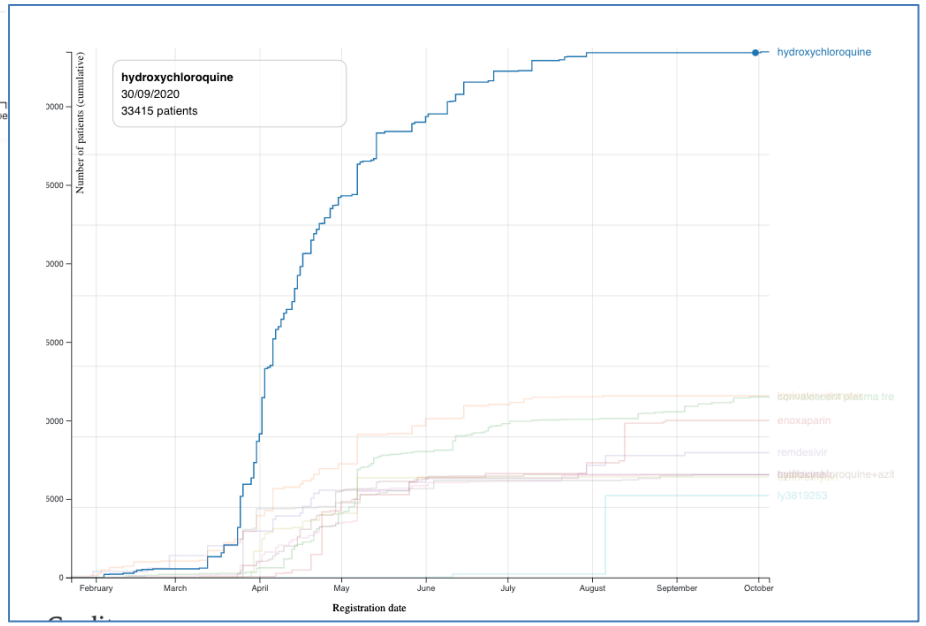
- [x] Not published (1,815 studies)
- [x] Published (90 studies)

VISUALISATIONS: Romain Vuillemot - LIRIS, École Centrale de Lyon; Philippe Rivière - LIRIS, VisionsCarto; Pierre Ripoll - LIRIS, INSA Lyon; Julien Barnier - Centre Max Weber, CNRS.

Living mapping



VISUALISATIONS: Romain Vuillemot - LIRIS, École Centrale de Lyon; Philippe Rivière - LIRIS, VisionsCarto; Pierre Ripoll - LIRIS, INSA Lyon; Julien Barnier - Centre Max Weber, CNRS.



Nguyen V et al. J Clin Epidemiol accepted

All data available on a platform covid-nma.com

92 RCTS

TREATMENT COMPARISONS

We report below the forest plots for the main treatment comparisons.

Please choose a Treatment Comparison type then a Treatment Comparison:

Anti-virals (30 comparisons)

Other antimicrobials (antibiotics, antimalarials, antiparasitics) (9 comparisons)

NSAIDs and Anti-inflammatories (2 comparisons)

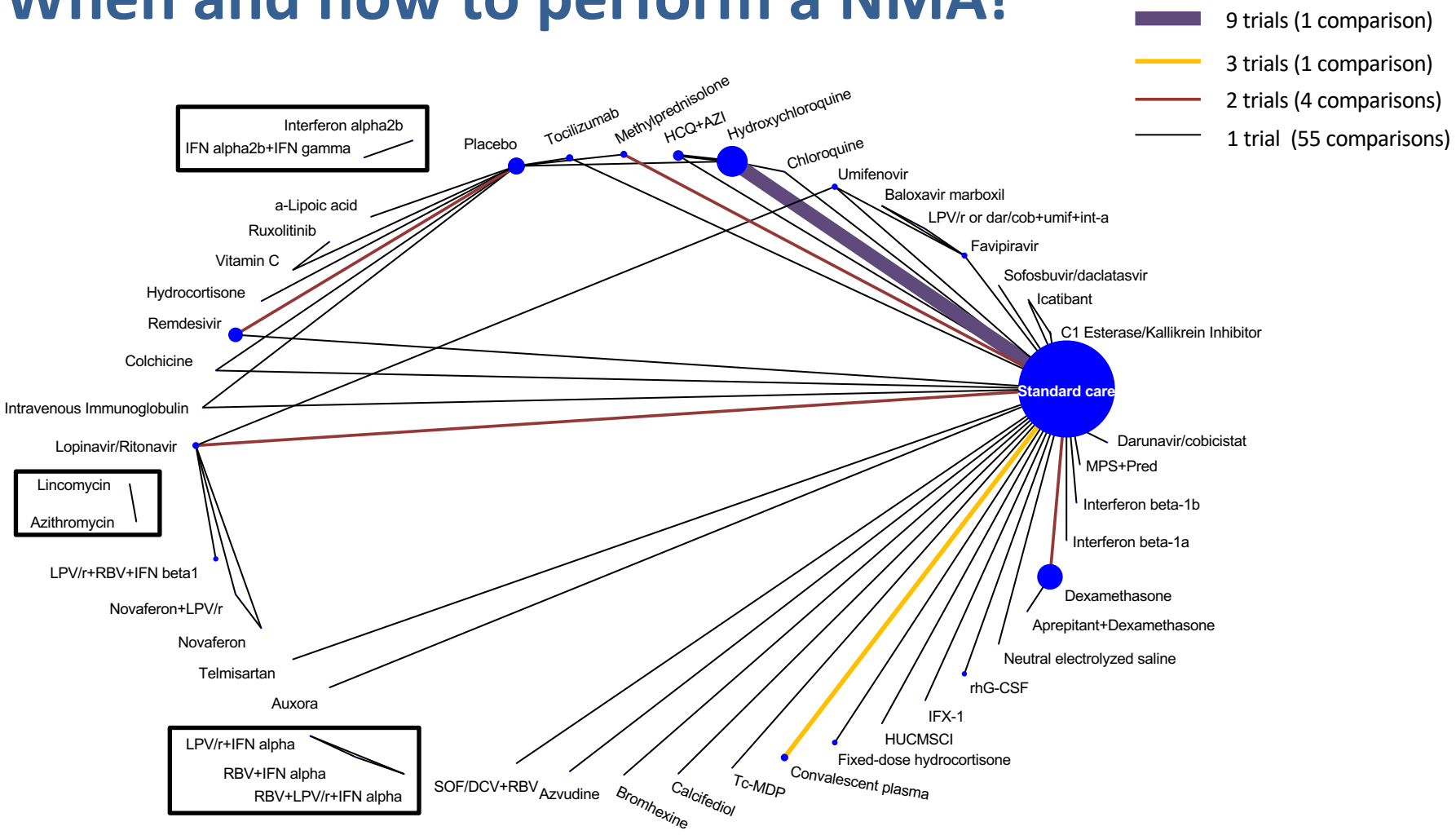
Kinase inhibitor (2 comparisons)

Corticosteroids (2 comparisons)

Monoclonal antibodies (5 comparisons)

- Favipiravir vs Favipiravir+Tocilizumab new (1 RCTs)
- Favipiravir vs Tocilizumab new (1 RCTs)
- IFX-1 vs Standard care (1 RCTs)
- Tocilizumab vs Standard care/Placebo update (2 RCTs)
- Tocilizumab vs Favipiravir+Tocilizumab new (1 RCTs)

When and how to perform a NMA?



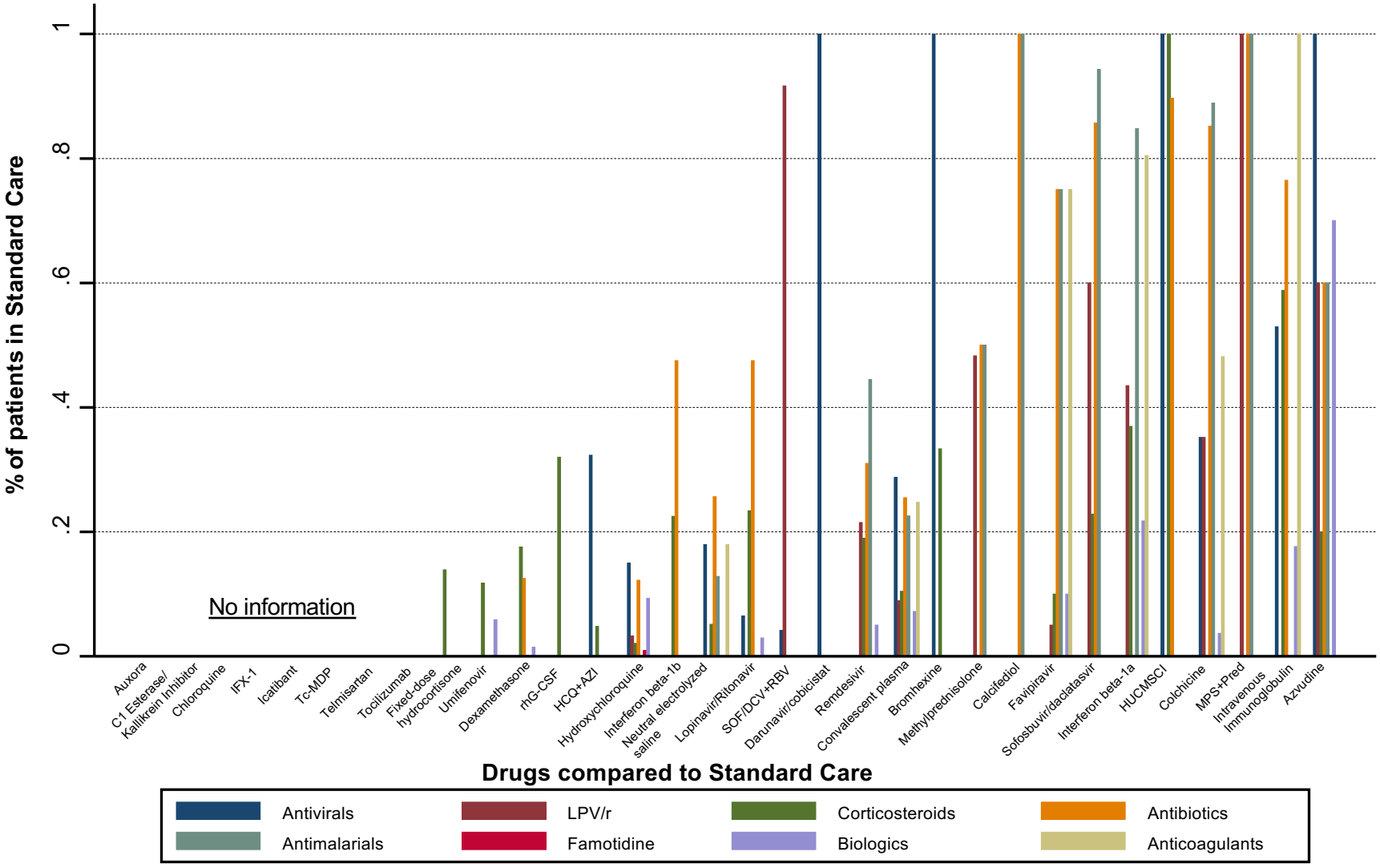
Very few studies per comparison

Transitivity assumption cannot be evaluated

It requires distribution of effect modifiers to be similar across comparisons

With 1-2 studies we cannot obtain any distribution

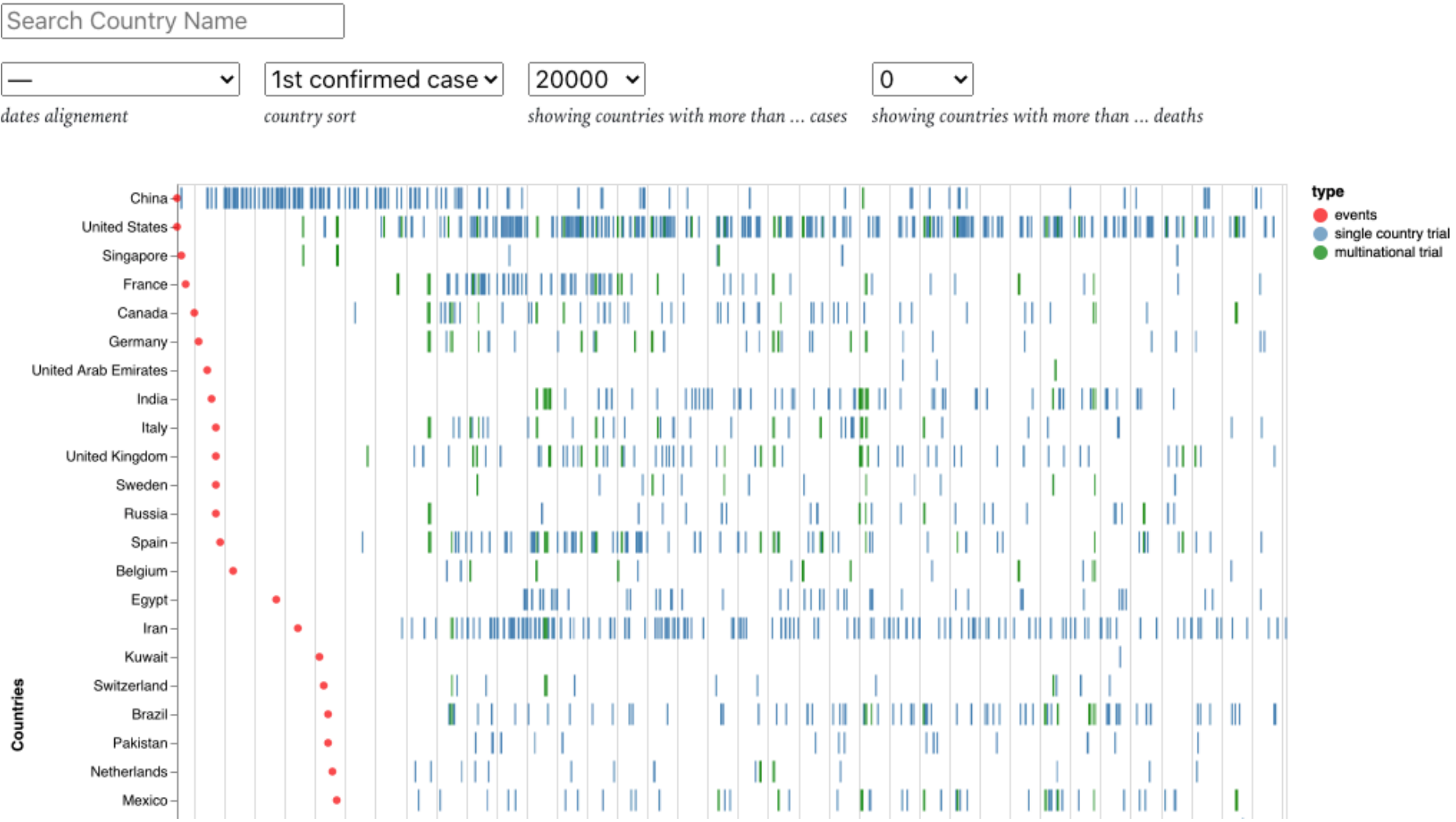
Definition of Standard of care



Living monitoring/feedback

- **Monitoring**
  - Quality indicators (risk of bias, outcomes)
  - Transparency indicators
    - Completeness of reporting
    - Access to protocol, statistical analysis plan, CSR
    - Posting data on registry
    - Data sharing (intended and realized)

- **Feedback loop**
  - Individual results
  - Aggregated results
  - automatic e-mails to investigators of completed trials to encourage them to post results on registries



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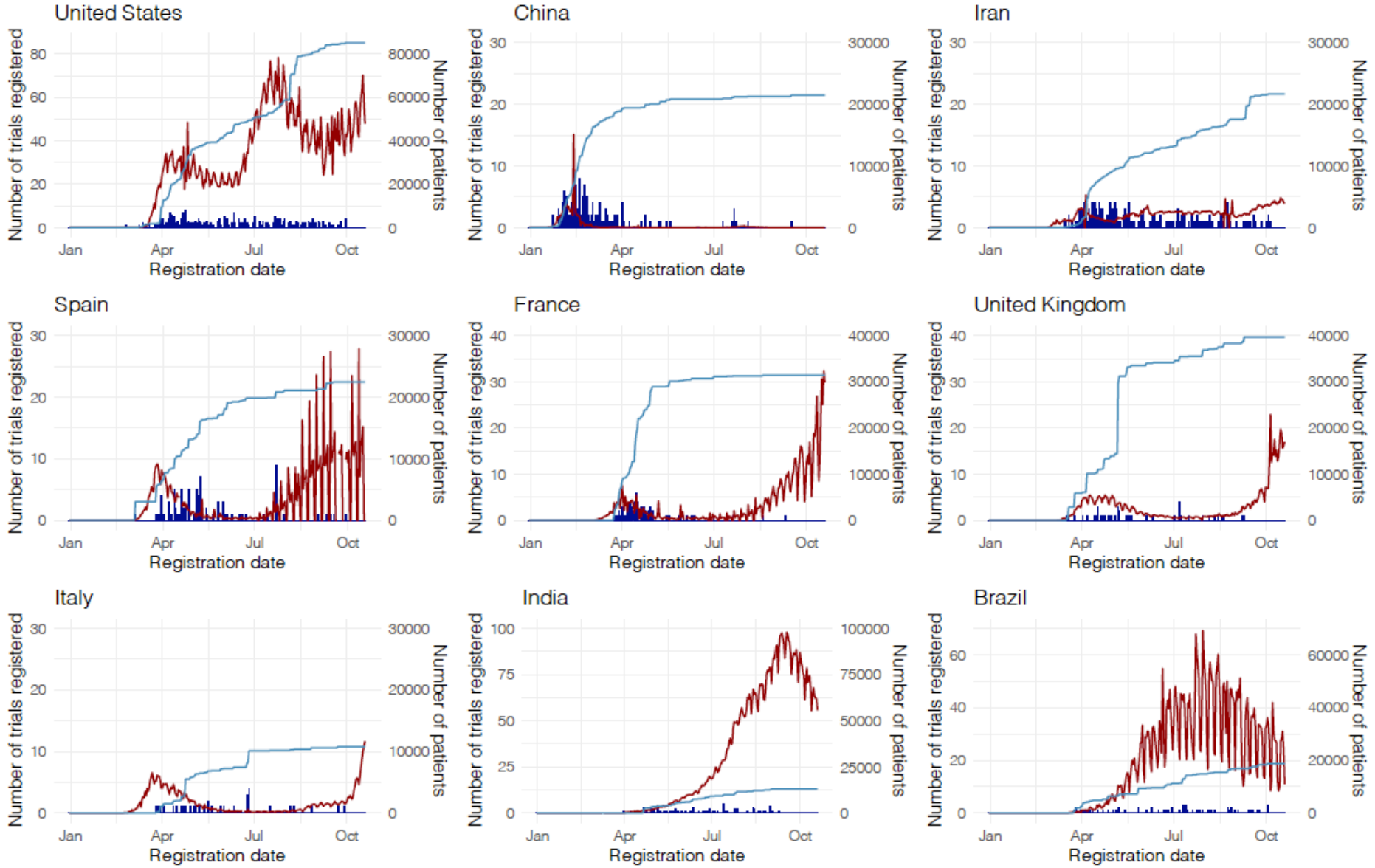


Nguyen V et al. J Clin Epidemiol accepted

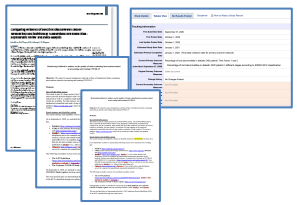
Platform extraction données

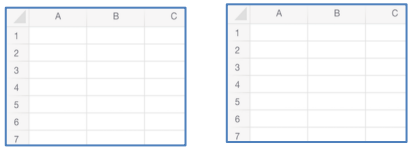
Form to request for missing data

Data source

Double data extraction

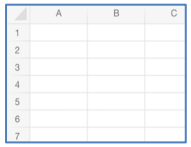
Publication /Protocol/SAP/ registres/CSR





Automatic identification of discrepancies

Consensus + Quality control



Online

Update database

Preprint updates

Contact authors

External quality control

Analysis (forest plot)

Synthesis (SOF)

Context

- Difficult decisions have to be made every day to overcome this pandemic.
- Thousands of randomized controlled trials (RCTs) have been initiated during the pandemic.
- Their results are frequently rushed to publication or communicated through non–peer-reviewed preprints.

Workplan

- Implementation of the request for IPD and living quality control

- Synthesis with interpretation

Screening

- Large search strategy
  - PubMed, Medarxiv etc
  - Manual screening every day
  - > 45,000 records screened up to now

- Reduction of the workload
  - L-OVE platform
  - Cochrane COVID trial registry

Flexibility of the protocol

- Study design
- Research question
- Search strategy
- Source of evidence
- Type of evidence