From an evidence synthesis ecosystem to a new evidence ecosystem

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Evidence synthesis

« *The ultimate goal of systematic reviews and meta-analysis is to create an effective marketplace for synthesis in which policy-makers (..)always seek the best evidence because they know it will be available, and researchers synthesize evidence because they know it will make a difference.* » (C A. Donnelly, Nature 2018)

The current evidence synthesis ecosystem does not fulfil this goal.

Mass production of systematic reviews and meta-analyses

- Low quality
- Redundant
- Not covering all evidence
- Delay in producing the review (2-3 years)
- Rarely updated
- Rely on primary evidence of low quality

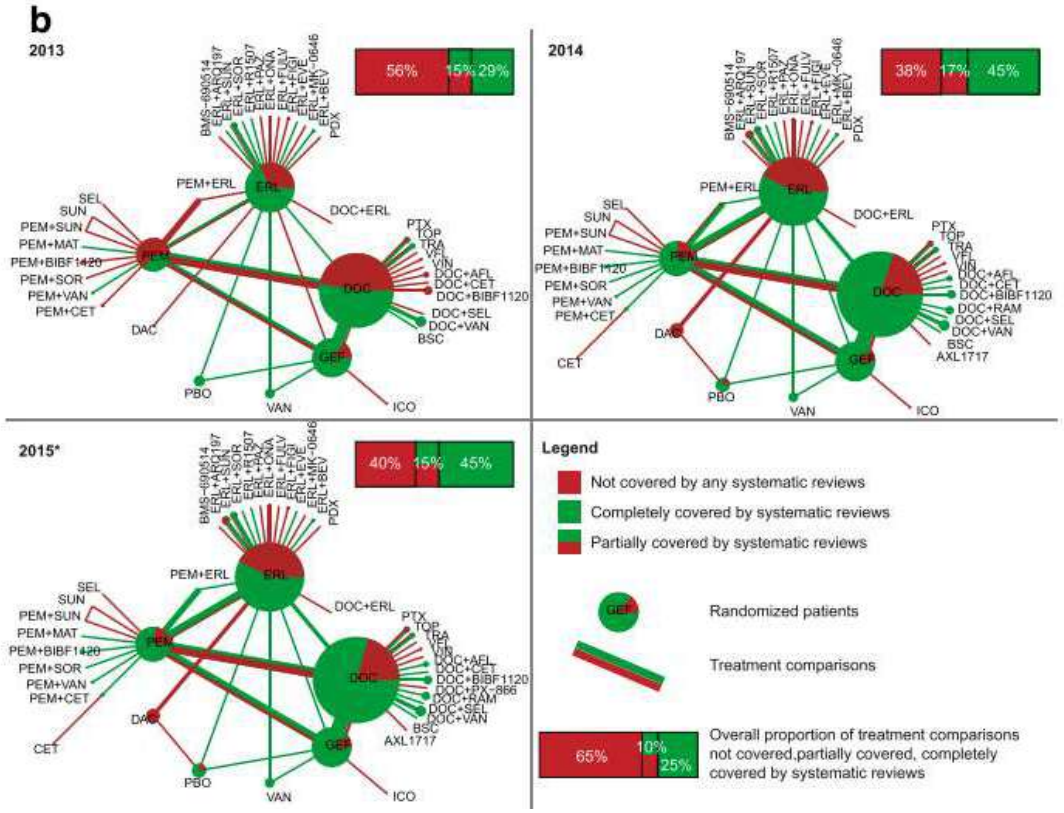
Créquit et al. BMC Medicine (2016) 14:8
DOI 10.1186/s12916-016-0555-0

BMC Medicine

RESEARCH ARTICLE Open Access

Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer

Perrine Créquit[1,2†], Ludovic Trinquart[1,2,3,4*†], Amélie Yavchitz[1,2,3] and Philippe Ravaud[1,2,3,4,5]



- From 2009 to 2015 the evidence covered by existing systematic reviews was consistently incomplete and did not consider
  - 45 % to 70 % of trials;
  - 30 % to 58 % of patients;
  - 40 % to 66 % of treatments;
  - 38 % to 71 % of comparisons

Avoidable waste of research related to inadequate methods in clinical trials

Youri Yordanov,[1, 2] Agnes Dechartres,[1, 3, 4] Raphaël Porcher,[1, 3, 4] Isabelle Boutron,[1, 3, 4, 5]
Douglas G Altman,[6] Philippe Ravaud[1, 3, 4, 5, 7]

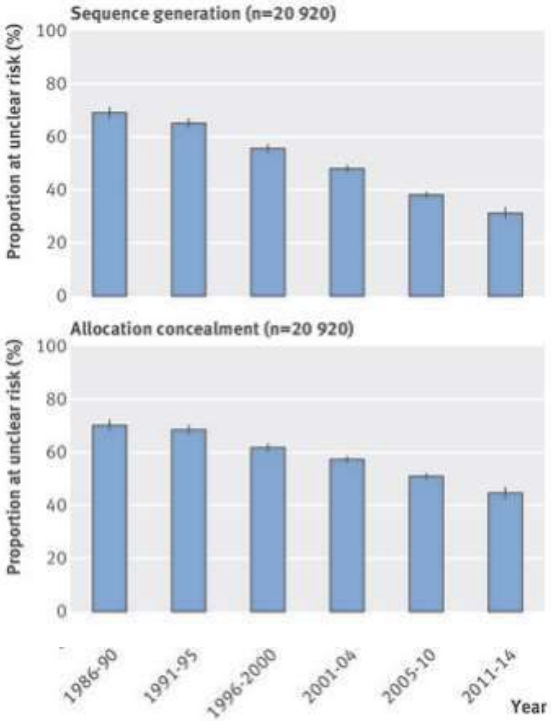
- 1286 trials included in 205 méta-analyses of Cochrane reviews
- 43% were at high risk of bias

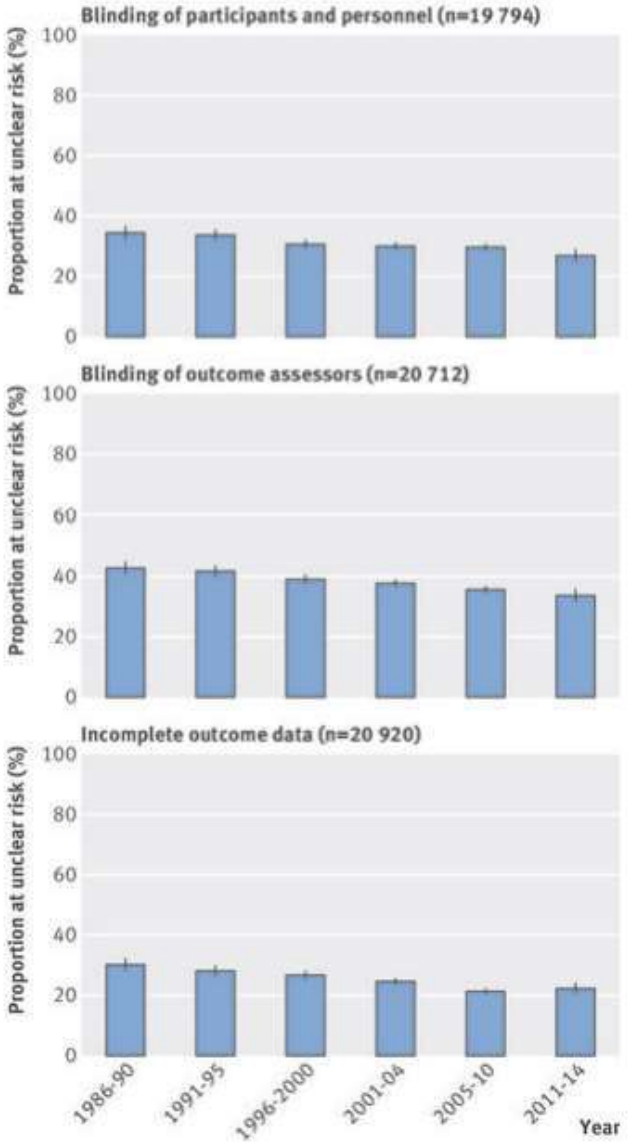
thebmj

RESEARCH

Evolution of poor reporting and inadequate methods over time in 20 920 randomised controlled trials included in Cochrane reviews: research on research study

Agnes Dechartres *associate professor*[1 4], Ludovic Trinquart *researcher*[1 4], Ignacio Atal *data scientist*[1 4], David Moher *senior scientist*[5], Kay Dickersin *professor*[6], Isabelle Boutron *professor*[1 4], Elodie Perrodeau *statistician*[1 3], Douglas G Altman *professor*[7], Philippe Ravaud *professor*[1 4 8]





Yordanov et al. BMC Medicine (2018) 16:87
https://doi.org/10.1186/s12916-018-1083-x

BMC Medicine

RESEARCH ARTICLE Open Access

Avoidable waste of research related to outcome planning and reporting in clinical trials

Youri Yordanov[1,2,3,4*], Agnes Dechartres[1,4,5,6], Ignacio Atal[1,4], Viet-Thi Tran[1,4], Isabelle Boutron[1,4,5,6], Perrine Crequit[1,4] and Philippe Ravaud[1,4,5,6,7]

- 2711 trials included in 290 systematic reviews
  - 78% trials excluded from at least one meta-analysis on critical outcome

- Each trial contribute to an average of 55% meta-analyses of critical outcomes

Opportunities and challenges

- Access to new source of data
  - Preprint, clinical trial registries, protocols, and clinical study reports from regulatory agencies or pharmaceutical companies
- Access to new types of data
  - IPD
  - Non randomized studies of routinely collected data (rich data, new design such as emulated trials, new statistical methods)
- New technology
  - AI tools, Large language models

Toward a new research ecosystem

Boutron, Crequit (….), Ravaud. J Clin Epidemiol 2020
Crequit, Boutron (…) Ravaud J Clin Epidemiol 2020
Ravaud, Crequit (…) Boutron. J Clin Epidemiol 2020

From meta-analysis to living meta-analysis to living network meta-analysis

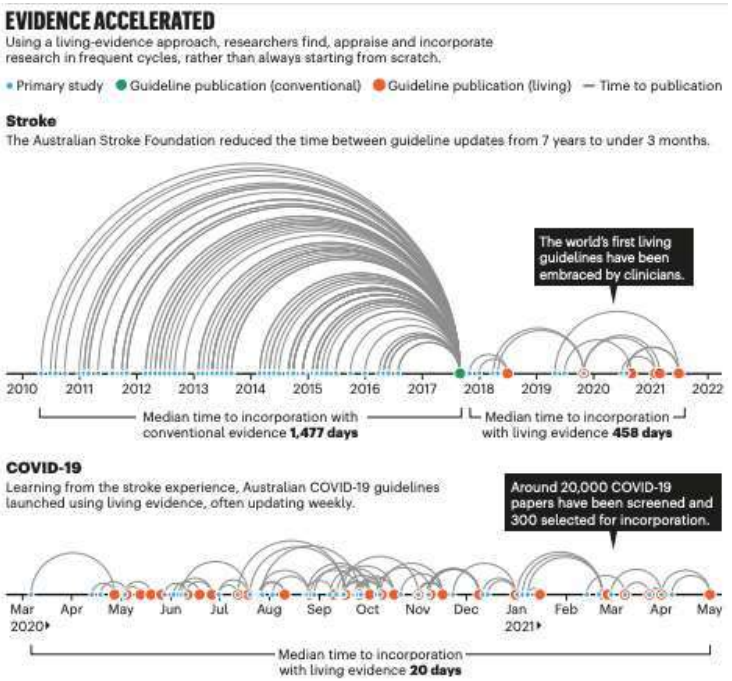
Decision makers need 'living' evidence synthesis

Julian H. Elliott, Rebecca Lawrence, Jan C. Minx, Olufemi T. Oladapo, Philippe Ravaud, Britta Tendal Jeppesen, James Thomas, Tari Turner, Per Olav Vandvik & Jeremy M. Grimshaw

Fund and use dynamic evidence summaries of the latest data to steer research, practice and policy.

Council, worried that the cacophony would create confusion and anxiety among already-stressed clinicians. We argued for key bodies to come together quickly and use robust, evidence-based processes to find signals in the

the evidence pipeline[3]. Take the example of remdesivir, an intravenous treatment originally developed for Ebola virus. In May 2020, weak but promising data suggested it could be used to treat COVID-19. Over the next 18 months,



Toward a new research ecosystem relying on a culture of continuous improvement

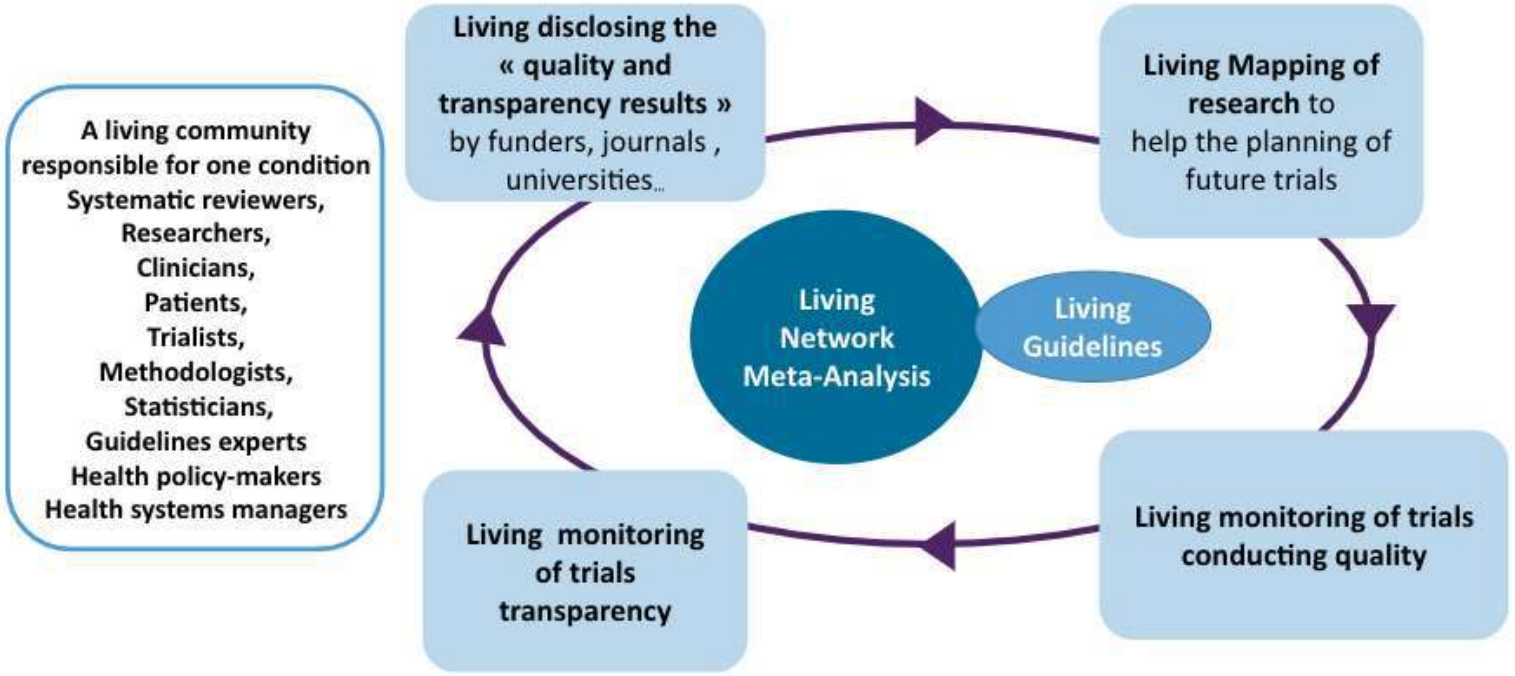
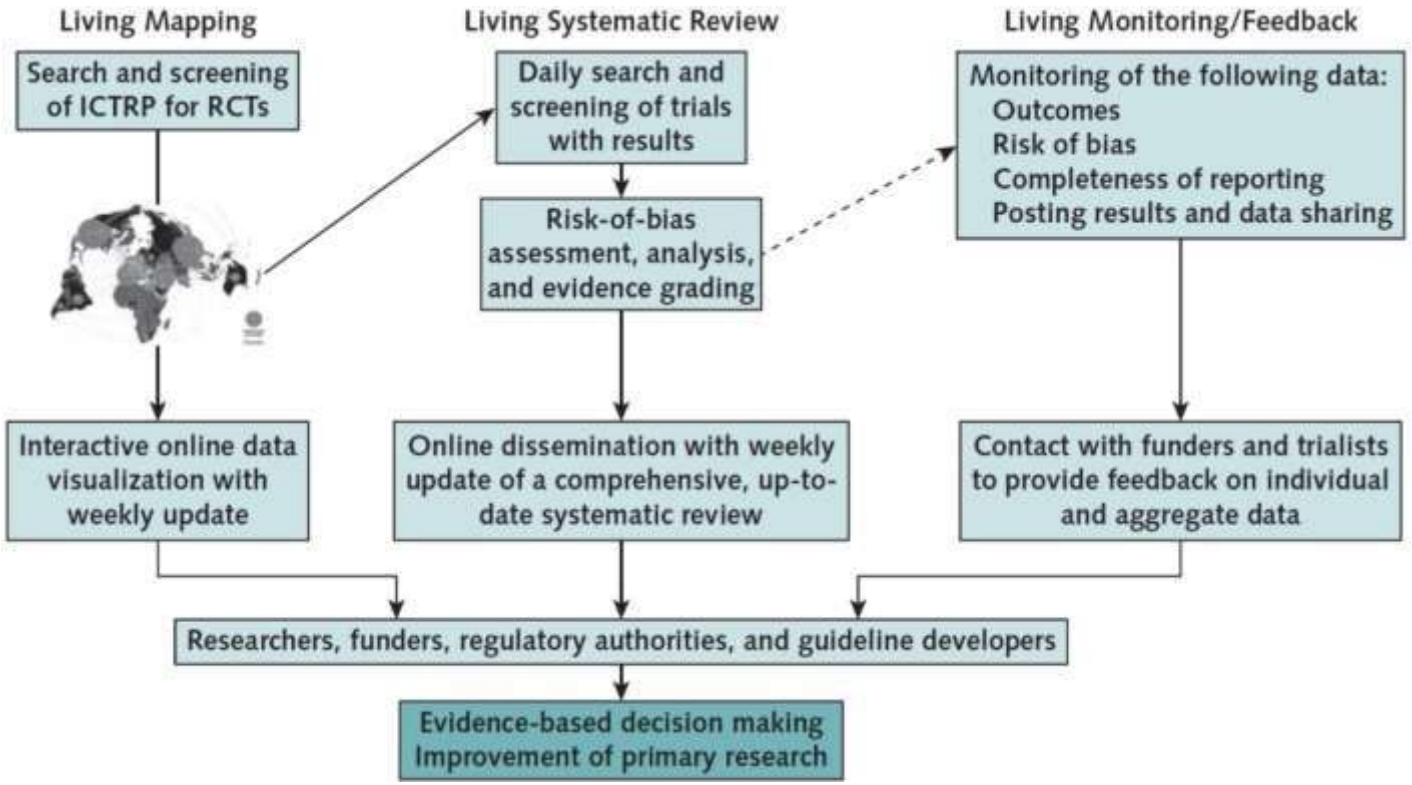


Fig. 1. Developing a culture of continuous improvement of clinical research for a specific disease.

Annals of Internal Medicine

The COVID-NMA Project: Building an Evidence Ecosystem for the COVID-19 Pandemic

Isabelle Boutron, MD, PhD; Anna Chaimani, PhD; Joerg J. Meerpohl, MD; Asbjørn Hróbjartsson, MD, PhD, MPhil; Declan Devane, PhD; Gabriel Rada, MD; David Tovey, MBChB; Giacomo Grasselli, MD; and Philippe Ravaud, MD, PhD, for the COVID-NMA Consortium*



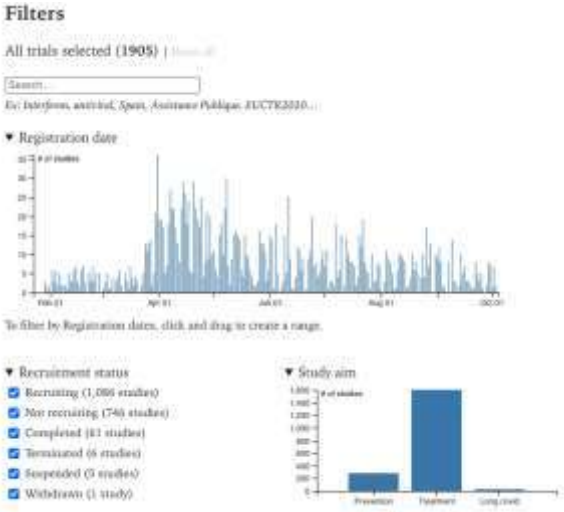
Boutron, …, Ravaud. Annals Internal Med 2020

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.

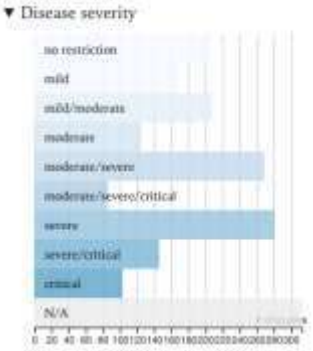
LIVING MAPPING

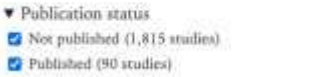


▼ Table

Show full table

Treatment (per arm)	Sample size		Severity at enrollment	Funding	Reg. number
(1) Umifenovir vs (2) Umifenovir + interferon alpha		700	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	NCT04401579
(1) Tocilizumab vs (2) Standard of care		100	Severe/critical	Beneficência Portuguesa de São Paulo	NCT04412603
(1) Placebo vs (2) Placebo		358	Severe	CTI BioPharma	NCT04409261
(1) L-citrulline vs (2) Placebo		100	Critical	Rennes University Hospital	NCT04429438
(1) mRNA-1273 vs (2) mRNA-1273		600	Healthy volunteers	ModernaTX, Inc.	NCT04405076
(1) Ozanimod vs (2) Standard of care		44	Moderate/severe	Fran?ois Lalouche	NCT04405102
(1) Emtricitabine + tenofovir vs (2) Placebo		1378	Health workers	Hospital Italiano de Buenos Aires	NCT04403271
(1) Budesonide + formoterol vs (2) Placebo		600	Severe	Stanford University	NCT04416678
(1) Enoxaparin vs (2) Standard of care		1000	Moderate	University of Zurich	NCT04401709
(1) ChAdOx1-nCoV-19 vaccine vs (2) MenACWY vaccine		10260	Healthy volunteers	University of Oxford	NCT04324606
(1) Chloroquine vs (2) Lopinavir + ritonavir		112	No restriction on type of patients	The Fifth Affiliated Hospital Sun Yat-Sen University	ChiCTR2000029781
(1) Resveratrol + Vitamin D3 vs (2) Vitamin D3		200	Mild/moderate	Marvin McCreary, MD	NCT04403854
(1) Sargramostim vs (2) Placebo		30	Moderate/severe	Singapore General Hospital	NCT04403529
(1) Vitamin C vs (2) Placebo		800	Moderate/severe/critical	Université de Sherbrooke	NCT04401150
(1) Enoxaparin vs (2) Enoxaparin		208	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	Ebera Biotech Inc.	NCT04401478
(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		96	Severe/critical	4Joints Pharmaceuticals, Inc.	NCT04402060
(1) Favipiravir vs (2) Standard of care		50	Mild/moderate	Bangladesh Medical Research Council (BMRC)	NCT04402202
(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	NCT04402678
(1) Dornase alfa vs (2) Placebo		60	Critical	Boston Children's Hospital	NCT04402944
(1) Brensocatib vs (2) Placebo		200	Moderate/severe	University of Dundee	ISRCTN20984012
(1) Ivermectin vs (2) Ivermectin vs (3) Placebo		45	No restriction on type of patients	Lagos University Teaching Hospital	ISRCTN49302886
(1) CK06 300 vs (2) Standard of care		20	Severe/critical	Center for Genetic Engineering and	RPCEC00000317





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

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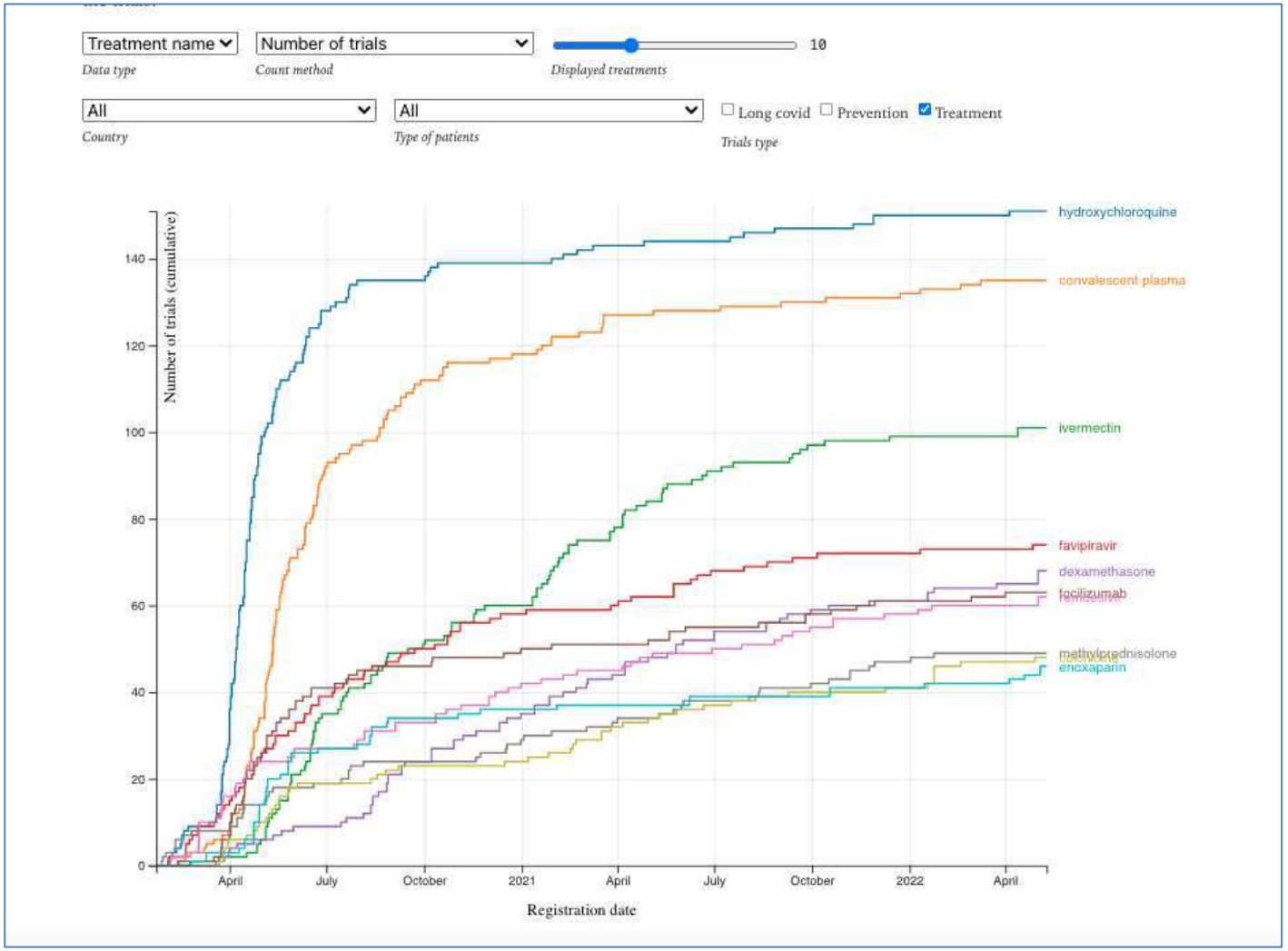
Living mapping



Nguyen V et al. J Clin Epidemiol 2021

Living review

https://covid-nma.com

WHO

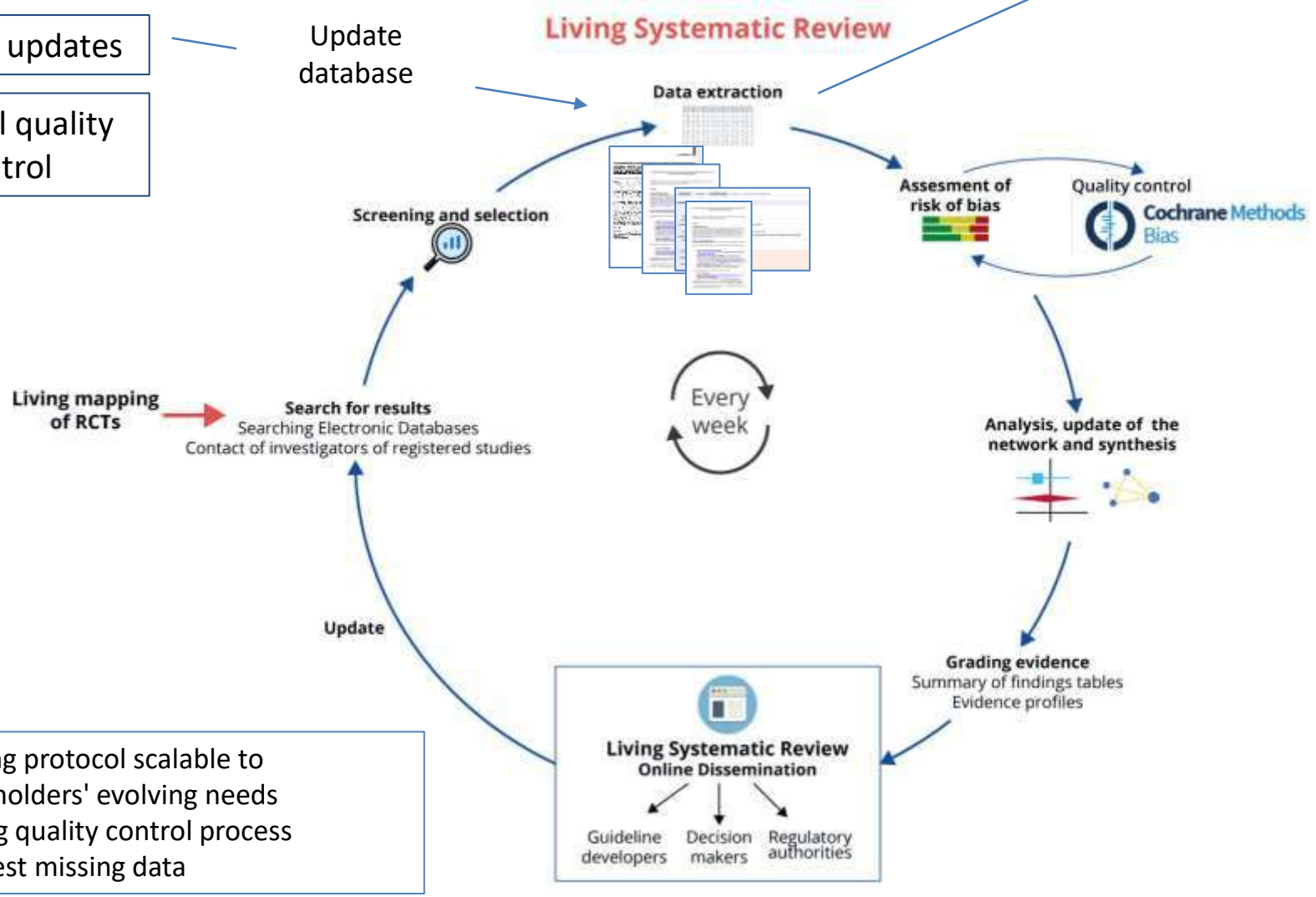
Form to request for missing data

Contact authors

Preprint updates

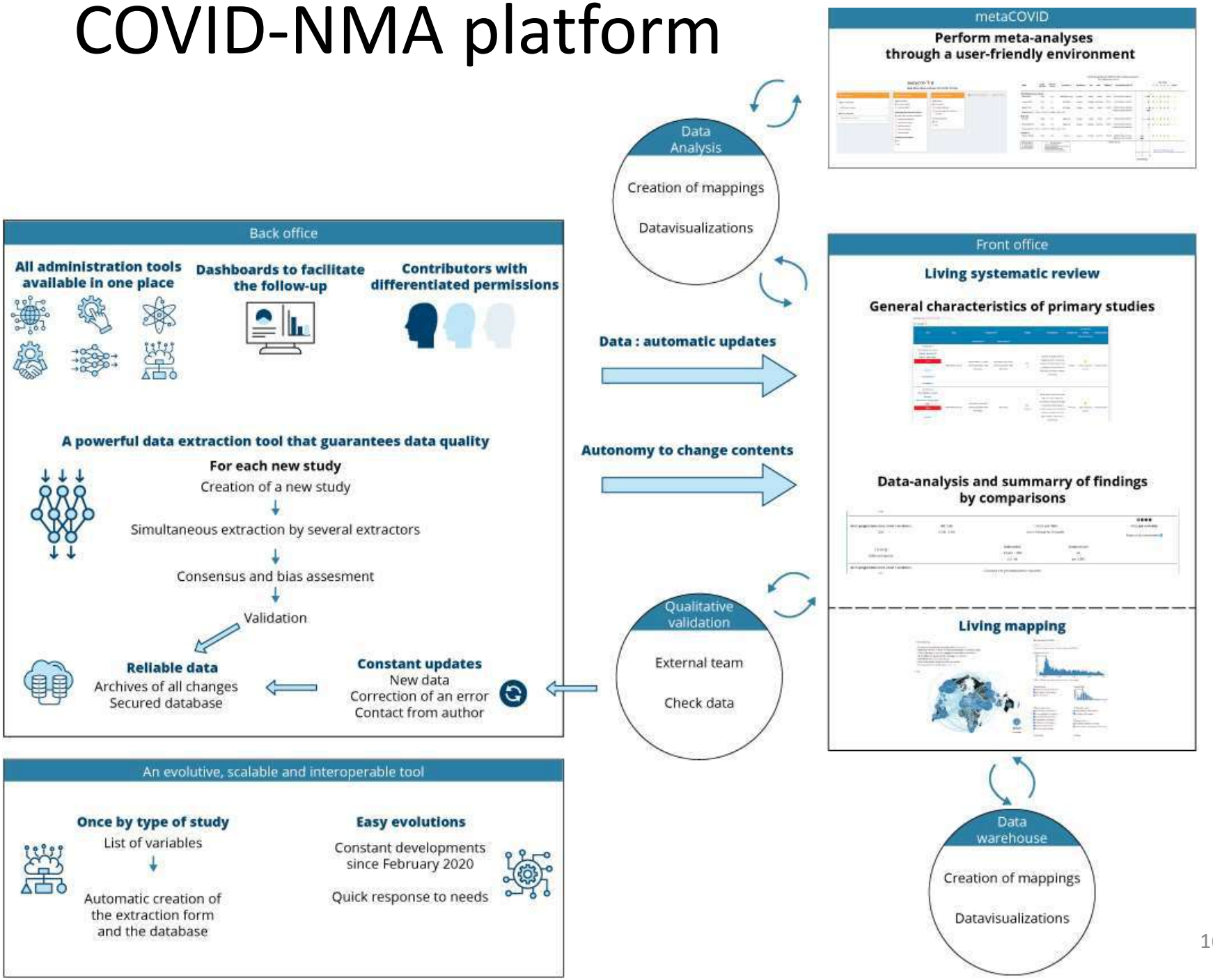
External quality control

Update database



- A living protocol scalable to stakeholders' evolving needs
- Strong quality control process
- Request missing data

COVID-NMA platform



Journal of Clinical Epidemiology 141 (2022) 46–53

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Secondary electronic sources demonstrated very good sensitivity for identifying studies evaluating interventions for COVID-19

Olivier Pierre[a,b,c], Carolina Riveros[a,b,c], Sarah Charpy[a,b,c], Isabelle Boutron[a,b,c,*]

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[b] *Clinical Epidemiology Unit, Hôtel-Dieu Hospital, Assistance Publique-Hôpitaux de Paris, (AP-HP), 75004, Paris, France*
[c] *Cochrane France, Hôtel-Dieu Hospital, 75004, Paris, France*

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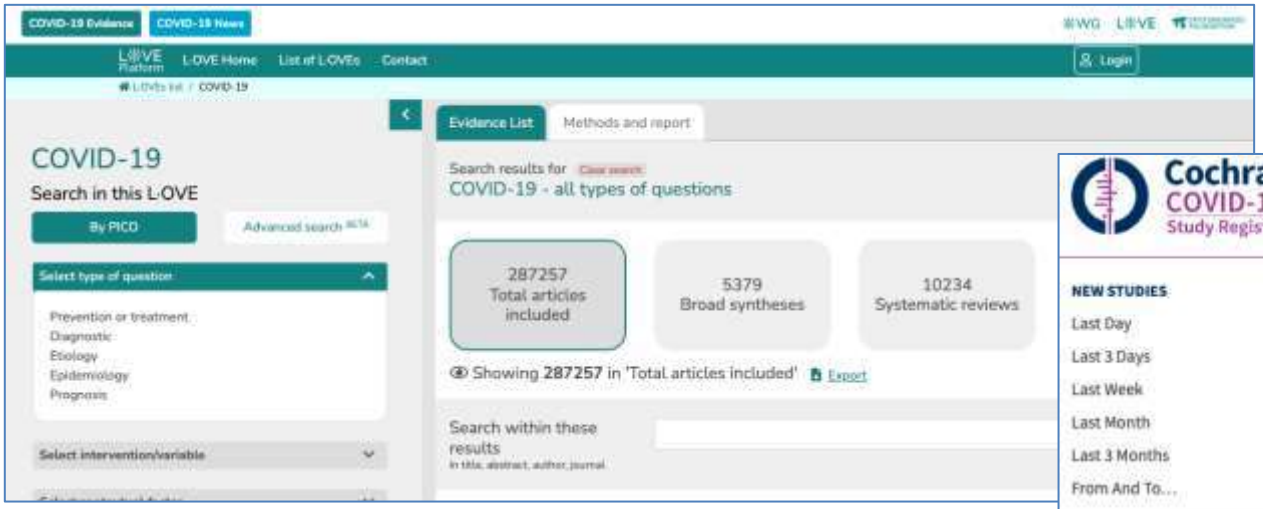

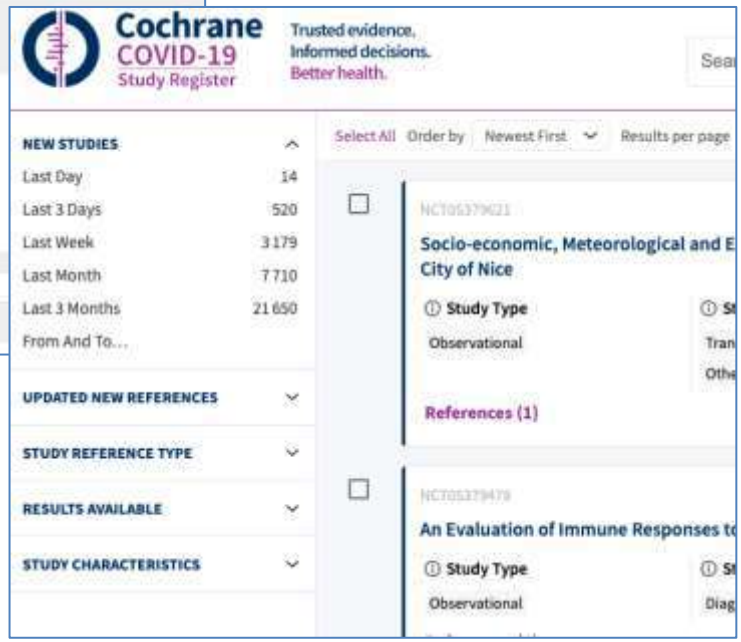

Scientometrics (2021) 126:5285–5304
https://doi.org/10.1007/s11192-021-03900-7

Day-to-day discovery of preprint–publication links

Guillaume Cabanac[1] · Theodora Oikonomidi[2] · Isabelle Boutron[2,3,4]

Received: 7 November 2020 / Accepted: 2 February 2021 / Published online: 18 April 2021
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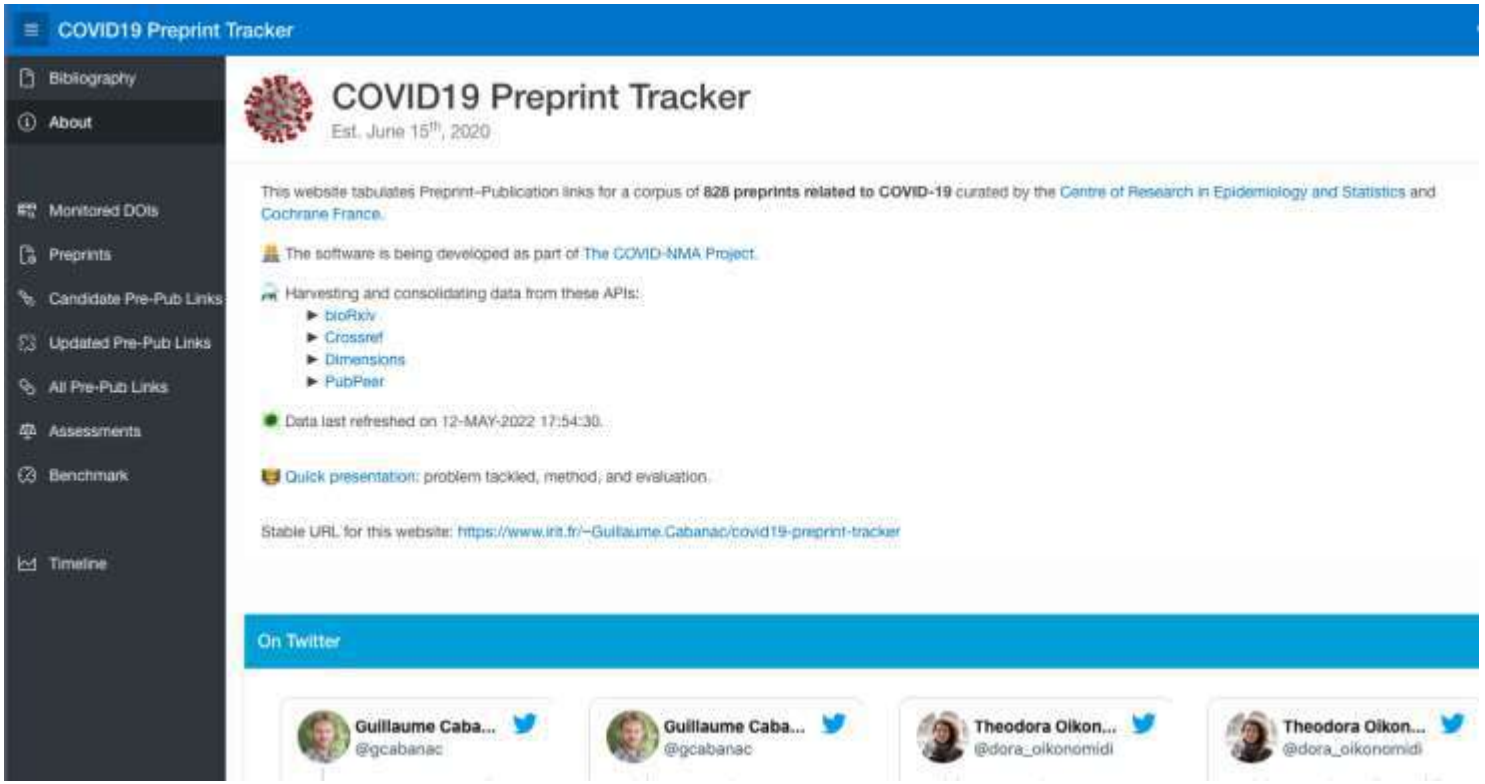
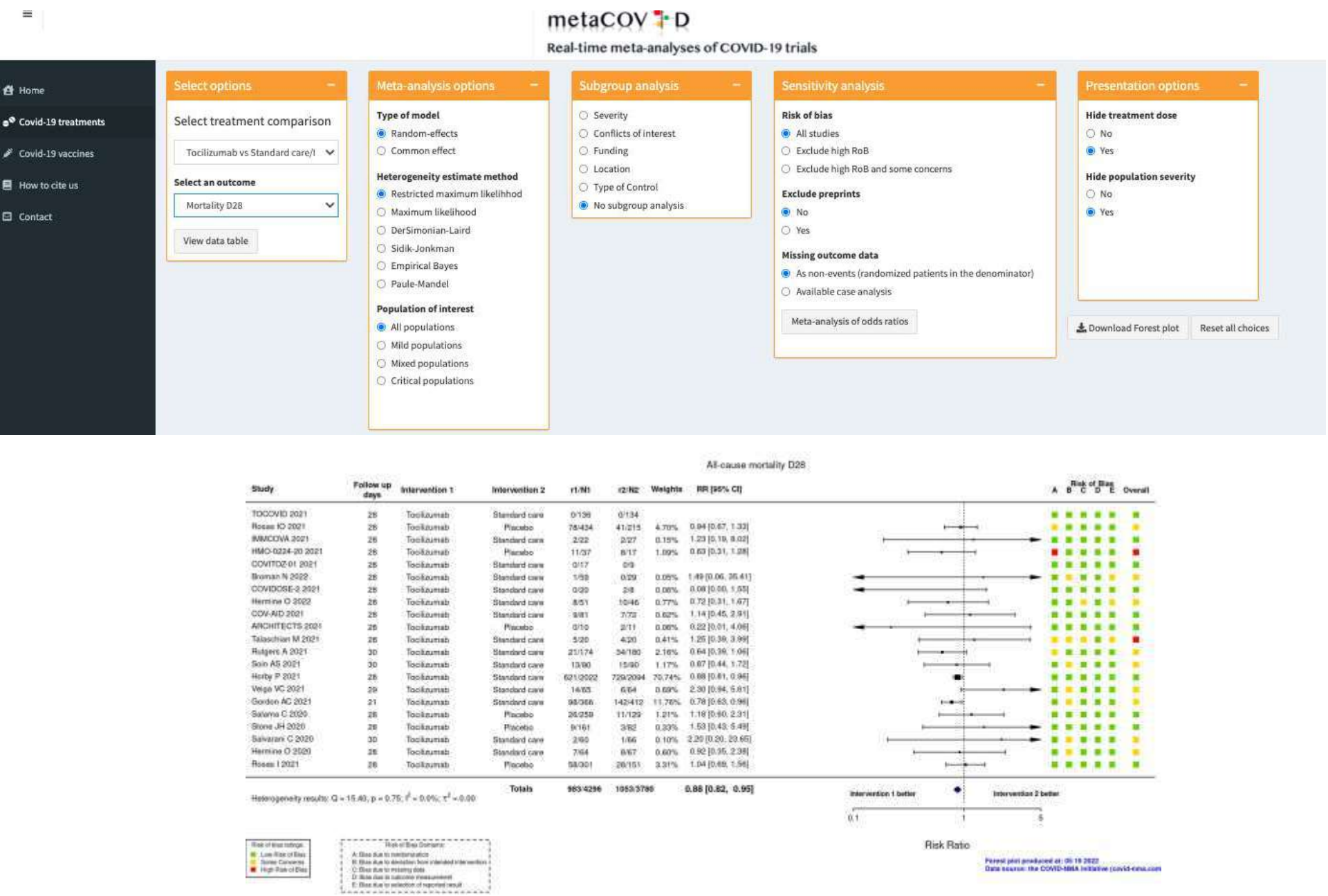




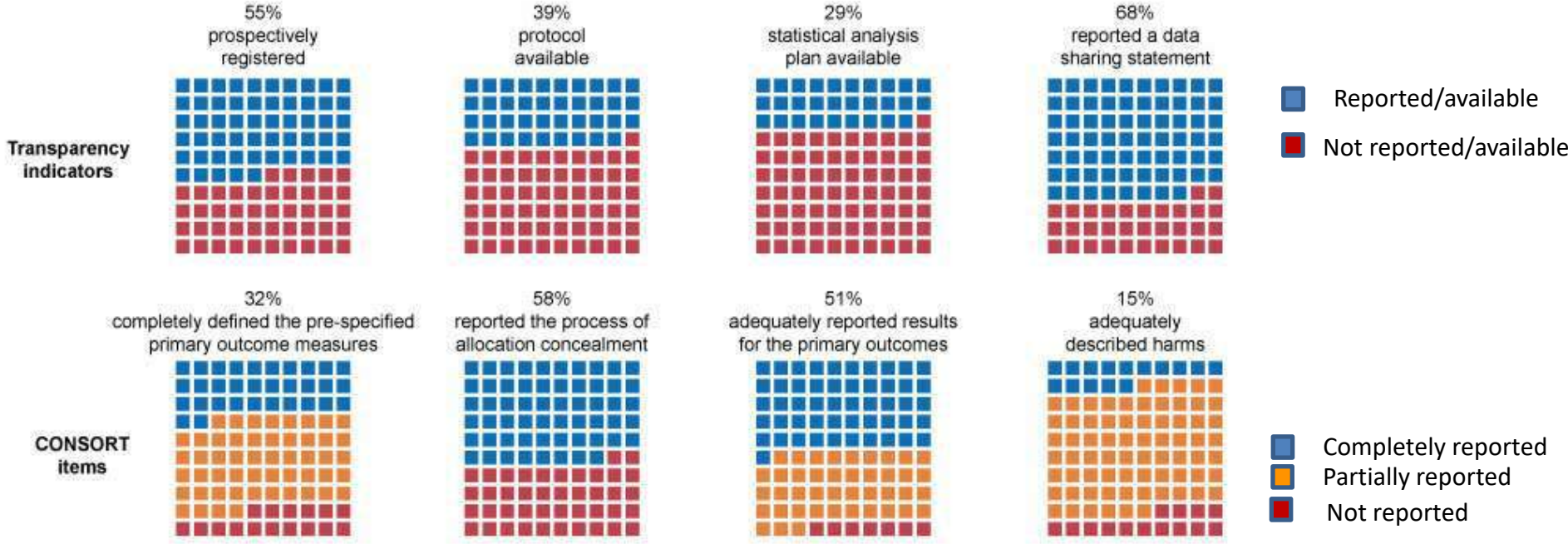
Evrenoglou T, Boutron I, Chaimani A, Res Synth Methods. 2023

Living monitoring/feedback

- **Monitoring /feedback**
  - Improving research planing
    - Contacting investigators to make sure they record all clinically relevant outcomes
  - Improving research transparency
    - Monitoring feedback

Montoring
COVID-19 randomised trials published in the first 17 months of the pandemic

244 trial reports



Kapp, Esmail, Ghosn, Ravaud, Boutron. BMC Med. 2022

Conclusion

- Novel approaches are needed to fulfil stakeholders' needs
- We cannot be satisfied with most our well conducted systematic reviews concluding '*evidence is of low quality, more research is needed*'
- Our role is also to avoid research waste and improve primary research
- We are in an ideal situation to actually improve primary research

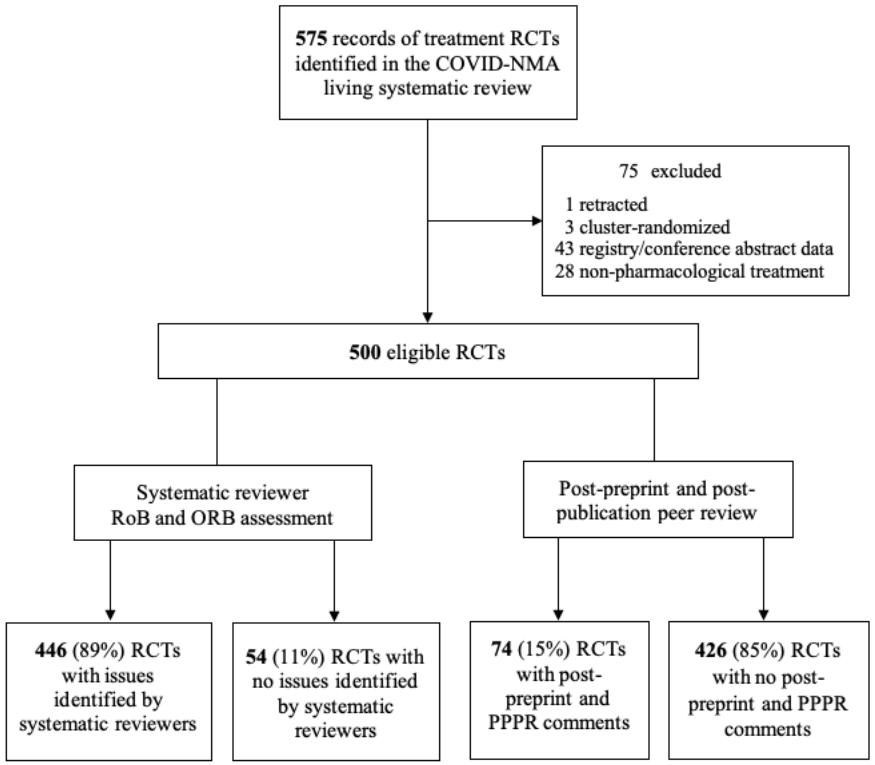


Figure 1: Flow chart of included RCTs

Sample: Randomized controlled trials (RCTs) evaluating pharmacological treatment for COVID-19 and

Data:

- Risk of bias and outcome reporting bias assessments conducted by systematic reviewers.
- Post-preprint/post-publication peer-review

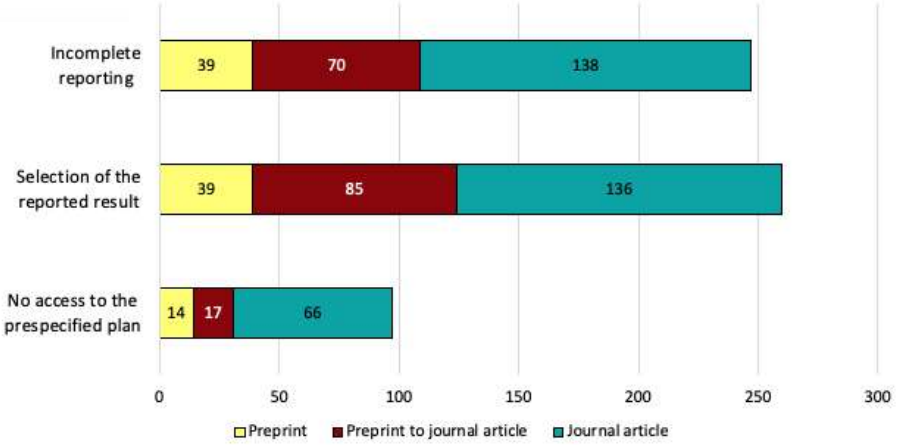


Figure 2: RCTs with resolvable issues identified by systematic reviewers (78%)