

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

RESEARCH ARTICLE

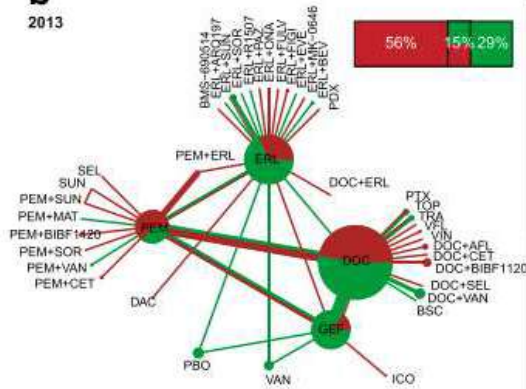
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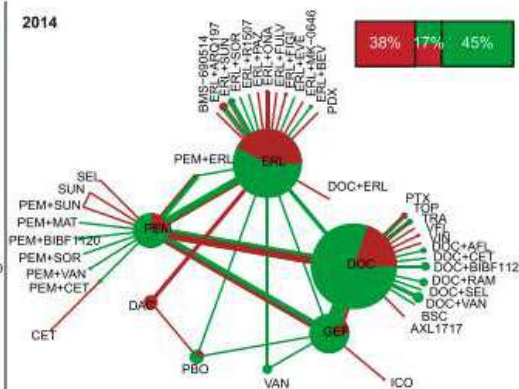
Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer

Perrine Créquit^{1,2†}, Ludovic Trinquart^{1,2,3,4*†}, Amélie Yavchitz^{1,2,3} and Philippe Ravaud^{1,2,3,4,5}

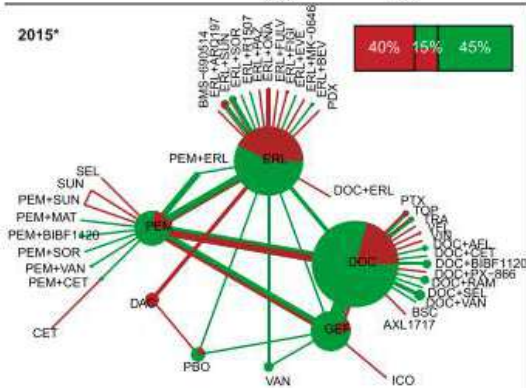
b
2013



2014



2015*



Legend

- Not covered by any systematic reviews
- Completely covered by systematic reviews
- Partially covered by systematic reviews



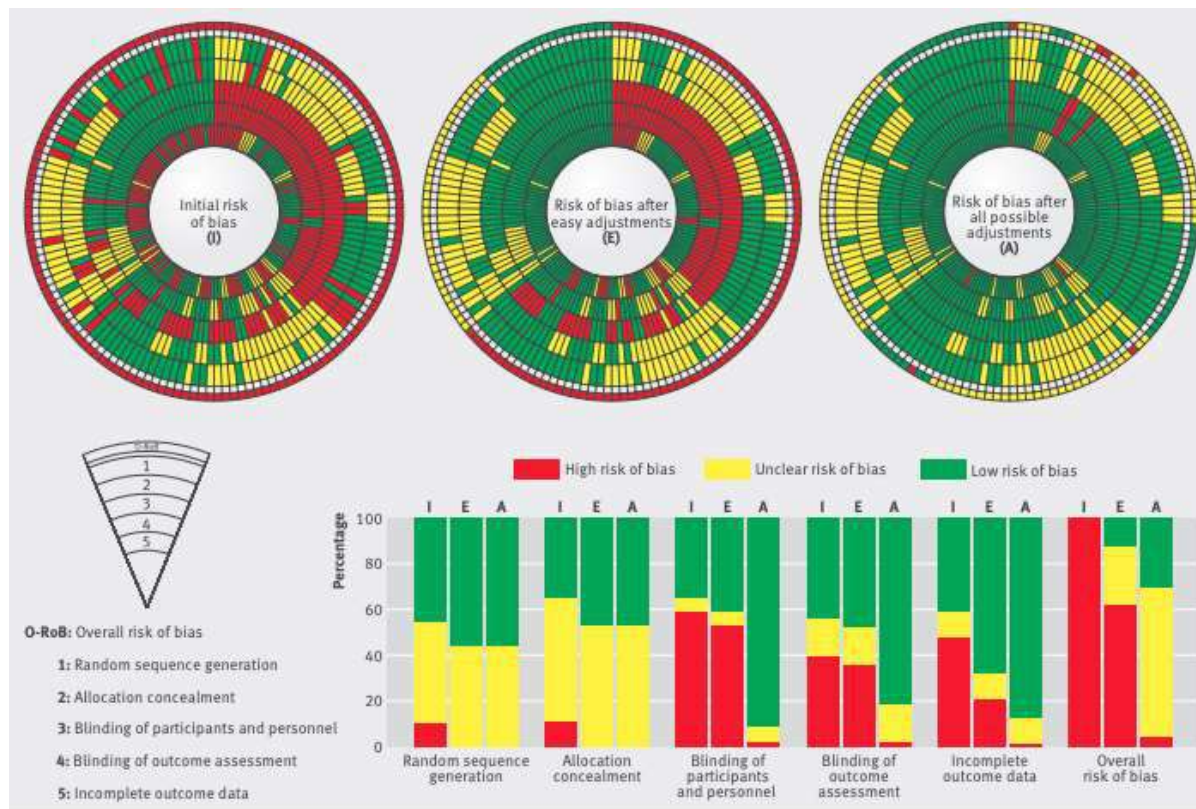
Overall proportion of treatment comparisons not covered, partially covered, completely covered by systematic reviews
 65% (red), 10% (green), 25% (red/green)

- 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

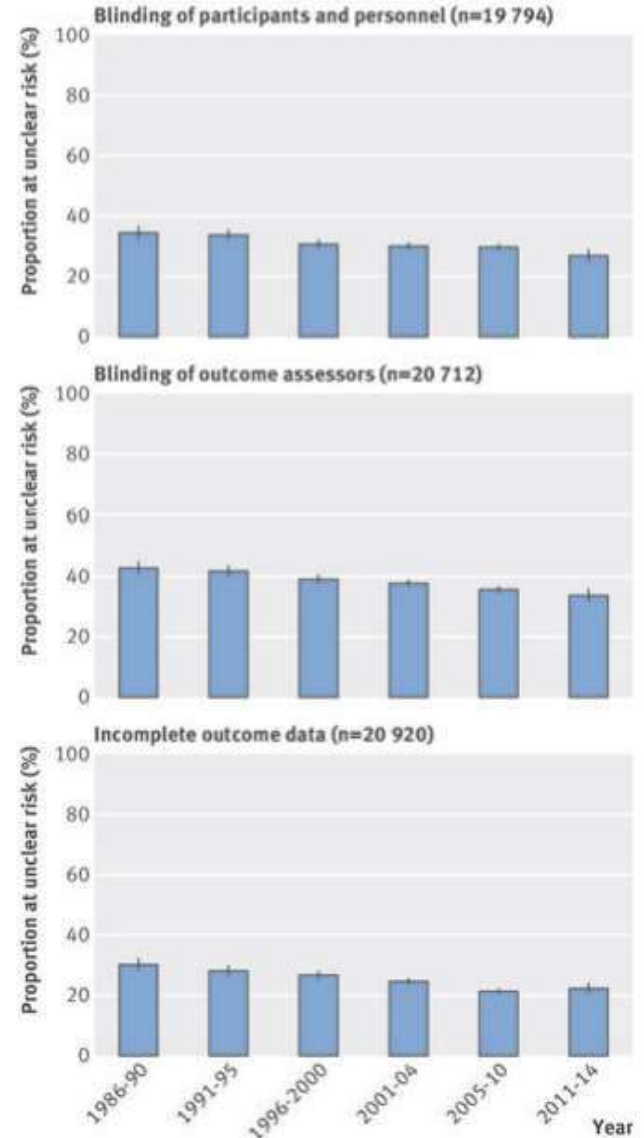
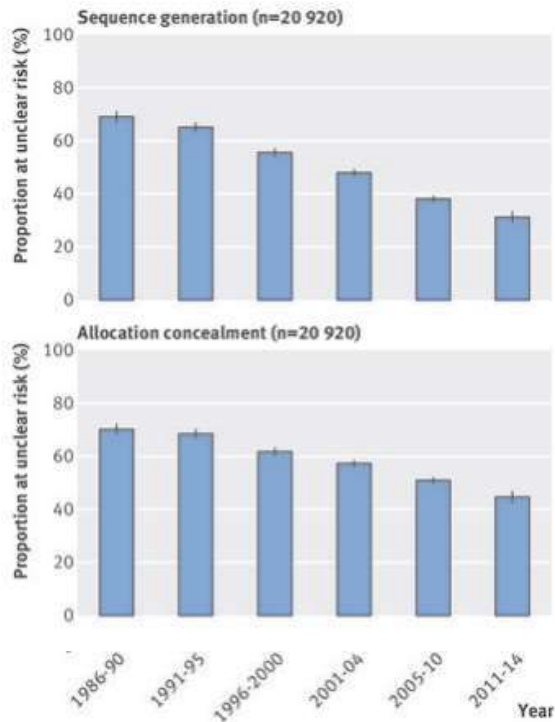
Youri Yordanov,^{1,2} Agnes Dechartres,^{1,3,4} Raphaël Porcher,^{1,3,4} Isabelle Boutron,^{1,3,4,5}
Douglas G Altman,⁶ Philippe Ravaud^{1,3,4,5,7}

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



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*¹⁴, Ludovic Trinquart *researcher*¹⁴, Ignacio Atal *data scientist*¹⁴, David Moher *senior scientist*⁵, Kay Dickersin *professor*⁶, Isabelle Boutron *professor*¹⁴, Elodie Perrodeau *statistician*¹³, Douglas G Altman *professor*⁷, Philippe Ravaut *professor*^{14,8}




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

Journal of Clinical Epidemiology 111 (2018) 111–119

EVIDENCE SYNTHESIS ECOSYSTEM SERIES

Future of evidence ecosystem series: 1. Introduction Evidence synthesis needs dramatic change

Isabelle Boutron^{a,b,c,d}, Perrine Créquit^{a,b,c,d}, Hywel C. Williams^b, Joerg Meerpohl^e, Jonathan C. Craig^f, Philippe Ravaud^{a,b,c,d}

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Abstract

Objectives: This article presents why the planning, conduct, and reporting of systematic reviews and meta-analyses of therapeutic interventions are suboptimal.

Study Design and Setting: We present an overview of the limitations of the current system of evidence synthesis for therapeutic interventions.

Results: Systematic reviews and meta-analyses are a cornerstone of health care decisions. However, despite the increasing number of published systematic reviews of therapeutic interventions, the current evidence synthesis ecosystem is far from properly addressing stakeholders' needs. This ecosystem produces little to no value for decision-makers because of scarce and insufficient planning with a process that is not always comprehensive and is prone to bias. Evidence synthesis depends on the quality of primary research, so primary research that is not available or biased is selectively reported, often impacting conclusions. However, the lack of interaction between the community of primary research producers and systematic reviewers impedes the optimal use of data. The current bias vulnerability method with ongoing research incorporation is a new statistical approach with the aim of its use within all approaches, more available data, and more transparent. All these changes need to be introduced into the future evidence synthesis.

Conclusion: Dramatic changes are needed to enable this future ecosystem to become more efficient and user-oriented and more useful for decision-making. © 2020 Published by Elsevier Inc.

Keywords: Systematic review; Meta-analysis; Evidence synthesis ecosystem; Evidence synthesis; Health care research; Health care decision; Health care

1. Introduction

The number of more than 10,000 new randomized controlled trials (RCTs) are published every year [1]. However, patients, clinicians, clinical practice guideline developers, researchers, policy makers, health system managers, and funders alike find it extremely challenging to

consider all the primary research findings on a given topic when making health care decisions [2]. They need a comprehensive, critical, up-to-date synthesis of all available evidence about the efficacy and safety of interventions. Accordingly, systematic reviews (i.e., a systematic identification, appraisal, and synthesis of all relevant prior studies on a specified topic according to a predetermined and explicit method [3]) and meta-analysis (i.e., the statistical aggregation of all relevant prior studies [4]) are a cornerstone of health care decisions [5].

Systematic reviews of RCTs have been developed to address this need and are usually considered the highest

Journal of Clinical Epidemiology 111 (2018) 111–119

EVIDENCE SYNTHESIS ECOSYSTEM SERIES

Future of evidence ecosystem series: 2. current opportunities and need for better tools and methods

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Abstract

To become more diverse and more useful for decision making, the current evidence synthesis ecosystem requires significant changes. Paper 1. Future of evidence ecosystem series: Reviewers have access to more sources of data (clinical trial registries, protocols, and clinical study reports from regulatory agencies or pharmaceutical companies) for more information on unpublished control trials. With all these newly available data, the management of multiple and scattered trial reports even more challenging. New types of data are also becoming available: individual patient data and modularly collected data. With the increasing number of diverse sources to be searched and the amount of data to be analyzed, the process tends to be inefficient. New approaches and tools, such as automation technologies and artificial intelligence, should help accelerate the process. The implementation of these new approaches and methods requires a substantial redesign and redesign of the current evidence synthesis ecosystem. The concept of a “living” evidence synthesis ecosystem, with living systematic reviews and living internet meta-analyses, has recently emerged. Such an evidence synthesis ecosystem implies incorporating evidence synthesis as a continuous process both around a clinical question of interest and as long as a small team independently answering a specific clinical question at a single point in time. © 2020 Elsevier Inc. All rights reserved.

Keywords: Systematic review; Evidence synthesis; Clinical study reports; Automation; Artificial intelligence; Living systematic reviews

As presented in paper 1 of the Future of evidence ecosystem series, the current evidence synthesis ecosystem—comprising for producing systematic reviews, meta-analyses, and network meta-analyses—requires significant changes to improve its important distribution to adapt to developments in health care and primary research, and become more useful in the decision-making process.

In this paper, we will provide both access to new sources and types of data and more developments of new methods, new technologies, and new tools presents a great opportunity to create and update an ecosystem that is better designed to support the production of updated high-quality evidence syntheses.

1. Using all existing sources and types of data

1.1. Answering using, comparing, and benchmarking all sources of data

As previously discussed in paper 1, most systematic reviews currently rely on summary data extracted from reports published in peer-reviewed journals or reported in conference abstracts. This approach limits important conclusions related to reporting that [1–6] and lack of

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EVIDENCE SYNTHESIS ECOSYSTEM SERIES

Future of evidence ecosystem series: 3. From an evidence synthesis ecosystem to an evidence ecosystem

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Abstract

The “one-off” approach of systematic reviews is no longer sustainable; we need to move toward producing “living” evidence synthesis (i.e., continuous, based on rigorous methods, and up-to-date). This implies creating the future evidence ecosystem, its infrastructure, and management. The three-stage production system—primary research, evidence synthesis, and guideline development—should work together to allow for continuous updating of systematic evidence and guidelines. It uses evidence synthesis, not just focusing on synthesis, should allow for building the data evidence synthesis ecosystem, primary researchers, guideline developers, health technology assessment agencies, and health policy authorities. This network of evidence synthesis stakeholders should select relevant clinical questions considered a priority topic. For each question, a multidisciplinary community including researchers, health professionals, guideline developers, policy-makers, patients, and methodologists needs to be established and commit to producing the initial evidence synthesis and keeping it up-to-date. Encouraging communities to work together continuously with bidirectional interaction requires greater resources, rewards, and the involvement of health care policy authorities to systemic activities. A better evidence ecosystem with collaboration and interaction between each part of the network of evidence synthesis stakeholders should permit living evidence synthesis to justify their status as evidence-informed decision making. © 2020 Elsevier Inc. All rights reserved.

Keywords: Systematic review; Evidence synthesis ecosystem; Evidence synthesis; Evidence synthesis; Primary research; Living meta-analysis; Living systematic reviews; Living systematic review; Living systematic review; Living systematic review

1. Introduction

As in some, limited, up-to-date, and updated synthesis of available evidence is arguably one of the most valuable contributions a research community can offer patients, health care providers, guideline developers, funders, health policymakers in health system managers, and other decision makers [1]. Changes in health care research, automation technologies, and the development of new methods

are converging to new ways to produce higher quality evidence syntheses (i.e., based on more rigorous methods and a timely, comprehensive search) for better health care decision making. However, these developments imply rethinking the evidence synthesis ecosystem, its infrastructure and management, and to move toward an evidence ecosystem.

The clinical research we can no longer afford the “one-off” approach of systematic reviews relying on reported information and dissemination of appraisal review teams (i.e., “classical” evidence [1]). A system based on multiple initiatives among less-organized groups of researchers working to answer research questions focusing on only some

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, Olufermi 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

evidence pipeline'. 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,

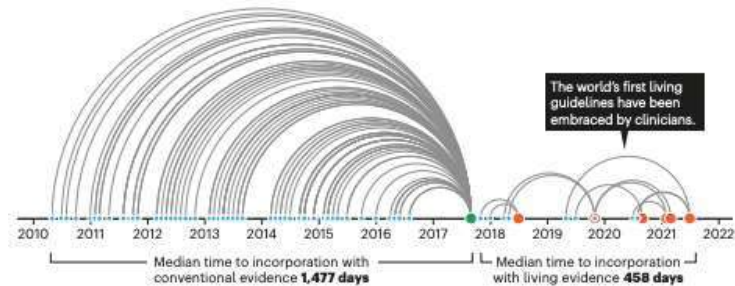
EVIDENCE ACCELERATED

Using a living-evidence approach, researchers find, appraise and incorporate research in frequent cycles, rather than always starting from scratch.

• Primary study • Guideline publication (conventional) • Guideline publication (living) — Time to publication

Stroke

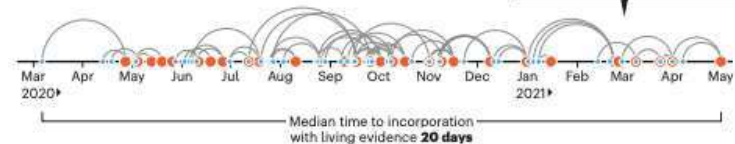
The Australian Stroke Foundation reduced the time between guideline updates from 7 years to under 3 months.



COVID-19

Learning from the stroke experience, Australian COVID-19 guidelines launched using living evidence, often updating weekly.

Around 20,000 COVID-19 papers have been screened and 300 selected for incorporation.



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

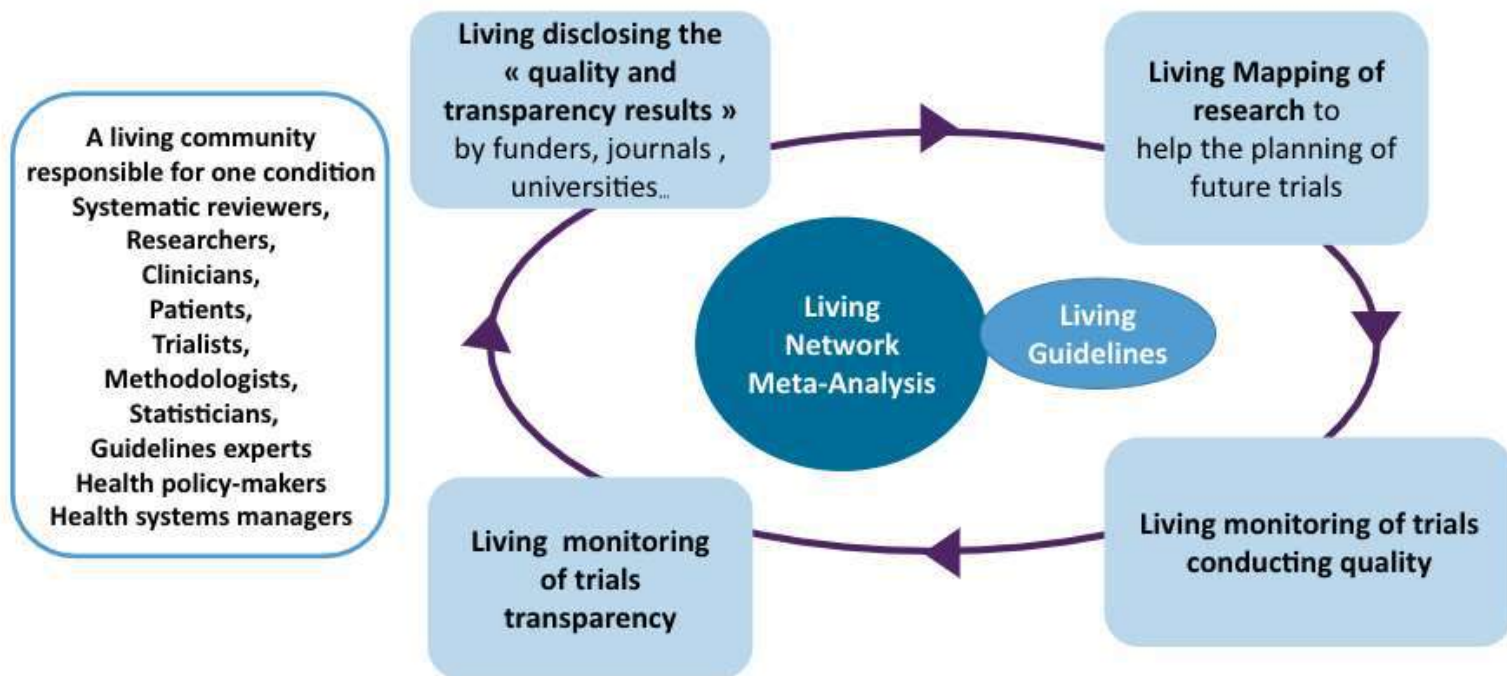
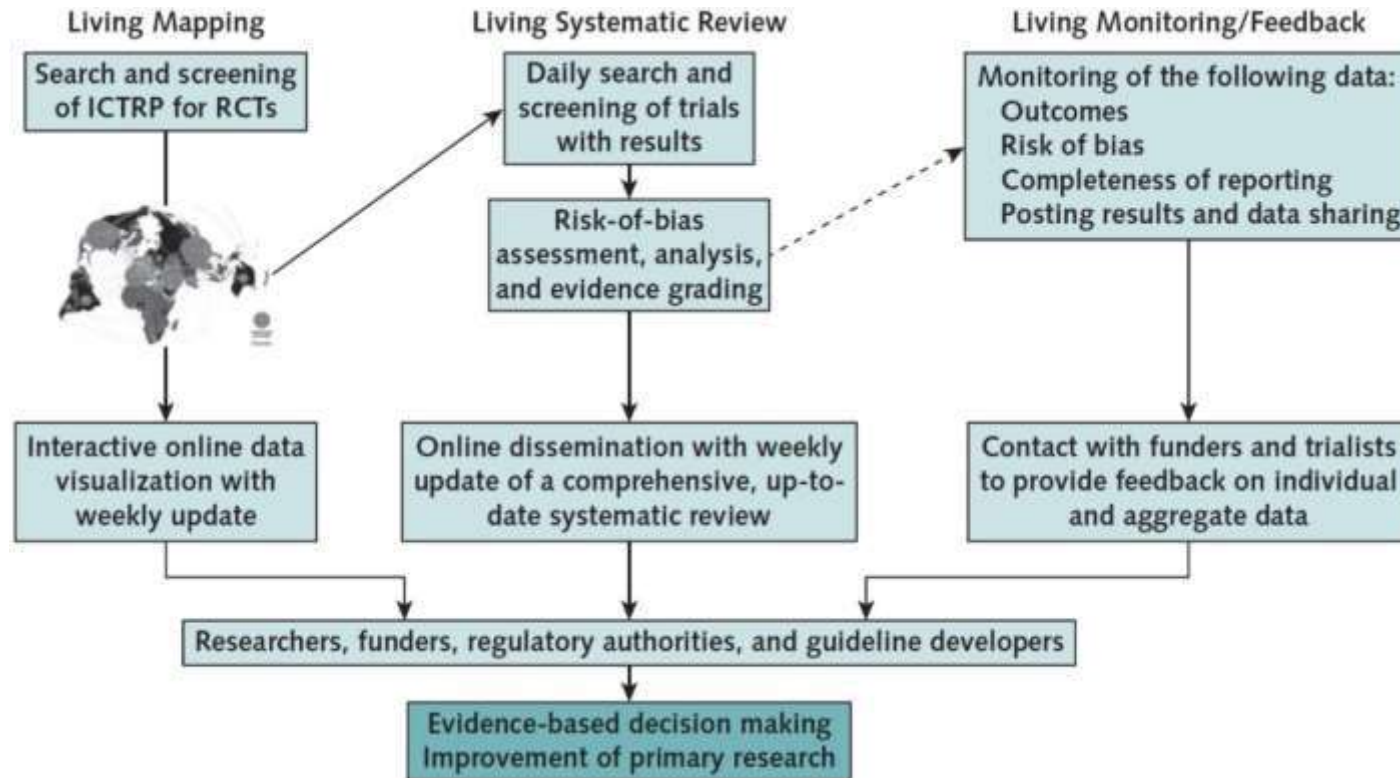


Fig. 1. Developing a culture of continuous improvement of clinical research for a specific disease.

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*



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

▼ Map



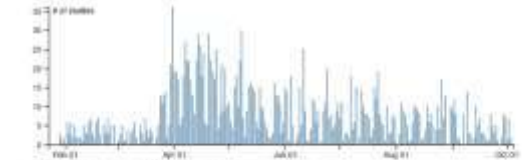
Filters

All trials selected (1905) | 1/10/2020

Search: []

Ex: Interferon, antiviral, Spain, Assistance Publique HUPICK2020...

▼ Registration date

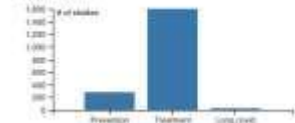


To filter by Registration dates, click and drag to create a range.

▼ Recruitment status

- Recruiting (1,086 studies)
- Not recruiting (746 studies)
- Completed (81 studies)
- Terminated (6 studies)
- Suspended (3 studies)
- Withdrawn (1 study)

▼ Study aim



▼ Table

Show full table:

Treatment (per arm)	Sample size	Severity at enrollment	Funding	Reg. number
(1) Uninfected vs (2) Uninfected + Interferon alpha	100	Moderate/severe	Tongji Hospital	NCT02244474
(1) Remdesivir vs (2) Remdesivir	400	Subcritical	Illness Sciences	NCT04292484
(1) Sodium Azithromycin vs (2) Standard of care vs (3) Sodium Azithromycin vs (4) Erythromycin vs (5) Standard of care	90	Moderate	Tongji Hospital, Tongji Medical College, Huacheng University of Science and Technology	NCT1920002742
(1) Chloroquine vs (2) Hydroxychloroquine + Remdesivir	40	No restriction on type of patients	Santa University	NCT04402694
(1) Tocilizumab vs (2) Standard of care	300	Subcritical	Benevolent (Instituto Portugues de Saude e Paula)	NCT04402693
(1) Hydroxychloroquine vs (2) Placebo	258	Severe	CFI BioPharma	NCT04404361
(1) L-citrulline vs (2) Placebo	100	Critical	Benevolent Hospital	NCT04404423
(1) mRNA-1273 vs (2) mRNA-1273	800	Healthy volunteers	ModernaTX, Inc.	NCT04405070
(1) Opimod vs (2) Standard of care	48	Moderate/severe	Française Laboratoire	NCT04405102
(1) Emricizumab + remdesivir vs (2) Placebo	1278	Health workers	Hospital Italiano de Buenos Aires	NCT04405271
(1) Budesonide + formoterol vs (2) Placebo	400	Severe	Signiford University	NCT04405970
(1) Enoxaparin vs (2) Standard of care	1000	Moderate	University of Zurich	NCT04406189
(1) Casirivir + ecallantide vs (2) MIVACVY vaccine	10260	Healthy volunteers	University of Oxford	NCT04406246
(1) Chloroquine vs (2) Hydroxychloroquine + remdesivir	112	No restriction on type of patients	The First affiliated Hospital Sun Yat-sen University	NCT04406274
(1) Remdesivir + Vitamin D3 vs (2) Vitamin D3	200	Mild/moderate	Marvin McCreary, MD.	NCT04406893
(1) Sangstatinone vs (2) Placebo	30	Moderate/severe	Singapore General Hospital	NCT04409023
(1) Vitamin C vs (2) Placebo	800	Moderate/subcritical	Université de Sherbrooke	NCT04409150
(1) Enoxaparin vs (2) Enoxaparin	100	Moderate/severe	Northwell Health	NCT04409283
(1) Angiotensin 1-7 vs (2) Placebo	200	Moderate/severe	Columbia University	NCT04409423
(1) Enox vs (2) Placebo	800	Subcritical	Elexis Biotech Inc.	NCT04409470
(1) Sodium Nitrate vs (2) Placebo	200	Critical	Hope Pharmaceuticals	NCT04409527
(1) Remdesivir + baricitinib vs (2) Remdesivir	1032	Moderate/severecritical	National Institute of Allergy and Infectious Diseases (NIH)	NCT04409570
(1) APL-8 vs (2) Placebo	66	Subcritical	Apoels Pharmaceuticals, Inc.	NCT04409593
(1) Favipiravir vs (2) Standard of care	70	Mild/moderate	Bangladesh Medical Research Council (BMRC)	NCT04409203
(1) Hydroxychloroquine vs (2) Standard of care	90	Mild/moderate	The First Hospital of Peking University	NCT04409274
(1) TD-0903 vs (2) Placebo	100	Subcritical/severe	Theravance Biopharma	NCT04409289
(1) Prone positioning vs (2) Standard of care	500	Subcritical/severe	University of Calgary	NCT04409270
(1) Dexamethasone vs (2) Placebo	60	Critical	Boots Children's Hospital	NCT04409344
(1) Brevectin vs (2) Placebo	200	Moderate/severe	University of Dundee	NCT04409402
(1) Ivermectin vs (2) Ivermectin vs (3) Placebo	400	No restriction on type of patients	Lagos University Teaching Hospital	NCT04409389
(1) C108 200 vs (2) Standard of care	20	Subcritical	Center for Biogenic Engineering and	NCT04409397

▼ Disease severity



▼ Type of pharmacological treatment



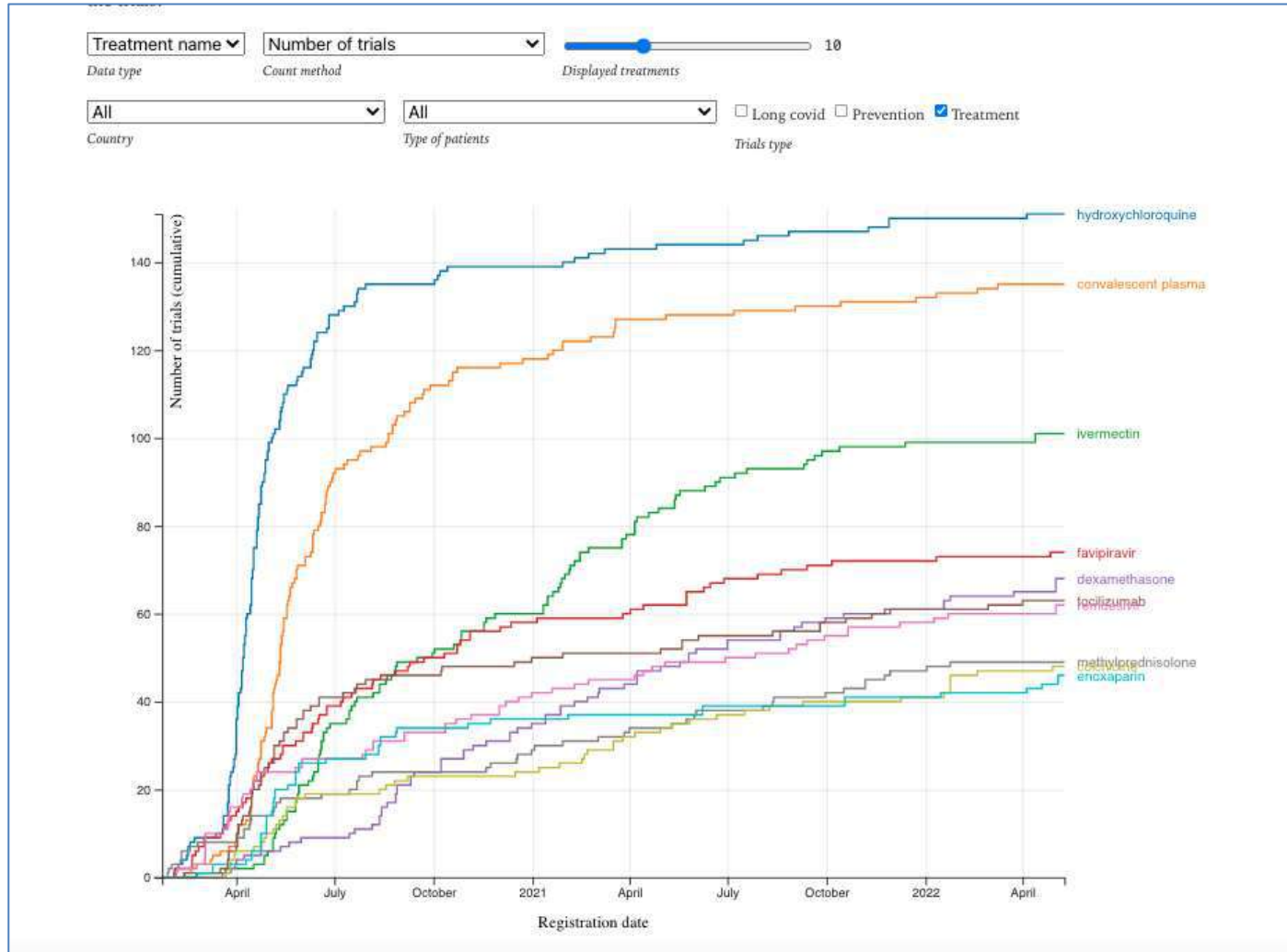
▼ Publication status

- Not published (1,815 studies)
- 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.

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



Living review

<https://covid-nma.com>

WHO

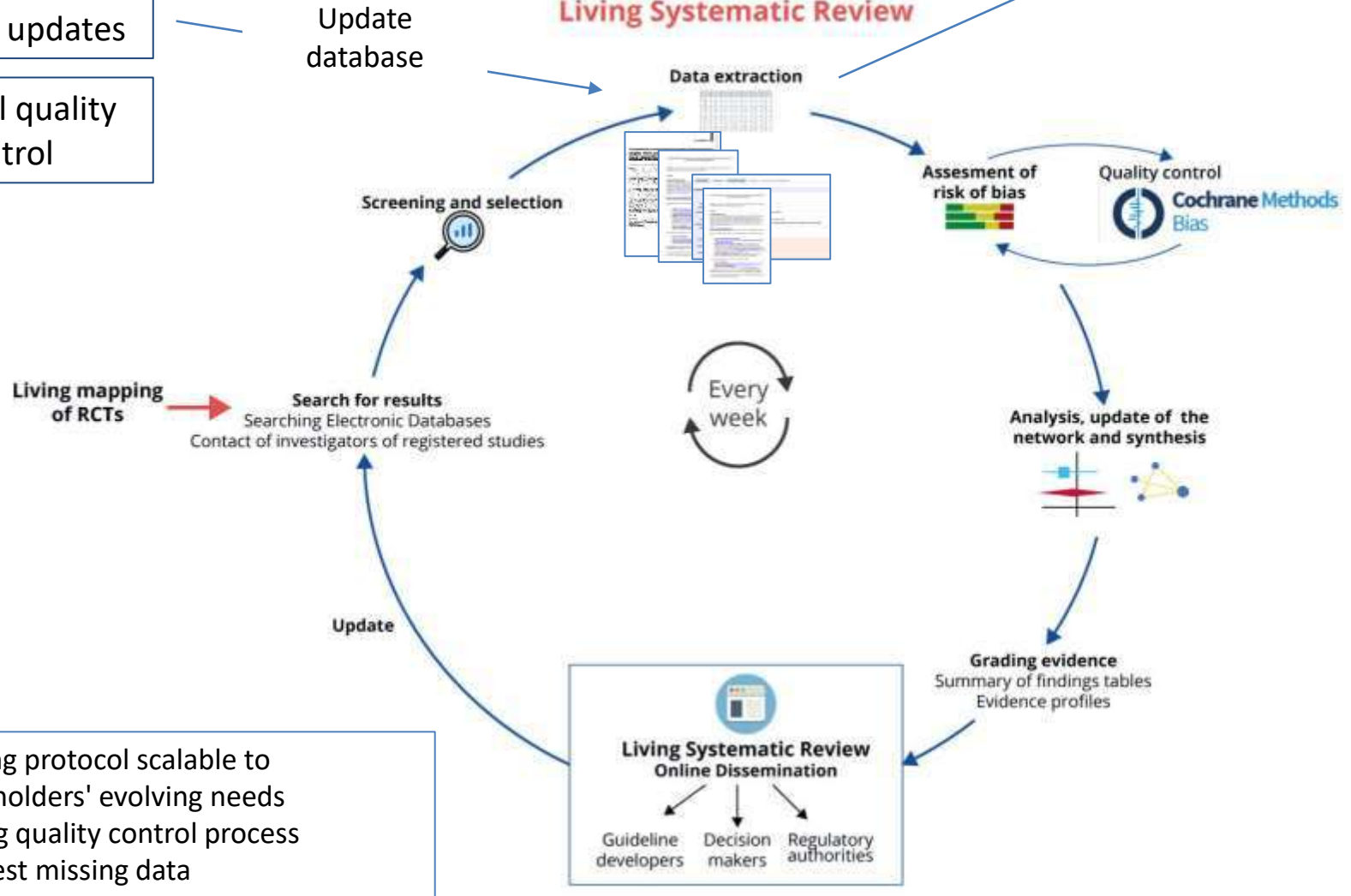
Form to request for missing data

Contact authors

Preprint updates

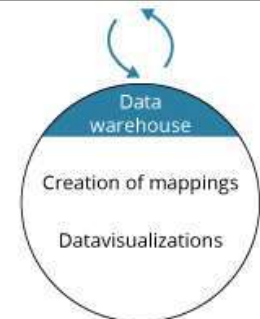
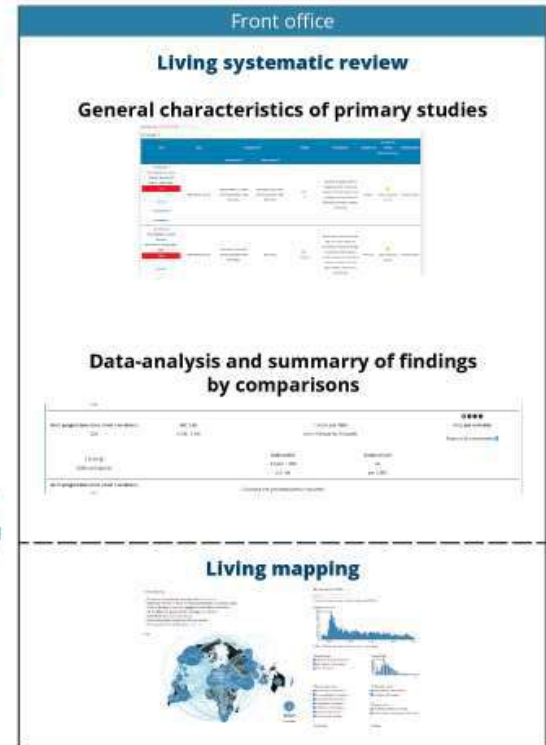
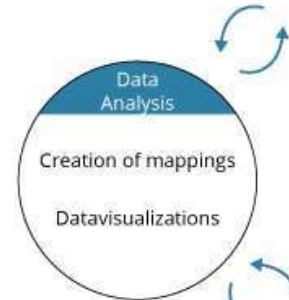
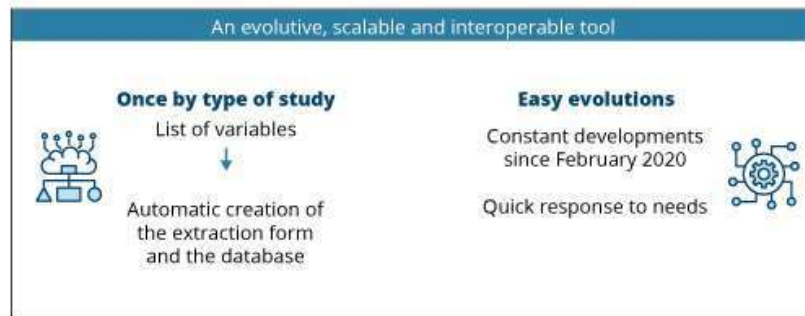
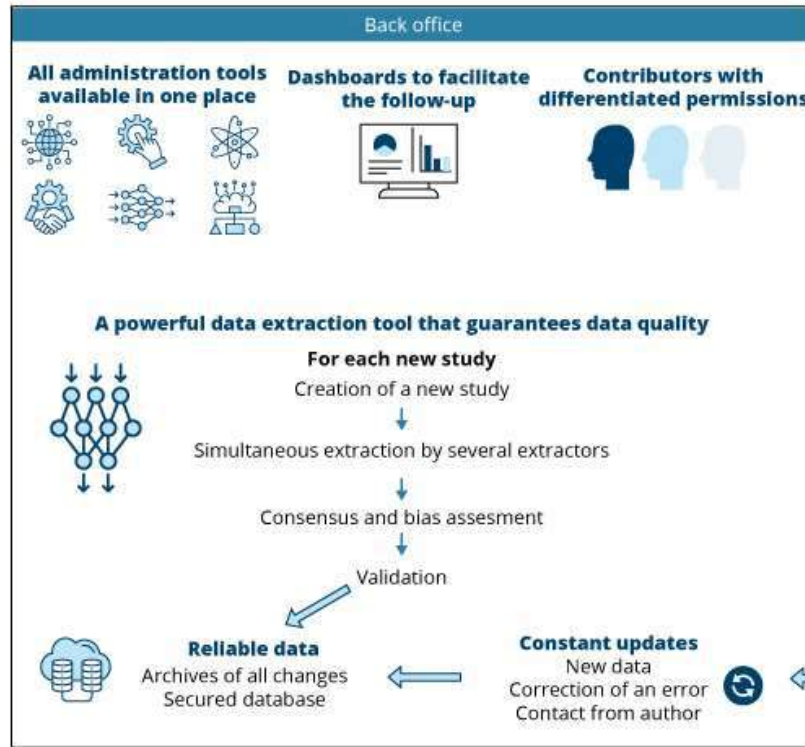
External quality control

Living Systematic Review



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

COVID-NMA platform





ORIGINAL ARTICLE

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

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COVID-19 Evidence COVID-19 News

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COVID-19

Evidence List Methods and report

Search results for COVID-19 - all types of questions

287257 Total articles included

5379 Broad syntheses

10234 Systematic reviews

Showing 287257 in 'Total articles included'

Select type of question

- Prevention or treatment
- Diagnostic
- Ecology
- Epidemiology
- Prognosis

Select intervention/variable

Cochrane COVID-19 Study Register

Trusted evidence. Informed decisions. Better health.

NEW STUDIES

Last Day	14
Last 3 Days	520
Last Week	3 179
Last Month	7 710
Last 3 Months	21 650
From And To...	

UPDATED NEW REFERENCES

STUDY REFERENCE TYPE

RESULTS AVAILABLE

STUDY CHARACTERISTICS

Socio-economic, Meteorological and E... City of Nice

Study Type: Observational

References (1)

An Evaluation of Immune Responses to

Study Type: Observational



Day-to-day discovery of preprint–publication links

Guillaume Cabanac¹ · Theodora Oikonomidi² · Isabelle Boutron^{2,3,4}

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The screenshot shows the 'COVID19 Preprint Tracker' website. The header is blue with the title 'COVID19 Preprint Tracker' and 'Est. June 15th, 2020'. A left sidebar contains navigation links: Bibliography, About, Monitored DOIs, Preprints, Candidate Pre-Pub Links, Updated Pre-Pub Links, All Pre-Pub Links, Assessments, Benchmark, and Timeline. The main content area includes a description of the website's purpose (tabulating preprint-publication links for 828 preprints related to COVID-19), a list of APIs used for data harvesting (bioRxiv, Crossref, Dimensions, PubPeer), and a 'Quick presentation' section. A blue bar at the bottom is labeled 'On Twitter' and features four profile cards for Guillaume Cabanac (@gcabanac) and Theodora Oikonomidi (@dora_oikonomidi).

Home

Covid-19 treatments

Covid-19 vaccines

How to cite us

Contact

Select options

Select treatment comparison

Tocilizumab vs Standard care/I

Select an outcome

Mortality D28

View data table.

Meta-analysis options

Type of model

- Random-effects
- Common effect

Heterogeneity estimate method

- Restricted maximum likelihood
- Maximum likelihood
- DerSimonian-Laird
- Sidik-Jonkman
- Empirical Bayes
- Paule-Mandel

Population of interest

- All populations
- Mild populations
- Mixed populations
- Critical populations

Subgroup analysis

- Severity
- Conflicts of interest
- Funding
- Location
- Type of Control
- No subgroup analysis

Sensitivity analysis

Risk of bias

- All studies
- Exclude high RoB
- Exclude high RoB and some concerns

Exclude preprints

- No
- Yes

Missing outcome data

- As non-events (randomized patients in the denominator)
- Available case analysis

Meta-analysis of odds ratios

Presentation options

Hide treatment dose

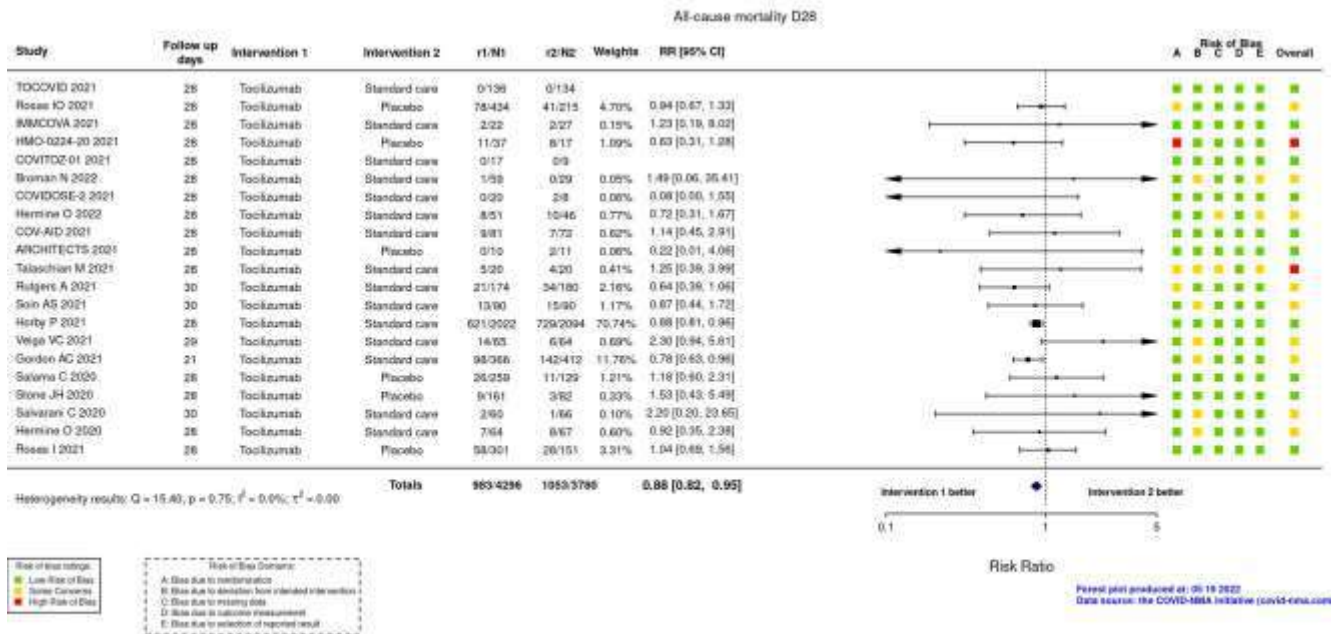
- No
- Yes

Hide population severity

- No
- Yes

Download Forest plot

Reset all choices

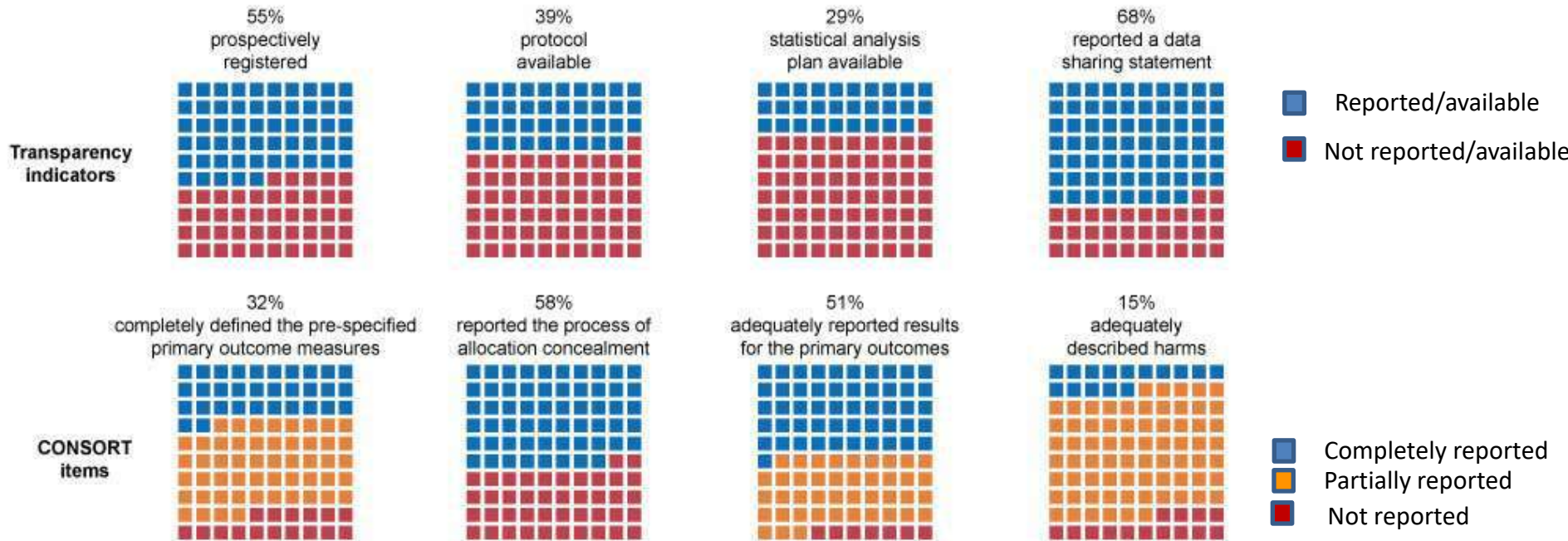


Living monitoring/feedback

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

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

244 trial reports



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

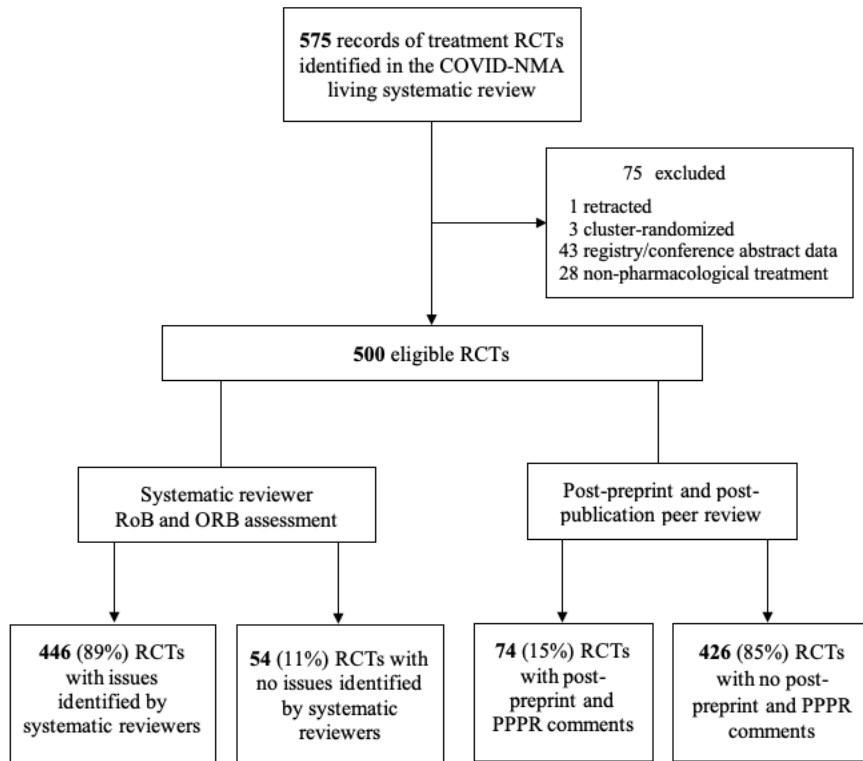


Figure 1: Flow chart of included RCTs

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

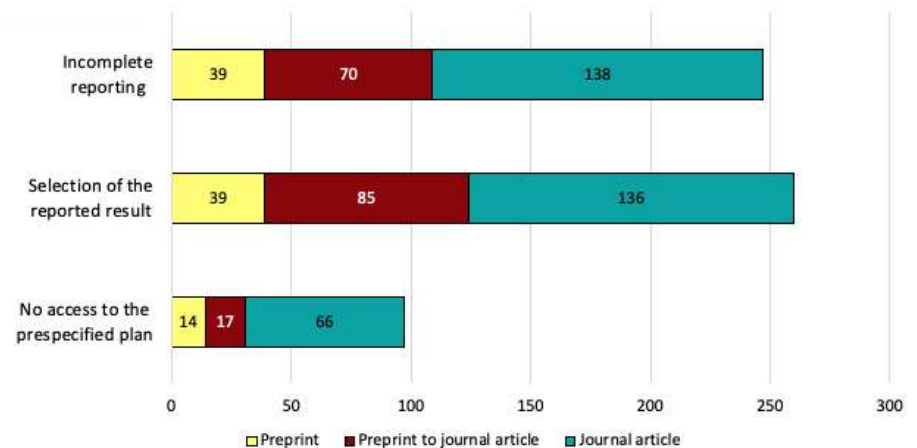


Figure 2: RCTs with resolvable issues identified by systematic reviewers (78%)