# Trust but Verify: Our experiences identifying fabricated or falsified trials in a systematic review

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**2015-2017**

MSc in Health Research Methodology (McMaster University)

**2017-2020**

PhD in Health Research Methodology (McMaster University)

**2020-2022**

Fellowship in Biomedical Informatics/ Methodology (Harvard Medical School)

**2022-**

Assistant Professor (McMaster University)

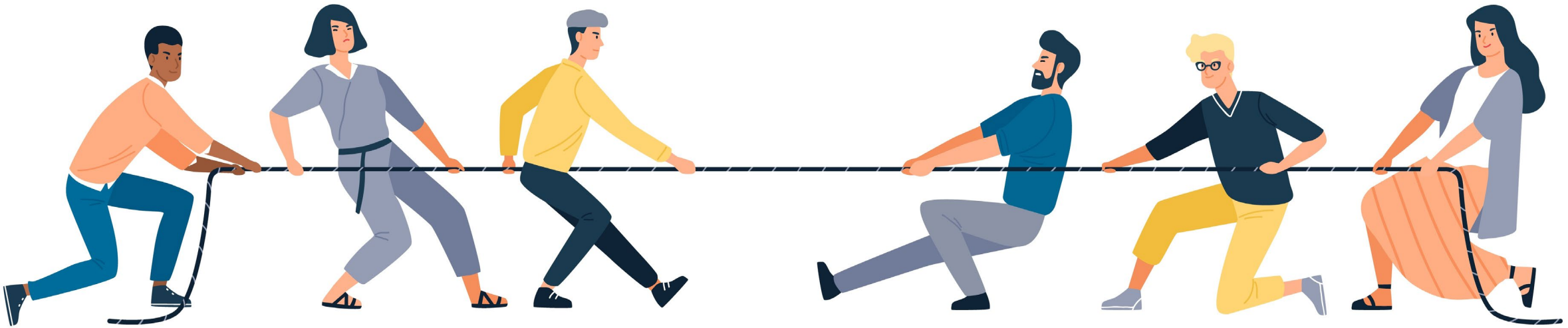
# Conflicts of Interest

**Member of the GRADE Working Group**

**Member of Cochrane**

**Consultancies**

- European Headache Federation
- Society for Evidence-Based Gender Medicine (SEGM)
- Association of Medical Microbiology and Infectious Disease Canada



# Scientific Integrity

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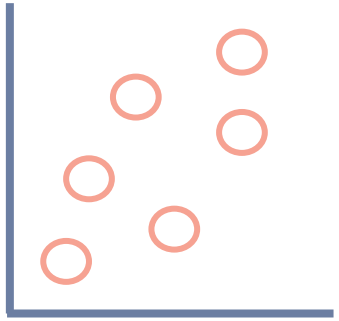
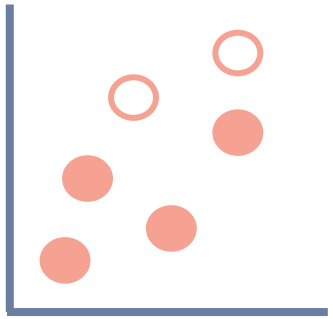
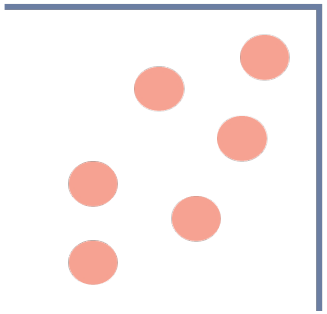
**Fabricated Study Data**



**Falsified Study Data**



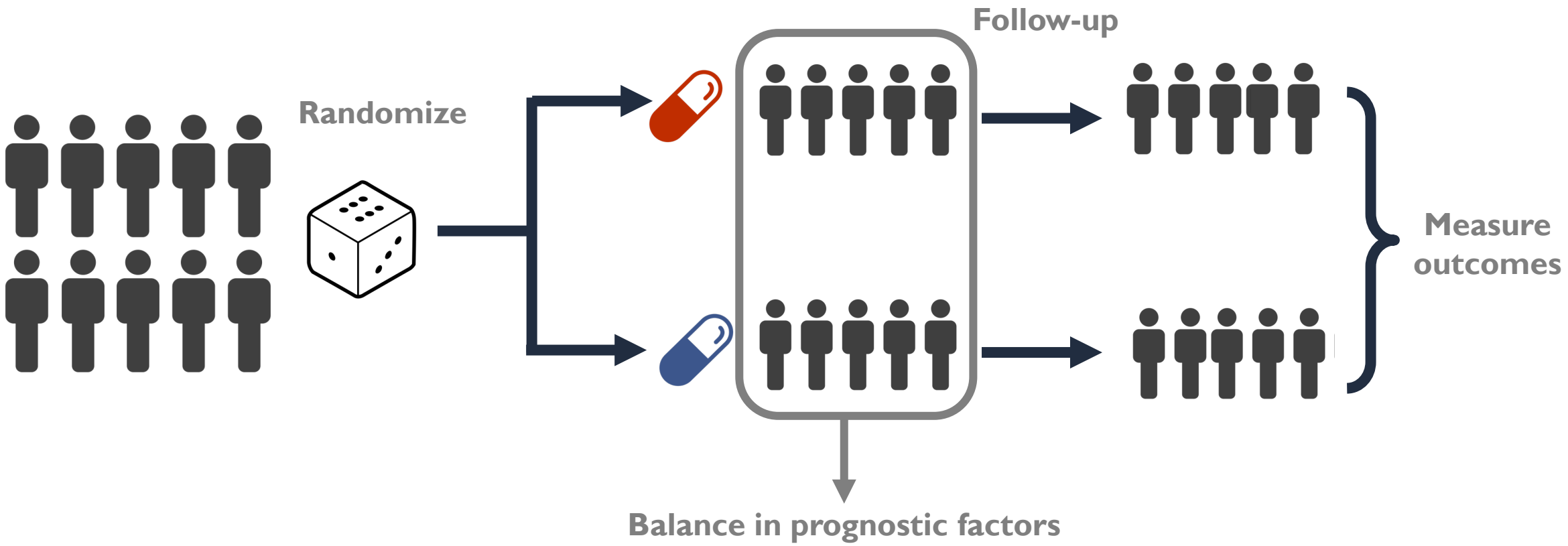
**Studies with errors in execution or analysis**



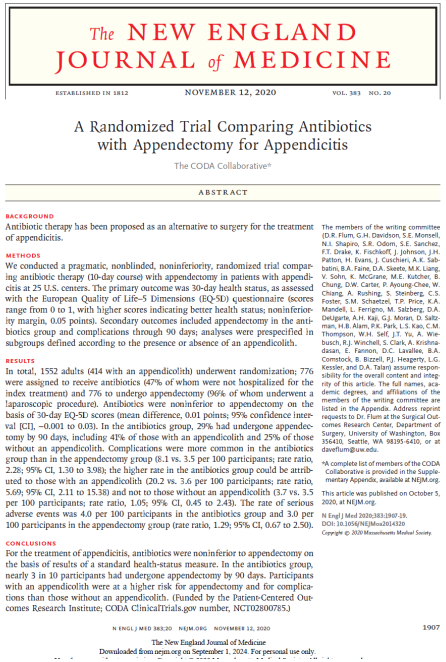
# Tools to Detect and Manage Problematic Studies

| Reference | Tool | Domains/Description |
|---|---|---|
| Moussa 2024 | Research Integrity in Guidelines and evIDence synthesis (RIGID) | A framework describing the integration of integrity assessments in evidence synthesis and guideline development |
| Mol 2023 | TRACT Checklist | Governance, author group, plausibility of intervention, timeframe, dropouts, baseline characteristics, and outcomes |
| Weibel 2022 | Research Integrity Assessment Tool | Retraction or expression of concern, trial registration, ethics approval, author group, methods, results |
| Alfirevic 2021 | Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST) | Research governance, baseline characteristics, feasibility |
| Grey 2020 | REAPPRAISED checklist | Research governance, ethics, authorship, productivity, plagiarism, research conduct, analyses and methods, image manipulation, statistics and data, errors, data duplication and reporting |

# Problematic Trials



# Baseline Characteristics Improbable with Randomization



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 12, 2020 VOL. 383 NO. 20

A Randomized Trial Comparing Antibiotics with Appendectomy for Appendicitis

The CODA Collaborative*

ABSTRACT

BACKGROUND

Antibiotic therapy has been proposed as an alternative to surgery for the treatment of appendicitis.

METHODS

We conducted a pragmatic, nonblinded, noninferiority, randomized trial comparing antibiotic therapy (10-day course) with appendectomy in patients with appendicitis at 25 U.S. centers. The primary outcome was 30-day health status, as assessed with the European Quality of Life–5 Dimensions (EQ-5D) questionnaire (scores range from 0 to 1, with higher scores indicating better health status; noninferiority margin, 0.05 points). Secondary outcomes included appendectomy in the antibiotics group and complications through 90 days; analyses were prespecified in subgroups defined according to the presence or absence of an appendicolith.

RESULTS

In total, 1552 adults (414 with an appendicolith) underwent randomization; 776 were assigned to receive antibiotics (47% of whom were not hospitalized for the index treatment) and 776 to undergo appendectomy (96% of whom underwent a laparoscopic procedure). Antibiotics were noninferior to appendectomy on the basis of 30-day EQ-5D scores (mean difference, 0.01 points; 95% confidence interval [CI], −0.001 to 0.03). In the antibiotics group, 29% had undergone appendectomy by 90 days, including 41% of those with an appendicolith and 25% of those without an appendicolith. Complications were more common in the antibiotics group than in the appendectomy group (8.1 vs. 3.5 per 100 participants; rate ratio, 2.28; 95% CI, 1.30 to 3.98); the higher rate in the antibiotics group could be attributed to those with an appendicolith (20.2 vs. 3.6 per 100 participants; rate ratio, 5.69; 95% CI, 2.11 to 15.38) and not to those without an appendicolith (3.7 vs. 3.5 per 100 participants; rate ratio, 1.05; 95% CI, 0.45 to 2.43). The rate of serious adverse events was 4.0 per 100 participants in the antibiotics group and 3.0 per 100 participants in the appendectomy group (rate ratio, 1.29; 95% CI, 0.67 to 2.50).

CONCLUSIONS

For the treatment of appendicitis, antibiotics were noninferior to appendectomy on the basis of results of a standard health-status measure. In the antibiotics group, nearly 3 in 10 participants had undergone appendectomy by 90 days. Participants with an appendicolith were at a higher risk for appendectomy and for complications than those without an appendicolith. (Funded by the Patient-Centered Outcomes Research Institute; CODA ClinicalTrials.gov number, NCT02800785.)

The members of the writing committee (D.R. Flum, G.H. Davidson, S.E. Monsell, N.I. Shapiro, S.R. Odom, S.E. Sanchez, F.T. Drake, K. Fischkoff, J. Johnson, J.H. Patton, H. Evans, J. Cuschieri, A.K. Sabbatini, B.A. Faine, D.A. Skeete, M.K. Liang, V. Sohn, K. McGrane, M.E. Kutcher, B. Chung, D.W. Carter, P. Ayoung-Chee, W. Chiang, A. Rushing, S. Steinberg, C.S. Foster, S.M. Schaetzel, T.P. Price, K.A. Mandell, L. Ferrigno, M. Salzberg, D.A. DeUgarte, A.H. Kaji, G.J. Moran, D. Saltzman, H.B. Alam, F.K. Park, L.S. Kao, C.M. Thompson, W.H. Self, J.T. Yu, A. Wiebusch, R.J. Winchell, S. Clark, A. Krishnadasan, E. Fannon, D.C. Lavallee, B.A. Comstock, B. Bizzell, P.J. Heagerty, L.G. Kessler, and D.A. Talan) assume responsibility for the overall content and integrity of this article. The full names, academic degrees, and affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Flum at the Surgical Outcomes Research Center, Department of Surgery, University of Washington, Box 356410, Seattle, WA 98195-6410, or at daveflum@uw.edu.

*A complete list of members of the CODA Collaborative is provided in the Supplementary Appendix, available at NEJM.org.

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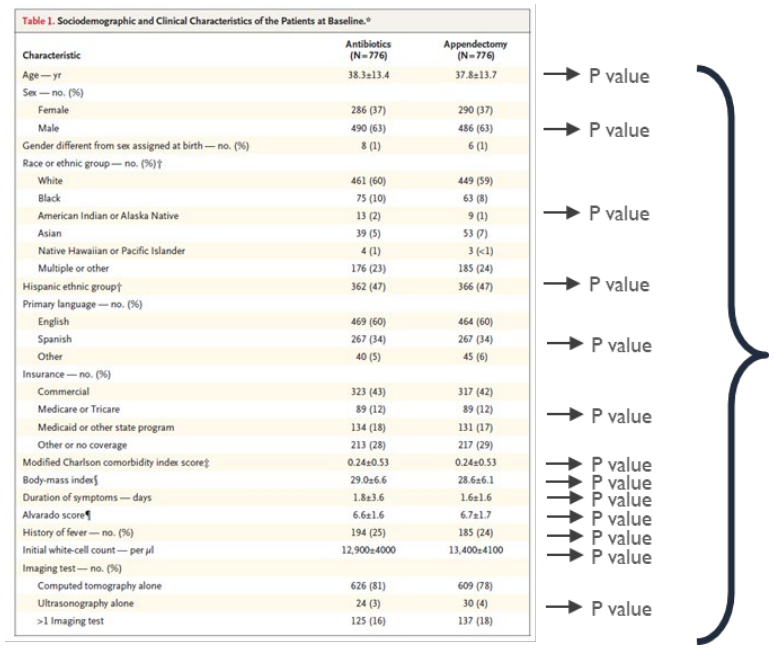

Table 1. Sociodemographic and Clinical Characteristics of the Patients at Baseline.*

| Characteristic | Antibiotics (N=776) | Appendectomy (N=776) |
|---|---|---|
| Age — yr | 38.3±13.4 | 37.8±13.7 |
| Sex — no. (%) | | |
| Female | 286 (37) | 290 (37) |
| Male | 490 (63) | 486 (63) |
| Gender different from sex assigned at birth — no. (%) | 8 (1) | 6 (1) |
| Race or ethnic group — no. (%)† | | |
| White | 461 (60) | 449 (59) |
| Black | 75 (10) | 63 (8) |
| American Indian or Alaska Native | 13 (2) | 9 (1) |
| Asian | 39 (5) | 53 (7) |
| Native Hawaiian or Pacific Islander | 4 (1) | 3 (<1) |
| Multiple or other | 176 (23) | 185 (24) |
| Hispanic ethnic group† | 362 (47) | 366 (47) |
| Primary language — no. (%) | | |
| English | 469 (60) | 464 (60) |
| Spanish | 267 (34) | 267 (34) |
| Other | 40 (5) | 45 (6) |
| Insurance — no. (%) | | |
| Commercial | 323 (43) | 317 (42) |
| Medicare or Tricare | 89 (12) | 89 (12) |
| Medicaid or other state program | 134 (18) | 131 (17) |
| Other or no coverage | 213 (28) | 217 (29) |
| Modified Charlson comorbidity index score‡ | 0.24±0.53 | 0.24±0.53 |
| Body-mass index§ | 29.0±6.6 | 28.6±6.1 |
| Duration of symptoms — days | 1.8±3.6 | 1.6±1.6 |
| Alvarado score¶ | 6.6±1.6 | 6.7±1.7 |
| History of fever — no. (%) | 194 (25) | 185 (24) |
| Initial white-cell count — per μl | 12,900±4000 | 13,400±4100 |
| Imaging test — no. (%) | | |
| Computed tomography alone | 626 (81) | 609 (78) |
| Ultrasonography alone | 24 (3) | 30 (4) |
| >1 Imaging test | 125 (16) | 137 (18) |

P value
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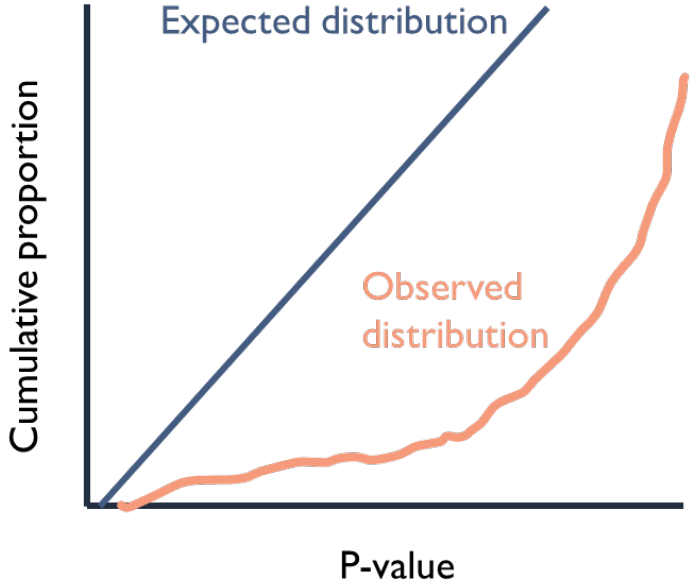
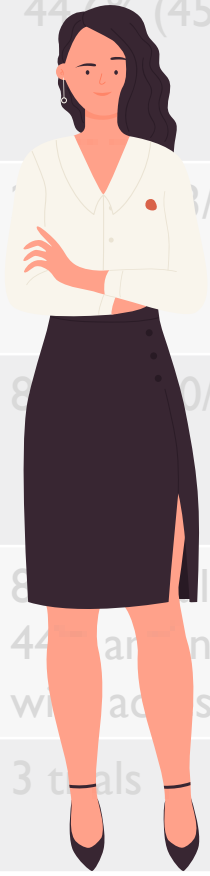


# Prevalence of Issues Related to Research Integrity

| Citation | Sample | Methods | Estimate |
|---|---|---|---|
| Mousa 2024 | 101 randomized trials considered for gidelines addressing PCOS | | 44.6% (45/101) |
| Weeks 2023 | 374 randomized trials in Cochrane reviews of pregnancy and childbirth | | /374) |
| Bordewijk 2020 | 35 randomized trials in women's health published by 2 authors | | ristics; chance 0/35) |
| Carlisle 2020 | 526 randomized trials submitted to *Anesthesiology* | bility of statistical summaries and tests, interrogation of IPD (repetition and duplication, end digit preference), | l; ng those ss to IPD |
| Roberts 2007 | Trials investigating mannitol for head injury | Investigation by Cochrane Collaboration + several other institutions | 3 trials |

The number of retractions in the scientific literature has been estimated at less than 1%, a figure which leads some to believe that research integrity concerns are not a widespread issue.



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| Weeks 2023 | 374 randomized trials in Cochrane reviews of pregnancy and childbirth | Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool (CPC-TST) | 24.9% (93/374) |
| Bordewijk 2020 | 35 randomized trials in women's health published by 2 authors | Identical or similar values in baseline characteristics; compatibility of baseline characteristics with chance | 85.7% (30/35) |
| Carlisle 2020 | 526 randomized trials submitted to *Anesthesiology* | Probability of baseline characteristics, plausibility of statistical summaries and tests, interrogation of IPD (repetition and duplication, end digit preference), | 8% overall; 44% among those with access to IPD |
| Roberts 2007 | Trials investigating mannitol for head injury | Investigation by Cochrane Collaboration + several other institutions | 3 trials |

# Living Systematic Review of Interventions for the Management of Long COVID

| Comparison | Recovery /important improvement | Fatigue | Physical function | Cognitive function | Mental health | Quality of life / Wellbeing | Serious adverse events |
|---|---|---|---|---|---|---|---|
| | Effect estimates | | | | | | |
| Physical and mental rehabilitation program vs. Usual care | 161 more per 1,000 (61 more to 292 more)<br>RR: 1.55 (1.21 to 2)a | -2 (-3.96 to -0.04) | 0.5 (-1.01 to 2.01) | 1 (-0.44 to 2.44) | -1 (-1.98 to -0.02)<br>-1.5 (-2.41 to -0.59) | 0.04 (0 to 0.08) | 20 more per 1,000 (10 fewer to 50 more) |
| CBT vs. Usual care | 326 more per 1,000 (100 more to 695 more)<br>RR: 2.24 (1.38 to 3.64)b | -8.4 (-13.11 to -3.69) | 4.9 (-1.89 to 11.69) | -5.2 (-7.97 to -2.43) | | | 0 more per 1,000 (30 fewer to 30 more) |
| A combinationn of probiotics and prebiotics ('Synbiotics') called SIM01 vs. Usual care | Fatigue<br>200 more per 1,000 (94 more to 336 more)<br>RR: 1.47 ( 1.22 to 1.79)a<br>Concentration<br>239 more per 1,000 (112 more to 401 more)<br>RR: 1.62 ( 1.29 to 2.04)b<br>Dyspnea<br>150 more per 1,000 (27 more to 290 more)<br>RR: 1.28 ( 1.05 to 1.54)c | | | | | 1.5 (-0.87 to 3.87) | 0 more per 1,000 (10 fewer to 10 more) |
| Intermittent aerobic exercise vs. Continuous aerobic exercise | | | 3.8 (1.12 to 6.48) | | 0 (-3.69 to 3.69) | | |
| Transcranial direct current stimulation, Physiotherapy, Education related to | 315 more per 1,000 (59 more to 699 more) | | | | | | 0 more per 1,000 |

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In response to growing concerns about untrustworthy trial publications, we incorporated methods to assess trials for signs of fabrication, falsification, or major errors.

# Methods: Systematic Review

Search

Screening

Data collection

Analysis

Certainty of evidence

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Search

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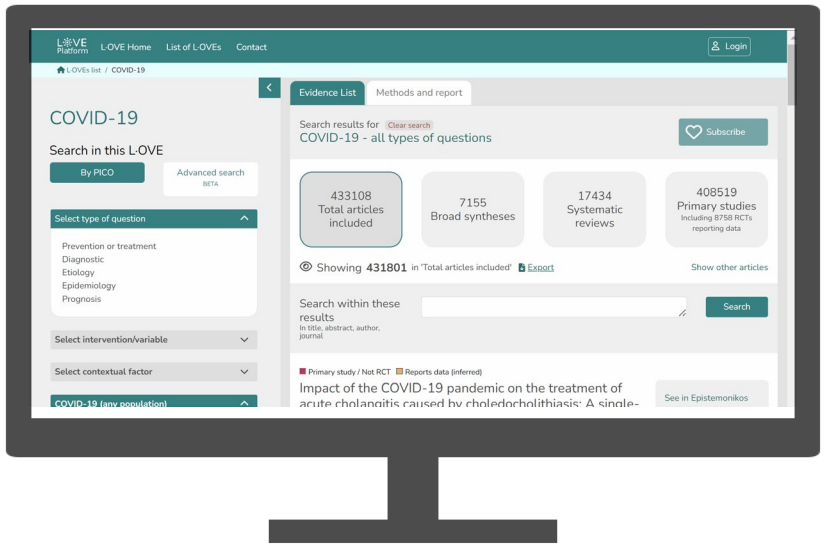


MEDLINE
EMBASE
CINAHL
PsycInfo
AMED
CENTRAL
EPISTEMONIKOS COVID-19 repository

*Inception to December 2023*

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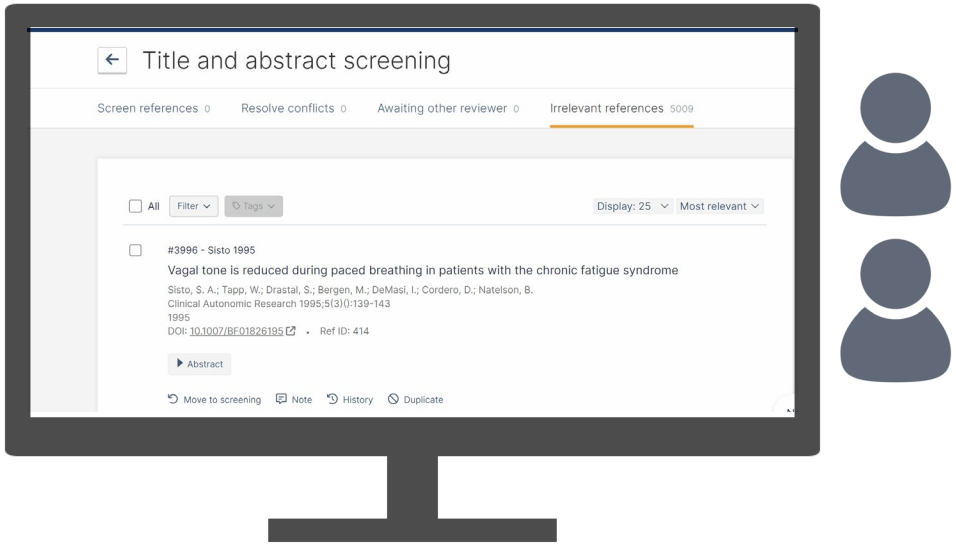



## Eligibility criteria

- **Adults** (≥18 years old)
- **Long COVID**: symptoms at three or more months following laboratory confirmed, probable, or suspected COVID-19 infection that persist for at least two months
- Randomized to any **pharmacologic or non-pharmacologic intervention**(s), placebo, sham, usual care
- Min 25 patients/arm

# Methods: Systematic Review

Search

Screening

Data collection

Analysis

Certainty of evidence

# Methods: Systematic Review

- Search
- Screening
- Data collection
- Analysis
- Certainty of evidence

| Data Collection | |
|---|---|
| **Trial characteristics**<br>- Country<br>- Registration<br>- Design<br>**Patient characteristics**<br>- Age, Sex<br>- Diagnostic criteria<br>- Time since infection<br>- Duration of long COVID symptoms<br>- Comorbidities | **Outcomes of interest:**<br>- Recovery or improvement<br>- Fatigue<br>- Post-exertional malaise<br>- Patient-reported function<br>- Cognitive function<br>- Mental health<br>- Dyspnea<br>- Quality of life<br>- Changes in education/ employment status<br>- Serious adverse events |


# Methods: Systematic Review

Search

Screening

Data collection

Analysis

Certainty of evidence

# Methods: Systematic Review

Search

Screening

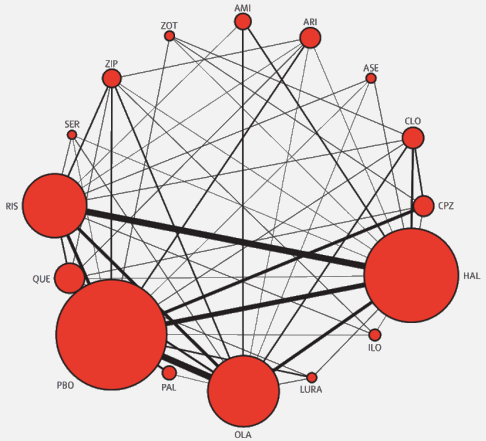
Data collection

Analysis

Certainty of evidence

Random-effects pairwise meta-analysis

Random-effects network meta-analysis



# Methods: Systematic Review

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Screening

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# Methods: Systematic Review

Search

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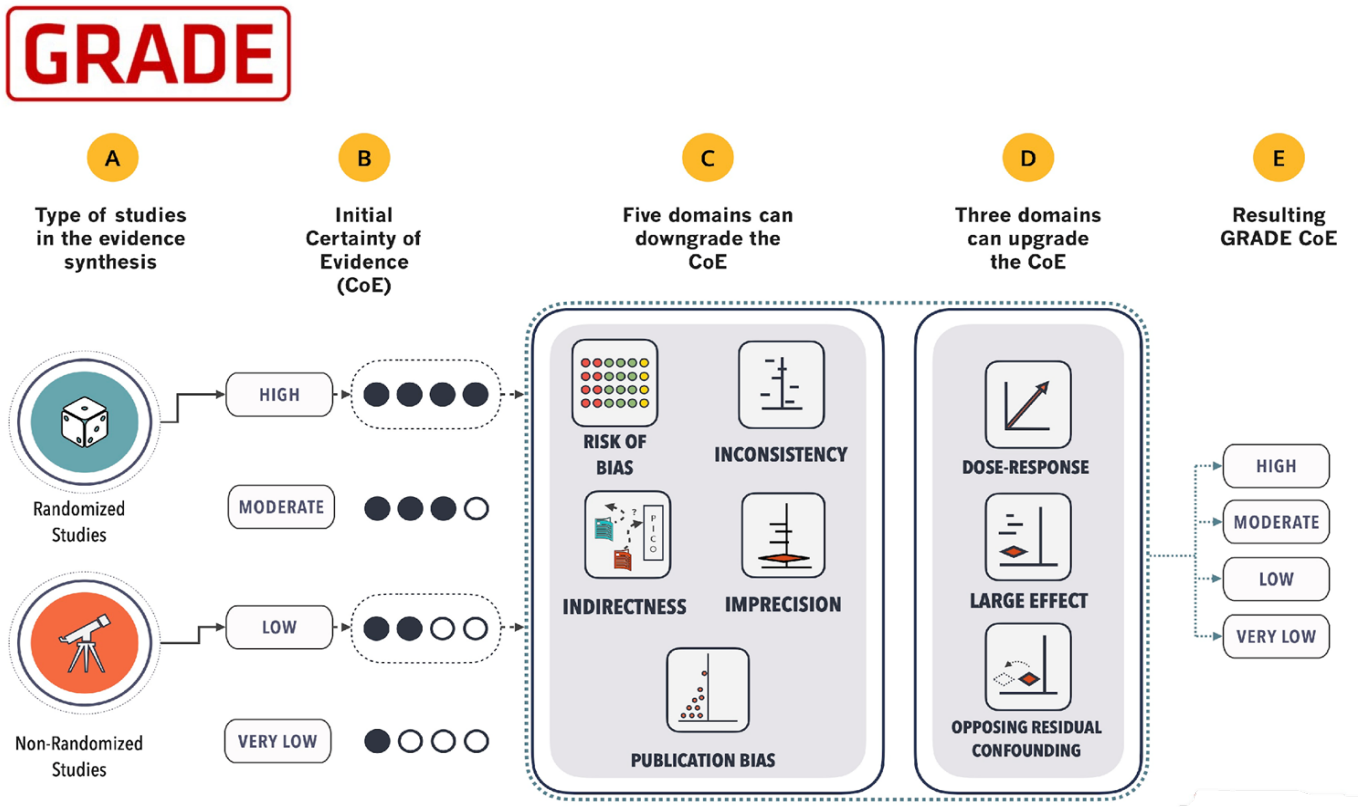

# Methods: Systematic Review

Search

Screening

Data collection

Analysis

Certainty of evidence

# Methods: Systematic Review

- Search
- Screening
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- Certainty of evidence

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RoB 2

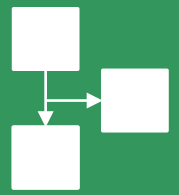
# Methods: Systematic Review

- Search
- Screening
- Data collection
- Analysis
- Certainty of evidence

| Data Collection | |
|---|---|
| **Trial characteristics**<br>- Country<br>- Registration<br>- Design<br>**Patient characteristics**<br>- Age, Sex<br>- Diagnostic criteria<br>- Time since infection<br>- Duration of long COVID symptoms<br>- Comorbidities | **Outcomes of interest**:<br>- Recovery or improvement<br>- Fatigue<br>- Post-exertional malaise<br>- Patient-reported function<br>- Cognitive function<br>- Mental health<br>- Dyspnea<br>- Quality of life<br>- Changes in education/ employment status<br>- Serious adverse events |

RoB 2

# TRACT Checklist

|  |  |  |  |  |  |  |
|---|---|---|---|---|---|---|
| Governance | Author group | Plausibility of intervention | Timeframe | Dropouts | Baseline characteristics | Outcomes |
| Absent or retrospective registration | Three or fewer authors | Insufficient or implausible description | Implausibly short time between ending recruitment/follow up and submission of the paper | Zero patients lost to follow-up despite long follow-up period | Perfect balance for multiple baseline characteristics | Effect size that is much larger than in other RCTs regarding the same topic |

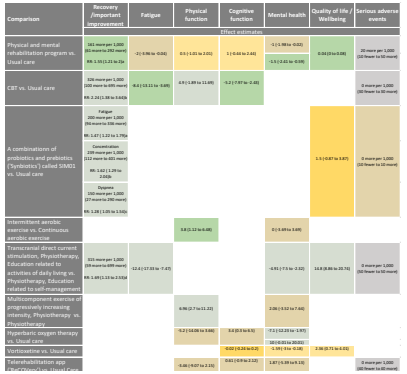
# Workflow





Trials with no concerns


Trials with concerns in one or more domains



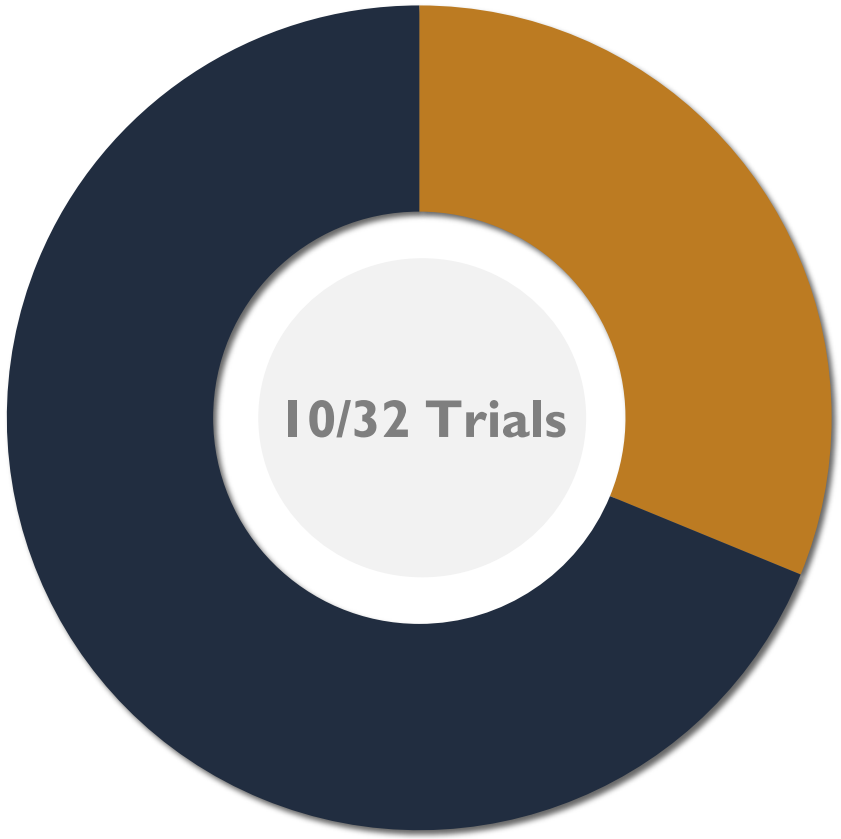

Primary analysis

Reviewed by core authorship group

Include

Exclude

# Characteristics of Problematic Trials

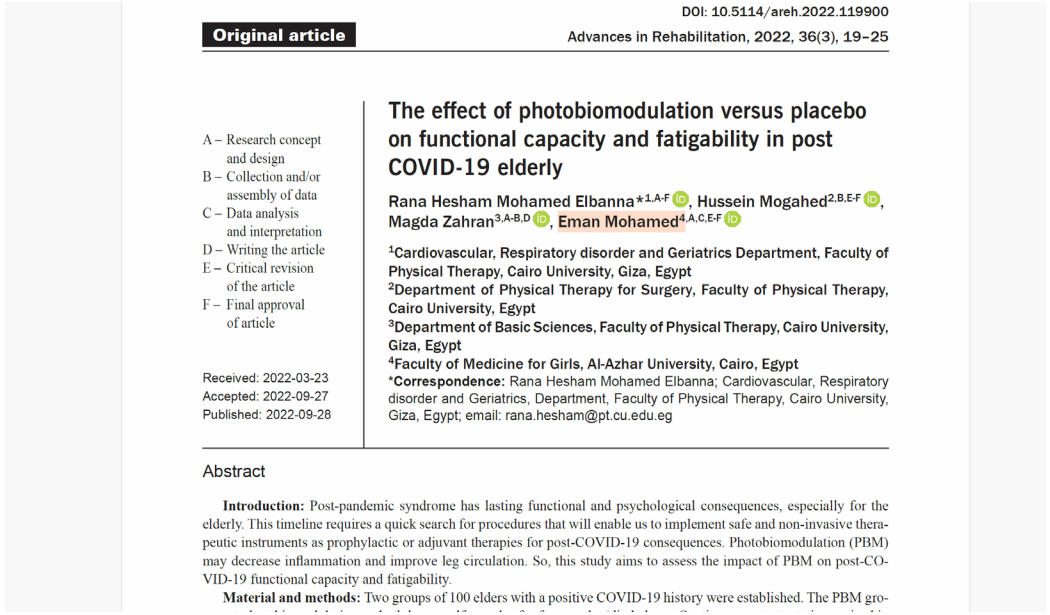



One third of trials contained issues that raised concerns about their integrity and were ultimately disregarded from our review.

# Characteristics of Problematic Trials

| Concerns | Number of trials |
|---|---|
| Fewer than three authors | 2 |
| Author with history of retraction(s) | 1 |
| Not registered | 4 |
| Retrospective registration | 3 |
| Critical design differences between trial report and trial registration | 2 |
| Inconceivably fast recruitment of participants within a single center | 1 |
| Improbably small number of participants (or 0 participants) discontinued the trial | 4 |
| Baseline characteristics unlikely with randomization | 3 |
| Suspicious outcome data | 2 |
| Implausibly positive results | 4 |

# Example Problematic Trial



DOI: 10.5114/areh.2022.119900
Original article
Advances in Rehabilitation, 2022, 36(3), 19–25

A – Research concept and design
B – Collection and/or assembly of data
C – Data analysis and interpretation
D – Writing the article
E – Critical revision of the article
F – Final approval of article

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## The effect of photobiomodulation versus placebo on functional capacity and fatigability in post COVID-19 elderly

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[2]Department of Physical Therapy for Surgery, Faculty of Physical Therapy, Cairo University, Egypt
[3]Department of Basic Sciences, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[4]Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
*Correspondence: Rana Hesham Mohamed Elbanna; Cardiovascular, Respiratory disorder and Geriatrics, Department, Faculty of Physical Therapy, Cairo University, Giza, Egypt; email: rana.hesham@pt.cu.edu.eg

Abstract

**Introduction:** Post-pandemic syndrome has lasting functional and psychological consequences, especially for the elderly. This timeline requires a quick search for procedures that will enable us to implement safe and non-invasive therapeutic instruments as prophylactic or adjuvant therapies for post-COVID-19 consequences. Photobiomodulation (PBM) may decrease inflammation and improve leg circulation. So, this study aims to assess the impact of PBM on post-COVID-19 functional capacity and fatigability.

**Material and methods:** Two groups of 100 elders with a positive COVID-19 history were established. The PBM gro-

1. Even, round numbers
2. Equal numbers of participants randomized to each arm without block randomization
3. Remarkably similar baseline characteristics across arms
4. 0 attrition
5. Exceptionally small variability in outcome measures
6. Trial registration describes a different trial
7. Author with a history of retractions due to research integrity issues

# Findings

| Comparison | Recovery /important improvement | Fatigue | Physical function | Cognitive function | Mental health | Quality of life / Wellbeing | Serious adverse events |
|---|---|---|---|---|---|---|---|
| | Effect estimates | | | | | | |
| Physical and mental rehabilitation program vs. Usual care | 161 more per 1,000 (61 more to 292 more)<br>RR: 1.55 (1.21 to 2)a | -2 (-3.96 to -0.04) | 0.5 (-1.01 to 2.01) | 1 (-0.44 to 2.44) | -1 (-1.98 to -0.02)<br>-1.5 (-2.41 to -0.59) | 0.04 (0 to 0.08) | 20 more per 1,000 (10 fewer to 50 more) |
| CBT vs. Usual care | 326 more per 1,000 (100 more to 695 more)<br>RR: 2.24 (1.38 to 3.64)b | -8.4 (-13.11 to -3.69) | 4.9 (-1.89 to 11.69) | -5.2 (-7.97 to -2.43) | | | 0 more per 1,000 (30 fewer to 30 more) |
| A combinationn of probiotics and prebiotics ('Synbiotics') called SIM01 vs. Usual care | Fatigue<br>200 more per 1,000 (94 more to 336 more)<br>RR: 1.47 ( 1.22 to 1.79)a<br>Concentration<br>239 more per 1,000 (112 more to 401 more)<br>RR: 1.62 ( 1.29 to 2.04)b<br>Dyspnea<br>150 more per 1,000 (27 more to 290 more)<br>RR: 1.28 ( 1.05 to 1.54)c | | | | | 1.5 (-0.87 to 3.87) | 0 more per 1,000 (10 fewer to 10 more) |
| Intermittent aerobic exercise vs. Continuous aerobic exercise | | | 3.8 (1.12 to 6.48) | | 0 (-3.69 to 3.69) | | |
| Transcranial direct current stimulation, Physiotherapy, Education related to activities of daily living vs. Physiotherapy, Education related to self-management | 315 more per 1,000 (59 more to 699 more)<br>RR: 1.69 (1.13 to 2.53)d | -12.4 (-17.33 to -7.47) | | | -4.91 (-7.5 to -2.32) | 14.8 (8.86 to 20.74) | 0 more per 1,000 (50 fewer to 50 more) |
| Multicomponent exercise of progressively increasing intensity, Physiotherapy vs. Physiotherapy | | | 6.96 (2.7 to 11.22) | | 2.06 (-3.52 to 7.64) | | |
| Hyperbaric oxygen therapy vs. Usual care | | | -5.2 (-14.06 to 3.66) | 3.4 (0.3 to 6.5) | -7.1 (-12.23 to -1.97)<br>10 (-0.01 to 20.01) | | |
| Vortioxetine vs. Usual care | | | | -0.02 (-0.24 to 0.2) | -1.59 (-3 to -0.18) | 2.36 (0.71 to 4.01) | |
| Telerehabilitation app ('ReCOVery') vs. Usual Care | | | -3.46 (-9.07 to 2.15) | 0.61 (-0.9 to 2.12) | 1.87 (-5.39 to 9.13) | | 0 more per 1,000 (40 fewer to 40 more) |
| Leronlimab vs. Usual care | | -0.08 (-0.65 to 0.49) | | 0.08 (-0.45 to 0.61) | 0.03 (-0.45 to 0.51) | | |
| Inspiratory muscle training vs. Usual care | | | | | | -1.3 (-5.9 to 3.3) | |
| Amygdala and insula retraining vs. Education related to self-management | | -1.48 (-3 to 0.04) | | | | | |
| Coenzyme Q10 vs. Usual Care | | | | | | -0.04 (-0.1 to 0.02) | 0 more per 1,000 (30 fewer to 30 more) |
| L-arginine, vitamin C vs. Usual care | 826 more per 1,000 (155 more to 3366 more)<br>RR: 10.5 (2.78 to | | | | | | 0 more per 1,000 (80 fewer to 80 more) |
| Glucosaminyl muramyl dipeptide ('Liposid') vs. | | | 6.88 (2.92 to 10.84) | | -2.47 (-4.52 to -0.42) | | |

**GRADE ratings and interpretation**

| | | | |
|---|---|---|---|
| **High certainty** | Definitely more effective | Definitely worse | Definitely no different |
| **Moderate certainty** | Probably more effective | Probably worse | Probably no different |
| **Low certainty** | May be more effective | May be worse | May be no different |
| **Very low certainty** | We are very uncertain | | |

# Findings

## Outcomes

| Comparison | Recovery /important improvement | Fatigue | Physical function | Cognitive function | Mental health | Quality of life / Wellbeing | Serious adverse events |
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| | Effect estimates | | | | | | |
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| CBT vs. Usual care | 326 more per 1,000 (100 more to 695 more)<br>RR: 2.24 (1.38 to 3.64)b | -8.4 (-13.11 to -3.69) | 4.9 (-1.89 to 11.69) | -5.2 (-7.97 to -2.43) | | | 0 more per 1,000 (30 fewer to 30 more) |
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# Findings

## Comparisons

| Comparison | Recovery /important improvement | Fatigue | Physical function | Cognitive function | Mental health | Quality of life / Wellbeing | Serious adverse events |
|---|---|---|---|---|---|---|---|
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**GRADE ratings and interpretation**

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# Findings

**GRADE ratings and interpretation**

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# Findings

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# Findings

| | |
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| Pharmacologic | Vortioxetine, leronlimab, glucosaminyl muramyl dipeptide (‘Licopid’), actovegin |
| Physical activity and rehabilitation | Acupuncture, inspiratory muscle training, active cycle of breathing |
| Behavioral interventions | Mobile educational application (‘Recovery’), amygdala and insula retraining |
| Diet and dietary supplements | Co-enzyme Q10, L-arginine and liposomal vitamin C, combination of trimethyl hydrazinium propionate and ethyl methyl hydroxy pyridine succinate (‘Brainmax’) |
| Medical devices and technologies | Hyperbaric oxygen, active high-definition transcranial direct current stimulation, photobiomodulation, active hydrogen therapy |
| Interventions for anosmia/ hyposmia | Alpha-lipoic acid, mometasone furoate nasal spray, a combination of ultramicronized palmitoylethanolamide and luteolin, pentasodium diethylenetriamine pentaacetate intranasal spray, injections of cerebrolysin |

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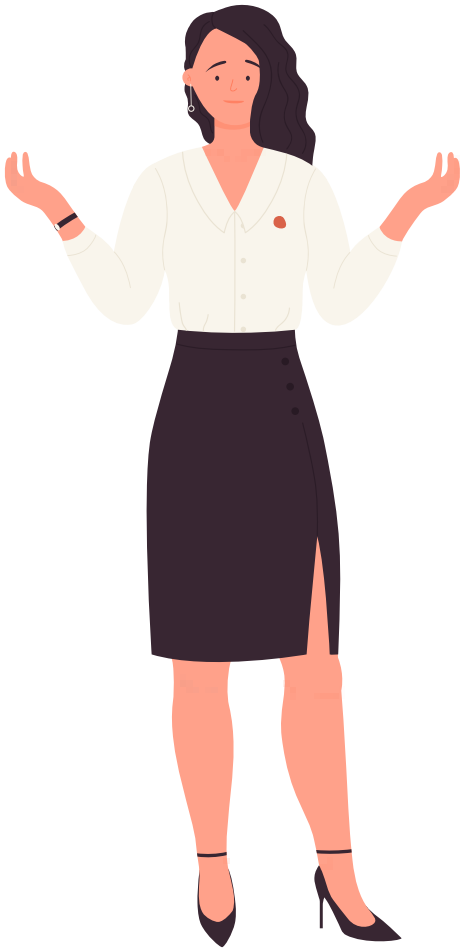
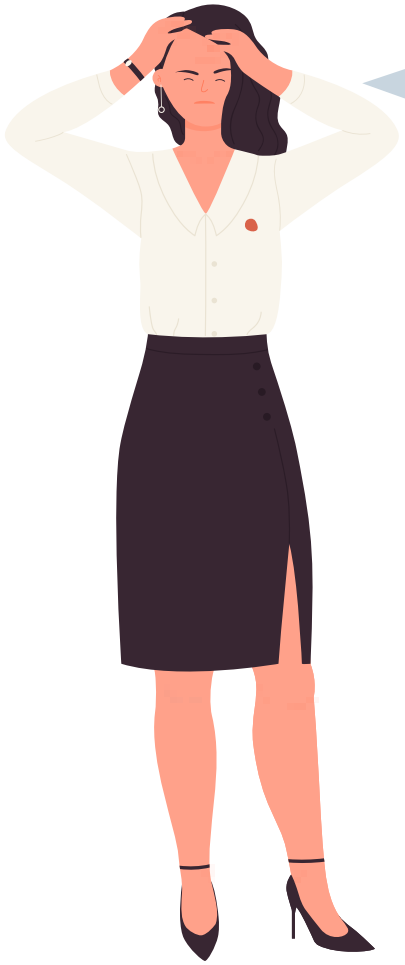
# Lessons Learned



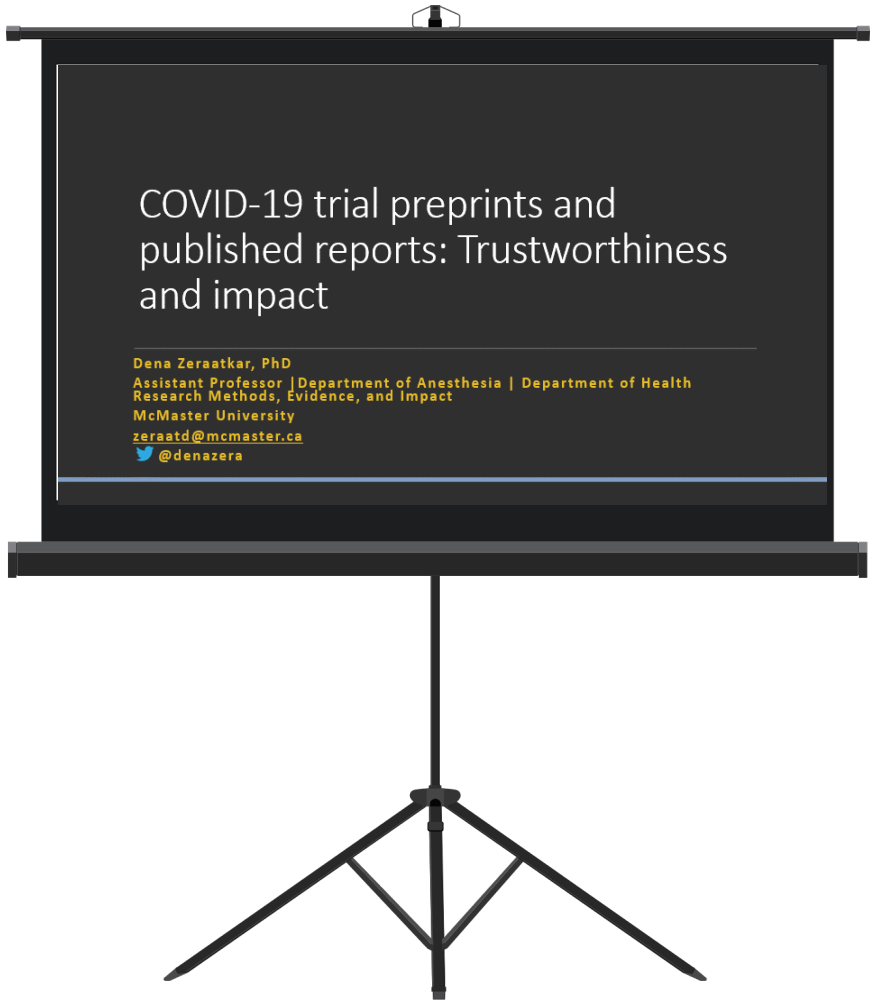
Our experience performing this exercise suggests that problematic trials are very common and so reviewers should certainly be vigilant and incorporate research integrity checks.

# Lessons Learned



It's difficult to judge whether a trial is fabricated or whether data have been falsified

# Lessons Learned

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