

An introduction to prospective meta-analysis (PMA)



Cochrane Methods
Prospective Meta-analysis

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SYDNEY

Disclosures and acknowledgements

- Co/Associate Convenors Cochrane PMA Methods Group



- Chair & Co-chair of TOPCHILD Collaboration



- Steering Group, EPOCH Collaboration



- Chair & Steering Group, iCOMP Collaboration



- Members, NeOProm Collaboration



- Research associates, ANZCTR



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What is your professional background?

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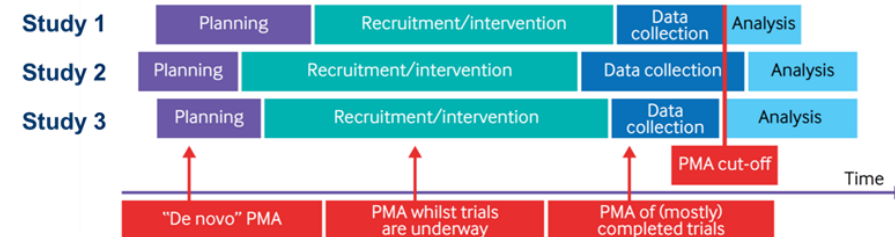
Why did you join the webinar today?

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Learning objectives

- ▶ Limitations of retrospective systematic reviews and meta-analyses
- ▶ Prospective meta-analyses
 - ▶ Definition
 - ▶ Main steps and differences to traditional systematic reviews and meta-analyses
 - ▶ Prospective meta-analyses and other 'Next Gen' methodologies

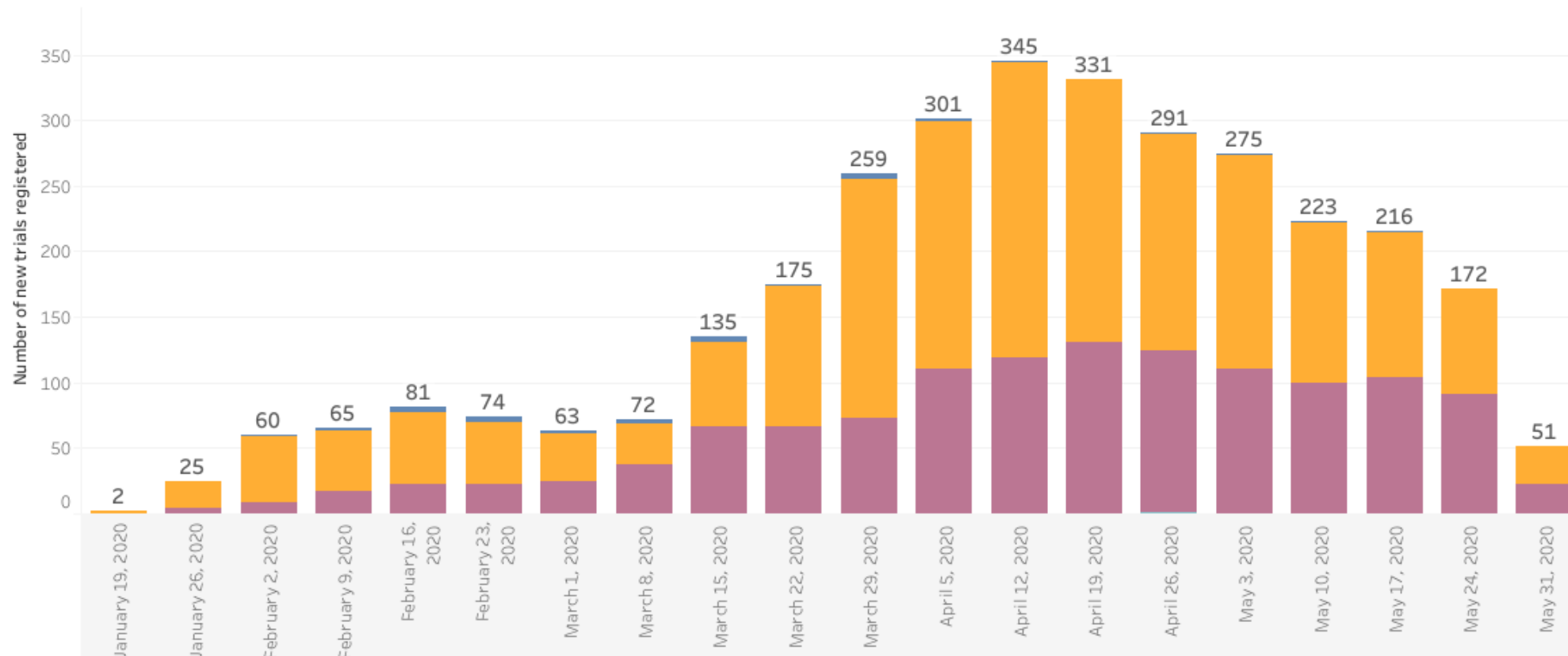
To help you pay attention, there will be a quiz!



COVID 19 - New trials emerged at unprecedented speed

Study type
■ Diagnostic test ■ Interventional (study) ■ Observational (study) ■ Unknown

New trials registered each week



The problem: Majority of trials underpowered to detect differences in important clinical outcomes

The target sample sizes we have...

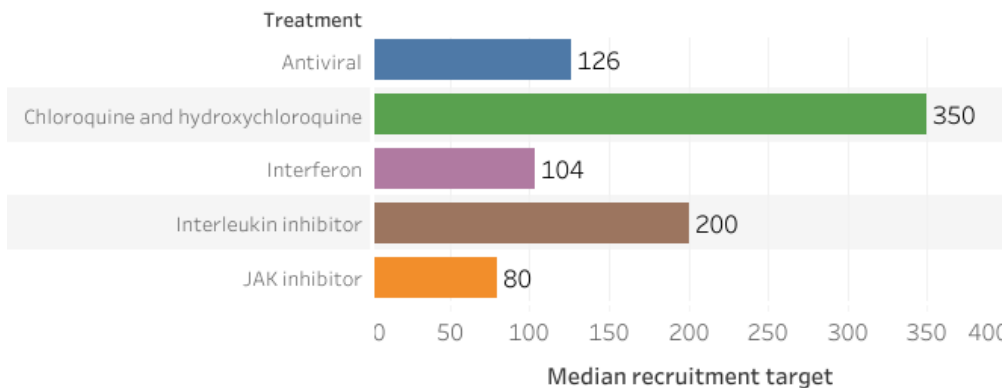


Figure. Median target sample size for COVID trials by treatment up to May 2020

Source: Trials registered on primary WHO trial registries and ClinicalTrials.gov, accumulated on <https://covid.inato.com/>,

The sample sizes we need to detect differences in mortality...

	Death rate control group	Death rate intervention group	Absolute risk difference	Required sample size	Required sample size subgroup differences
Scenario 1	25%	20%	5%	2,188	~10,000
Scenario 2	30%	27%	3%	7,106	~30,000

Table. Power calculations for reduction of absolute death for hospitalised COVID-19 patients 80% power at $\alpha=0.5$ (Mortality rates source: PMID: 32171076)

But: many trials are addressing the same research question

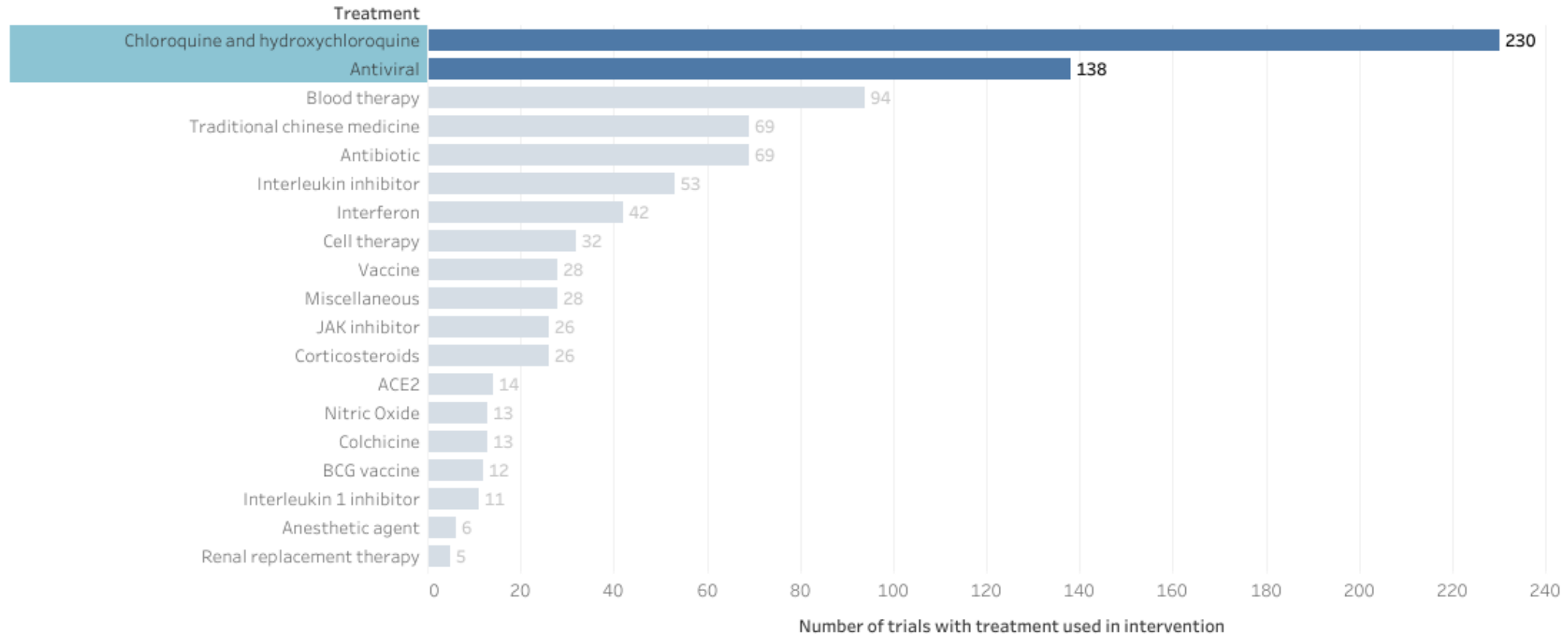
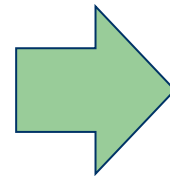
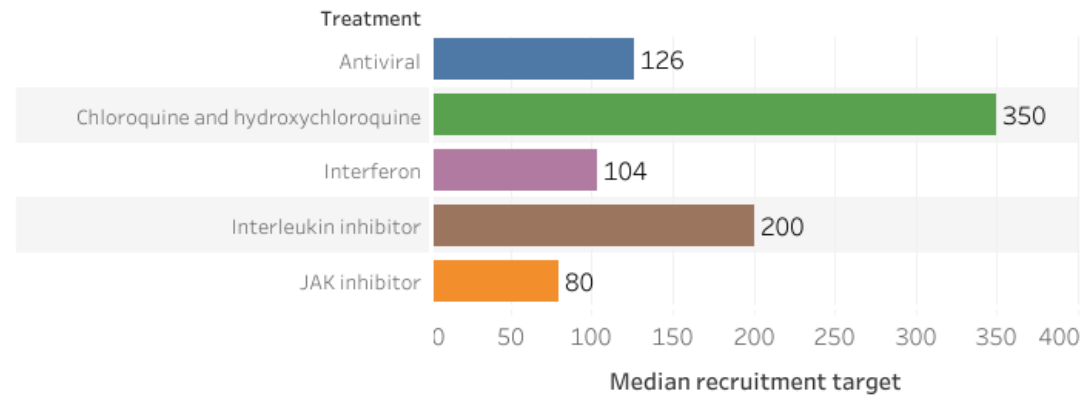


Figure. Number of trials per treatment category for currently registered COVID trials May 2020

Source: Trials registered on primary WHO trial registries and ClinicalTrials.gov, accumulated on <https://covid.inato.com/>,

The solution: Collaboration through Prospective Meta-Analysis!

Individual trials are underpowered



In combination, trials have excellent power to detect differences in mortality and other important outcomes

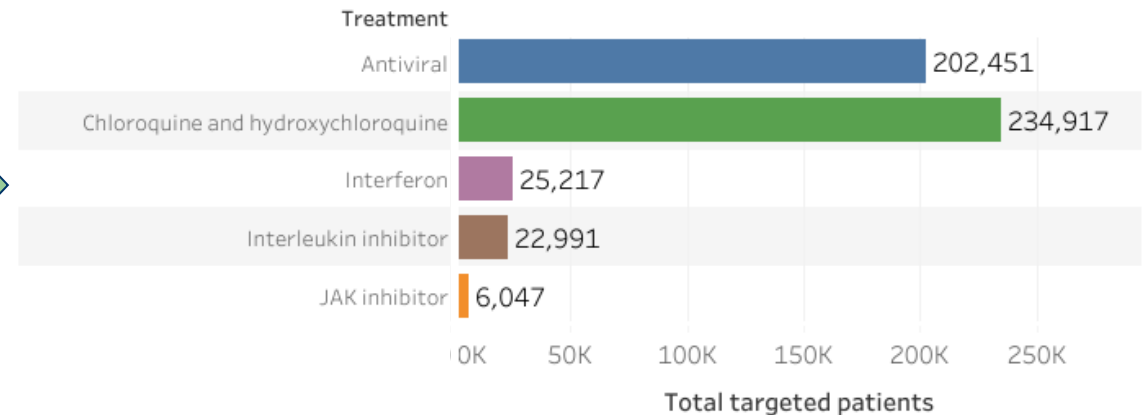


Figure. Median recruitment target individual patients May 2020

Source: Trials registered on primary WHO trial registries and ClinicalTrials.gov, accumulated on <https://covid.inato.com/>,

Figure. Total number of targeted patients per treatment across trials May 2020

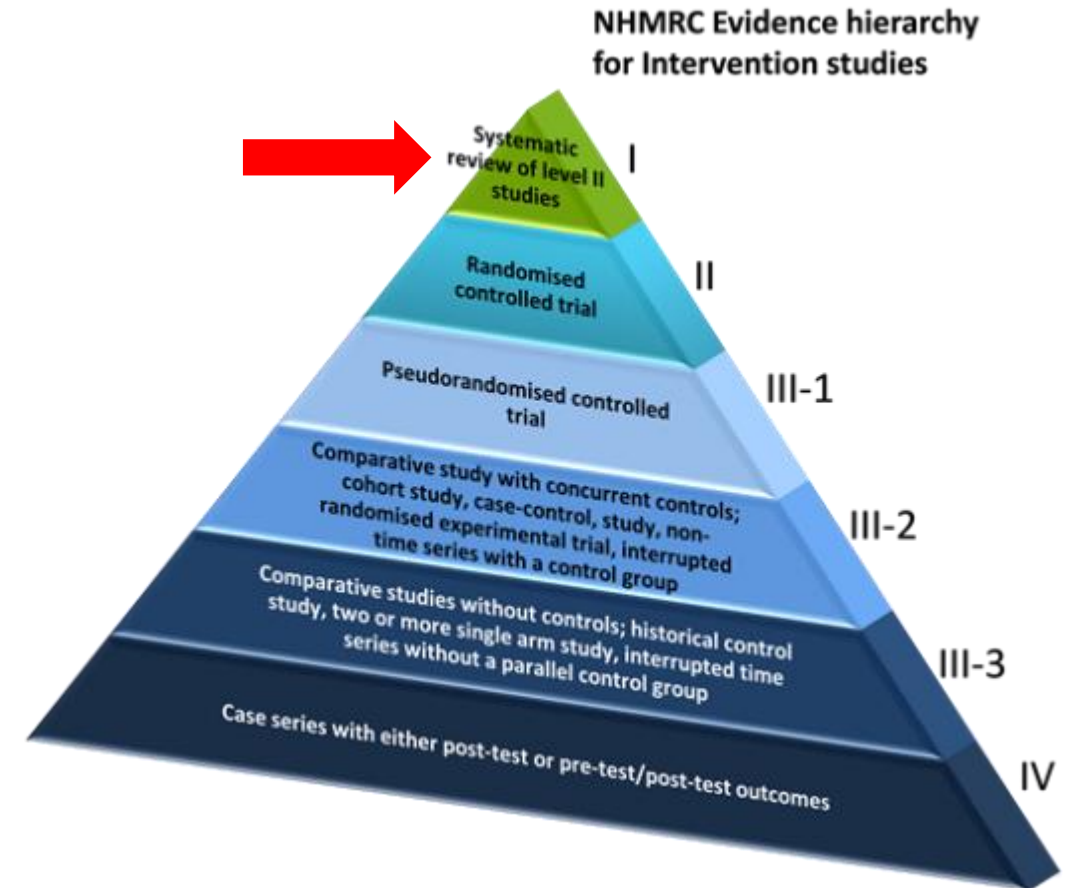
Source: Trials registered on primary WHO trial registries and ClinicalTrials.gov, accumulated on <https://covid.inato.com/>,

Why can't we wait for each trial to publish their results to then combine them in a traditional systematic review and meta-analysis?

Systematic reviews: top of evidence hierarchy

Widely used to inform healthcare policy and practice

Several limitations and potential sources of bias



Publication bias and selective outcome reporting

...and this is where we put the non-significant results.



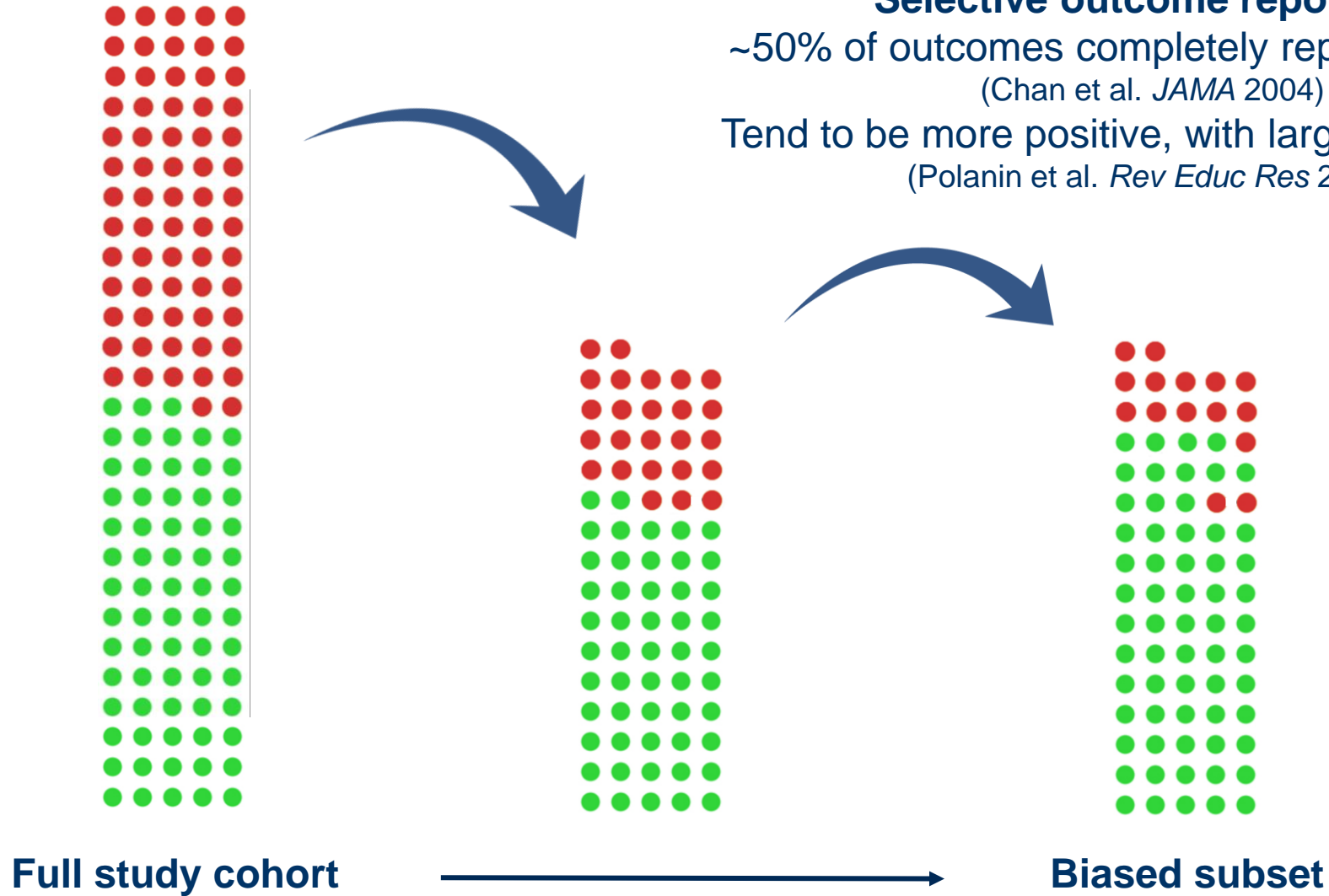
som^{ee}cards
user card

Publication bias:

~50% studies publish results
(Schmucker et al. *PloS one* 2014)

Selective outcome reporting:

~50% of outcomes completely reported per trial
(Chan et al. *JAMA* 2004)
Tend to be more positive, with larger effect sizes
(Polanin et al. *Rev Educ Res* 2016)

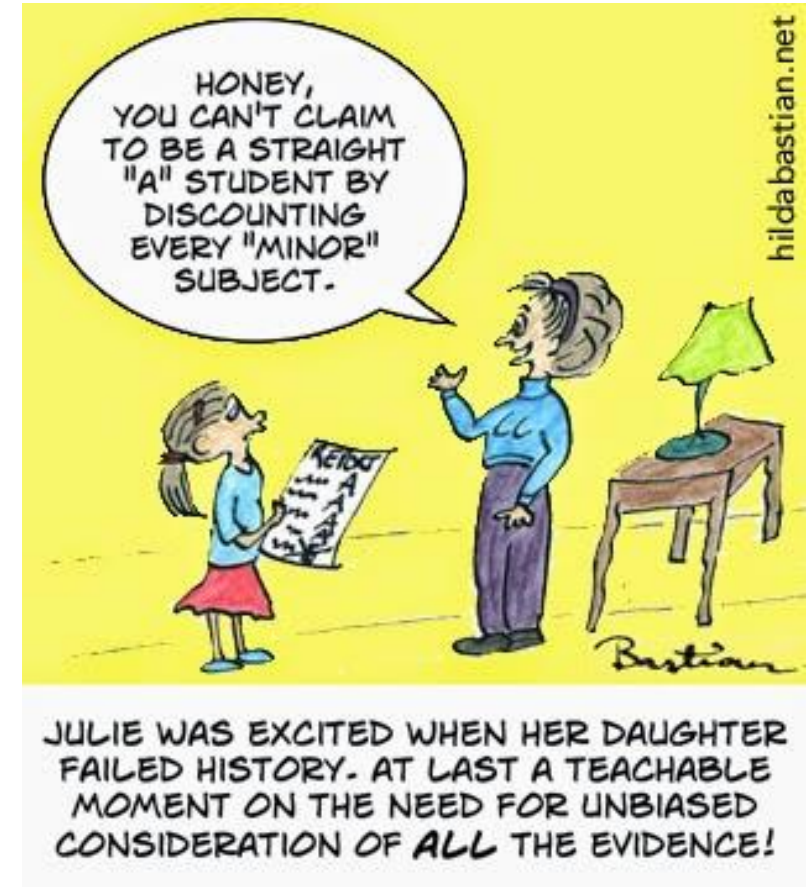


- Negative trial
- Positive trial

Figure adapted from De Vries et al. *Psychological Medicine*, 2018; 48(15), 2453-2455.

Retrospective inclusion of studies

- Knowledge of study results may influence hypothesis and selection criteria
- Meta-analyses on the same topic sometimes reach conflicting conclusions because of different eligibility criteria



Example: Julie's daughter knew she had failed history when she decided to exclude 'minor subjects' from her evidence synthesis

Differences between studies

Inconsistencies across individual studies in design, outcome measurement and analyses

Different populations

Different outcomes

Different measures

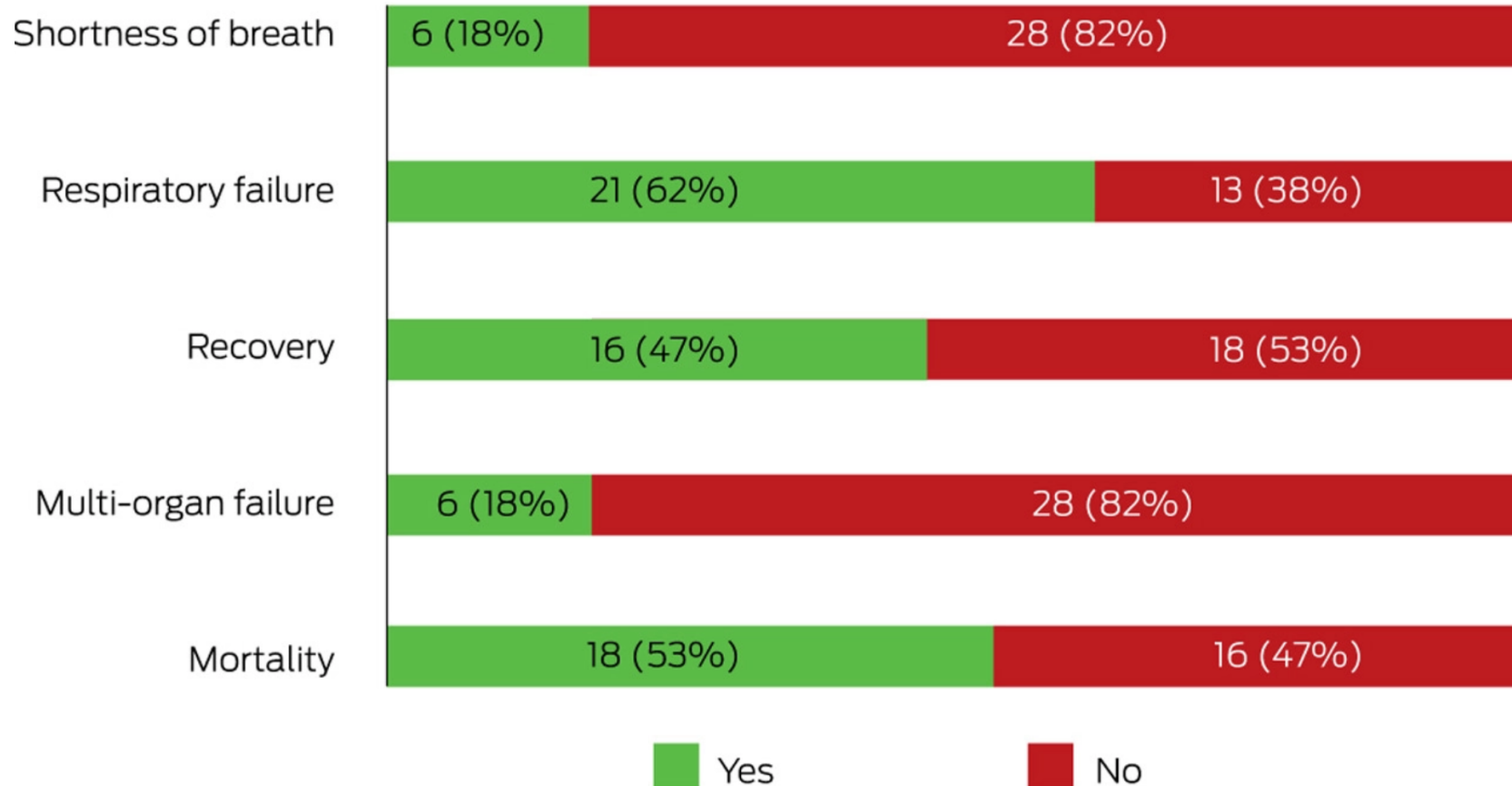
Different time points

Different analyses



➔ Synthesis difficult and sometimes impossible

Trials collecting core outcomes for COVID-19



Variation in what is being measured, and how.....

Intervention study	Anthropometric measures	Physical activity	Dietary intake	Sleep	Feeding
Study A	✓ Height, weight, BMI		✓ Food Freq checklist		✓ CFP Questionnaire
Study B	✓ Body comp. (DEXA scan)	✓ Accelerometer		✓ Accelerometer	✓ FPS Questionnaire
Study C	✓ BMI z-score	✓ Tummy time questionnaire	✓ NHANES questionnaire	✓ Bedtime self report	
Study D	✓ BMI, waist circumf.			✓ Hours slept self report	

Solution

Editorial

Next-generation systematic reviews: prospective meta-analysis, individual-level data, networks and umbrella reviews

John Ioannidis

“All primary original research may be designed, executed, and interpreted as prospective meta-analyses.”

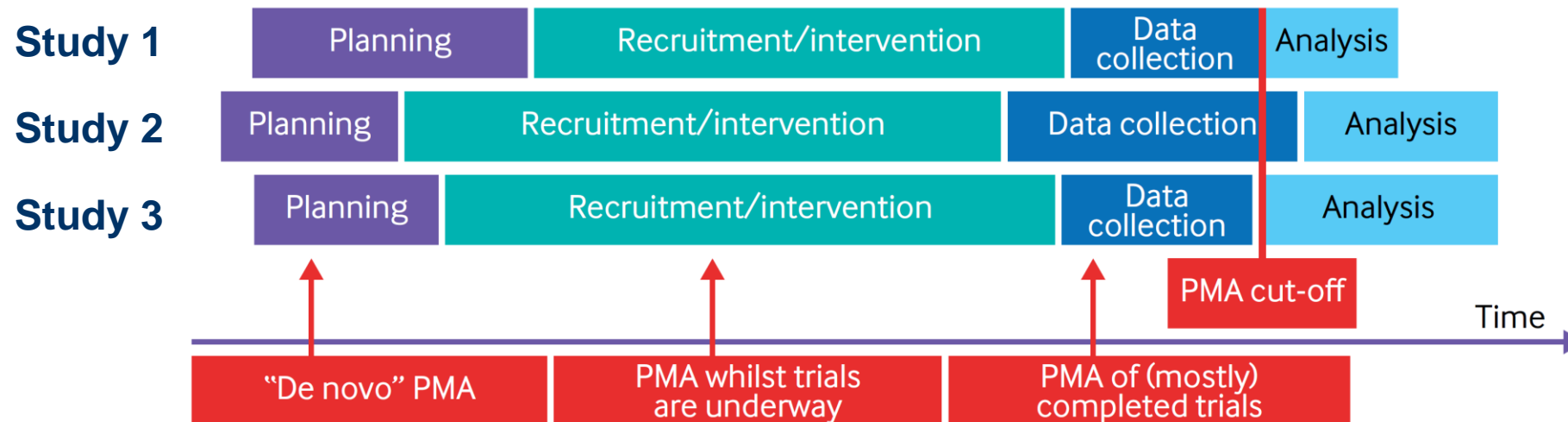
Ioannidis JP. Meta-research: The art of getting it wrong. Res Synth Methods 2010;1:169-84.
doi:10.1002/jrsm.19

Prospective meta-analysis



Definition prospective meta-analysis (PMA)

Studies are identified as eligible for inclusion in the meta-analysis, and hypotheses and analysis strategies are specified, **before** the results of the studies or cohorts related to the PMA research question are known



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Have you ever conducted a prospective meta-analysis?

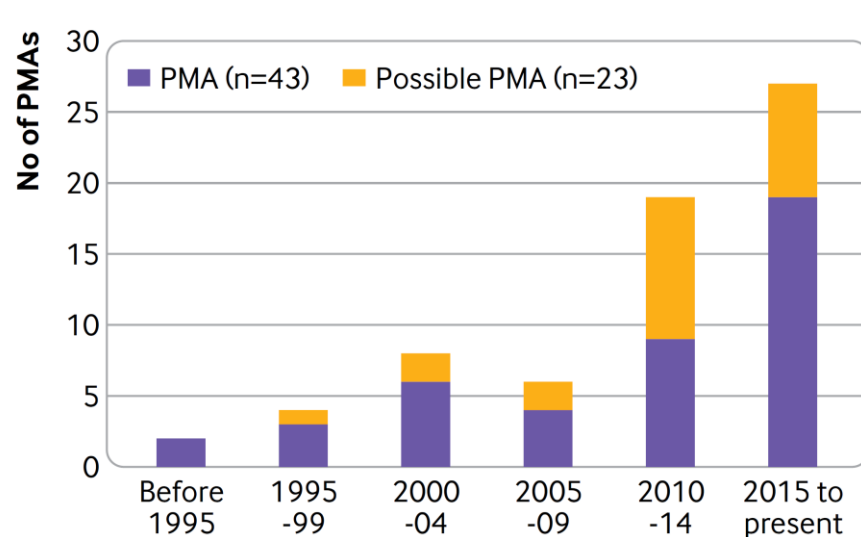


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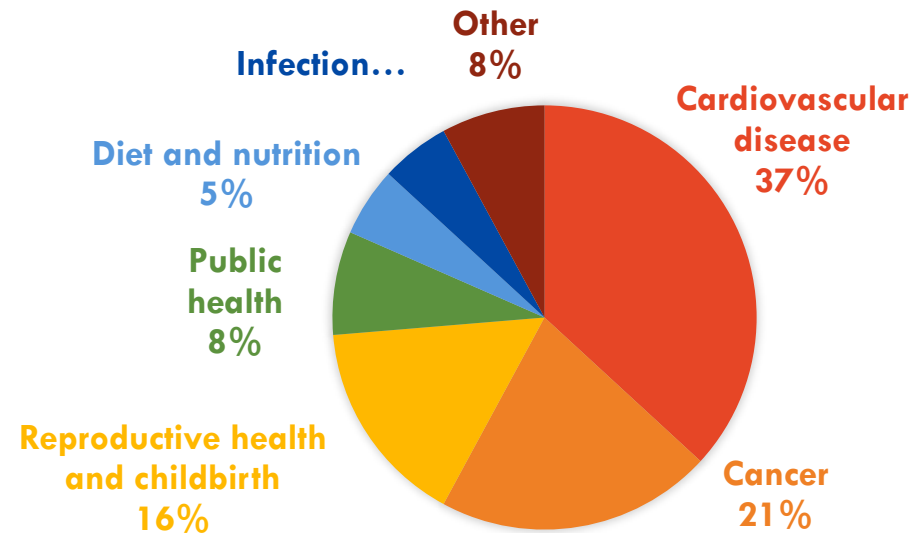
Prospective meta-analysis: scoping review

- Number is increasing
- Used in different areas of health research

Definition, methodology, and reporting of previous PMAs vary greatly



Seidler et al BMJ 2019

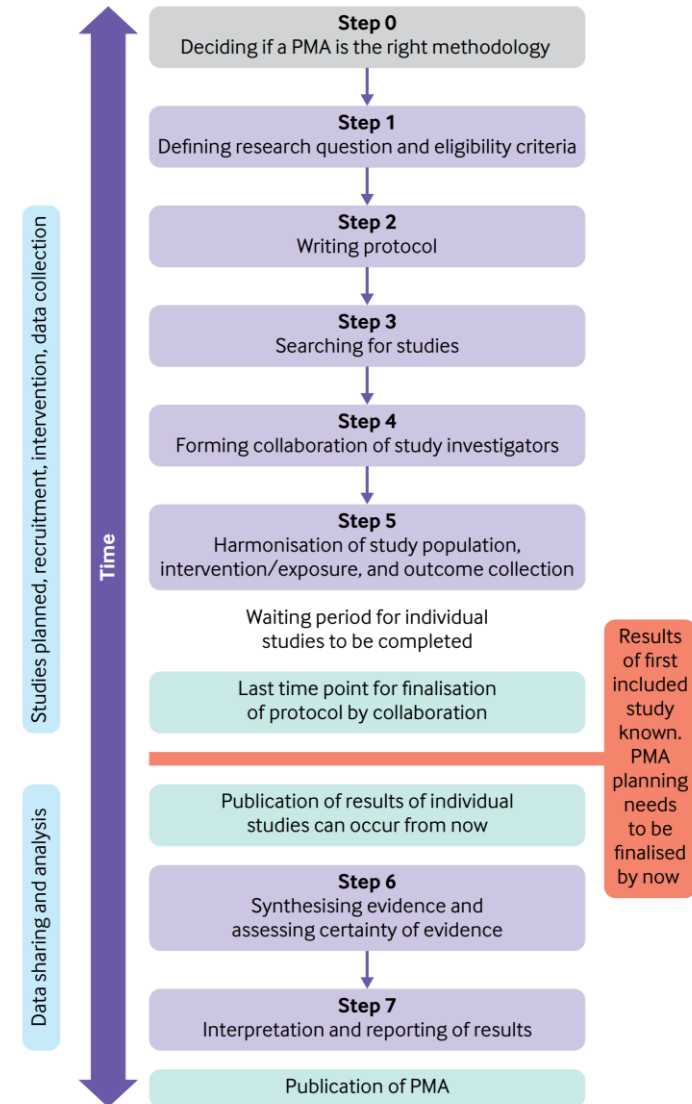


A guide to prospective meta-analysis

Anna Lene Seidler,¹ Kylie E Hunter,¹ Saskia Cheyne,¹ Davina Gherzi,^{1,2} Jesse A Berlin,³ Lisa Askie¹

Developed step-by-step guidance based on

- 1) Scoping review of methodology papers
- 2) Scoping review of existing PMAs
- 3) Expert opinions from the PMA methods group
- 4) Experiences with previous PMA

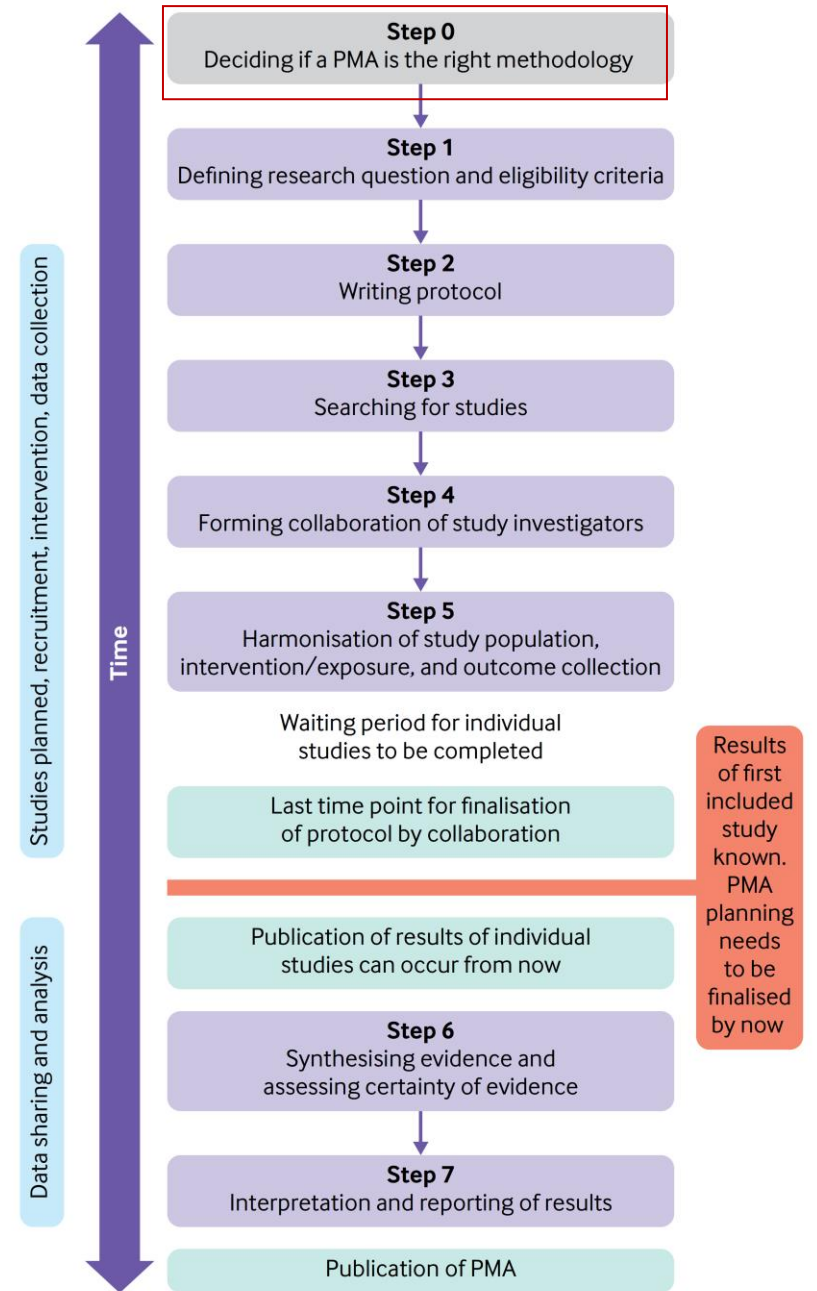


Step 0: Deciding if PMA is the right methodology

PMA should be considered for

- High priority research questions
- Limited previous evidence
- New studies expected to emerge

PMA can be a catalyst for initiating a programme of priority research



Steps 1 & 2: research question, eligibility criteria, protocol

Eligibility criteria & protocol:

- Before any results are known → avoid selective reporting bias and outcome-based selection of studies
- PROSPERO registration

Prospective meta-analyses can include:

- Interventional or observational studies
- Individual participant data (IPD) or aggregate data
- For aggregate data: FAME (Tierney et al 2021)


PLOS MEDICINE

advanced search

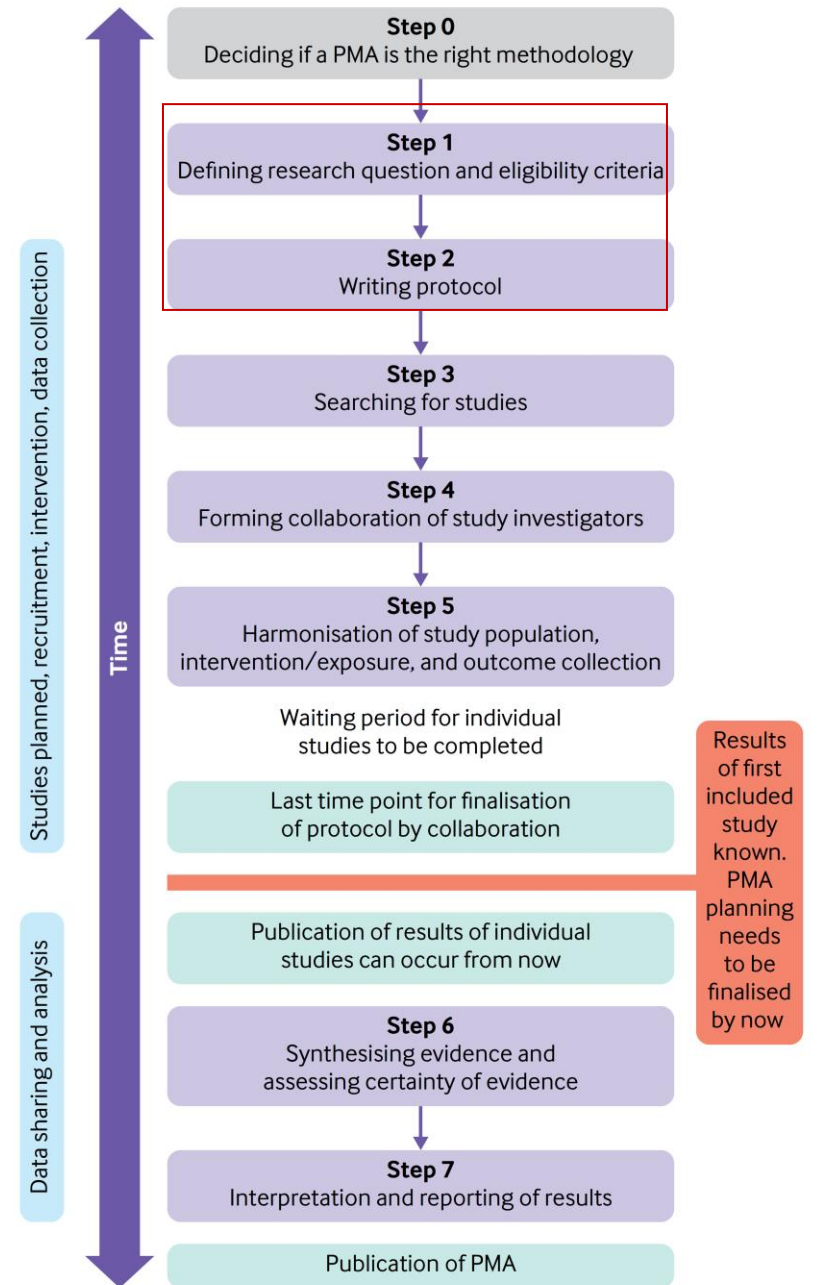
OPEN ACCESS

GUIDELINES AND GUIDANCE

A framework for prospective, adaptive meta-analysis (FAME) of aggregate data from randomised trials

Jayne F. Tierney , David J. Fisher, Claire L. Vale, Sarah Burdett, Larysa H. Rydzewska, Ewelina Rogozińska, Peter J. Godolphin, Ian R. White, Mahesh K. B. Parmar

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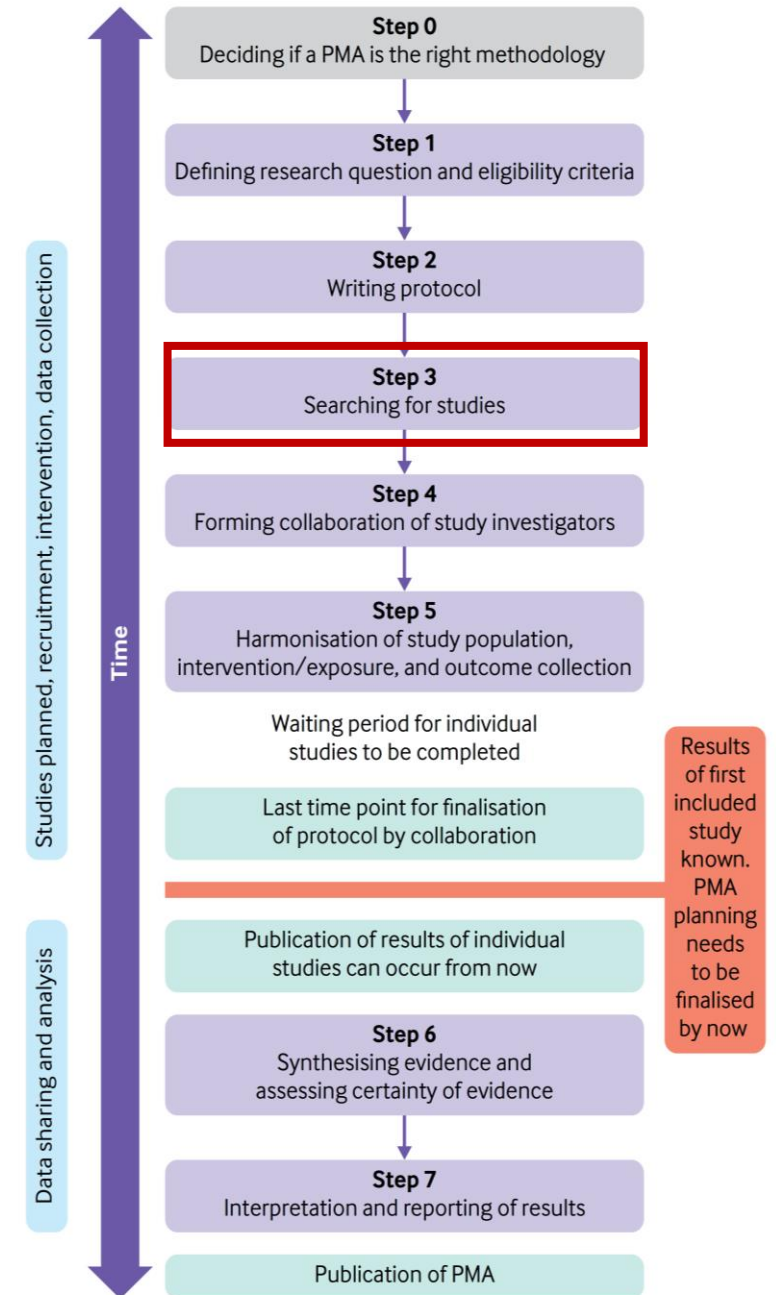


Step 3: Searching for studies



How to find planned and ongoing studies

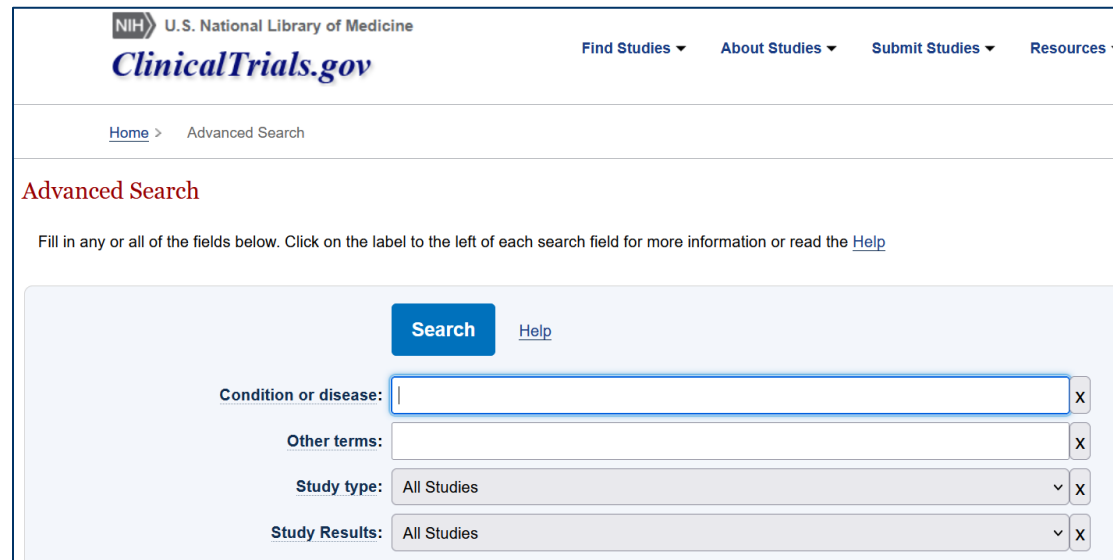
- Clinical Trial Registries
- Searching for protocols & cohort descriptions
- Approaching relevant stakeholders
- Publicising PMA through protocol, websites, research forums, conferences...



Searching for registration records: key recommendations

- Search ClinicalTrials.gov & World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) as a minimum (note different tools & rules)
- Avoid using search filters offered by registries, e.g. study type (interventional, observational)
- Test whether search strategy retrieves pre-identified eligible studies (if possible)

Hunter et al. 2021, *manuscript in preparation*



NIH U.S. National Library of Medicine
ClinicalTrials.gov
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Advanced Search

Fill in any or all of the fields below. Click on the label to the left of each search field for more information or read the [Help](#)

[Help](#)

Condition or disease: X

Other terms: X

Study type: All Studies ▾ X

Study Results: All Studies ▾ X



World Health Organization
International Clinical Trials Registry Platform
Search Portal

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[Search tips](#)

Restrict to COVID-19

Search for [clinical trials in children](#)

Without Synonyms

Phases are ▾

Phase 0

Phase 1



Step 4: Forming collaboration

Steering Group

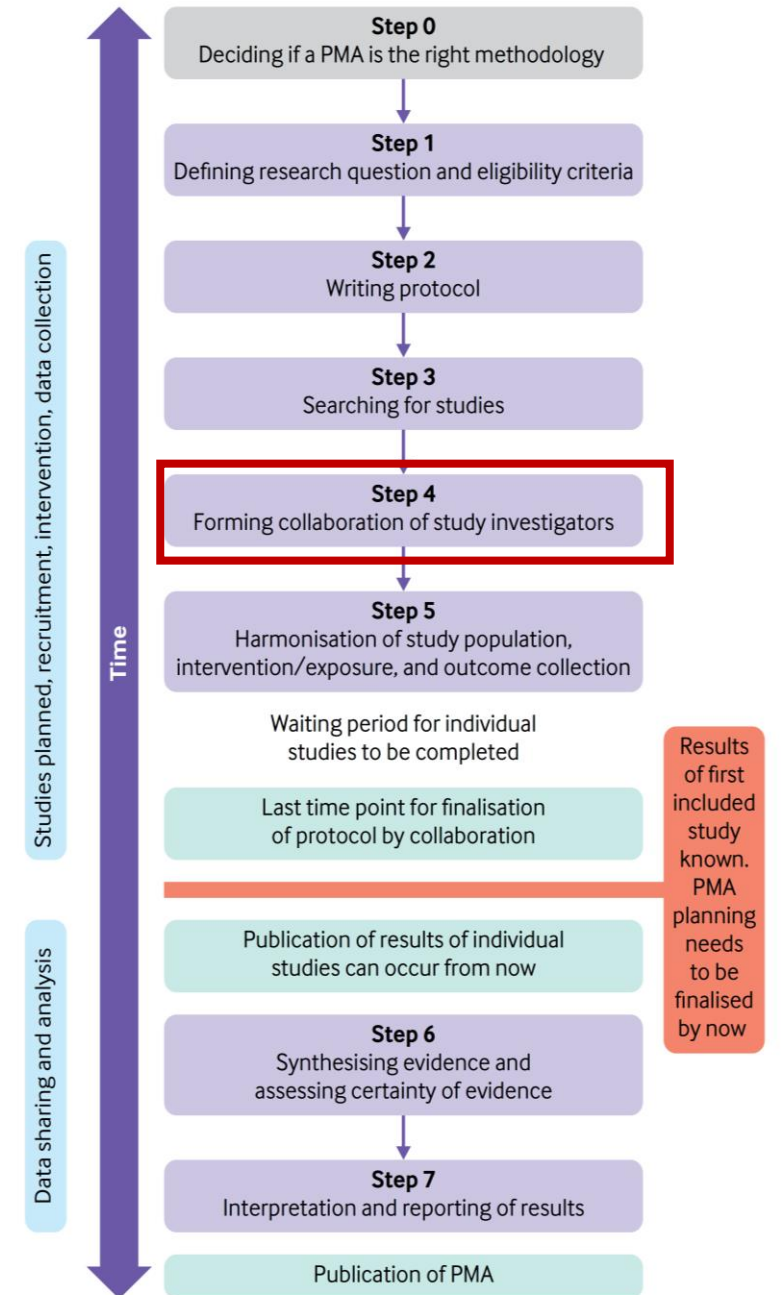
Chair, Co-Deputy Chairs and Senior Advisors,
Data & Project Management

Advisory Group

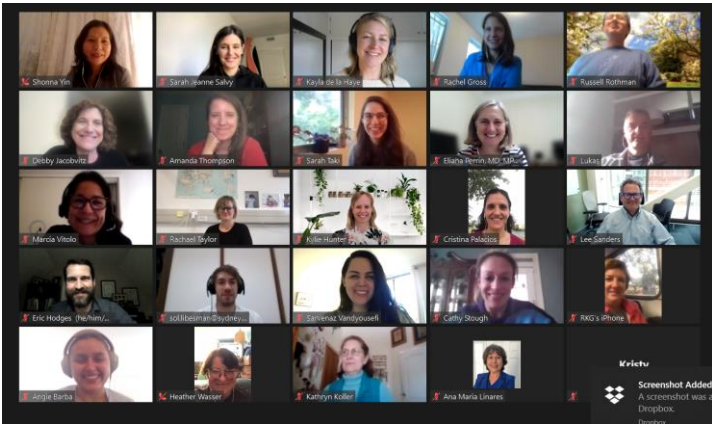
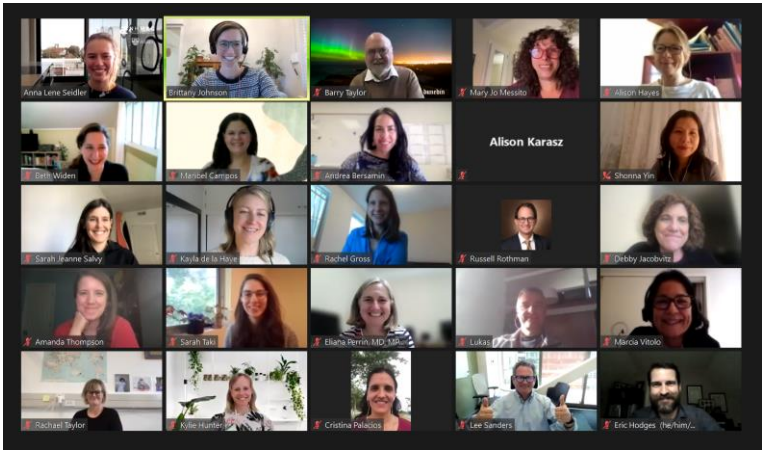
Clinicians, methodologists, policy makers,
economists, consumer representatives

Trial representatives

1-2 per trial



Prospective meta-analyses involve people!



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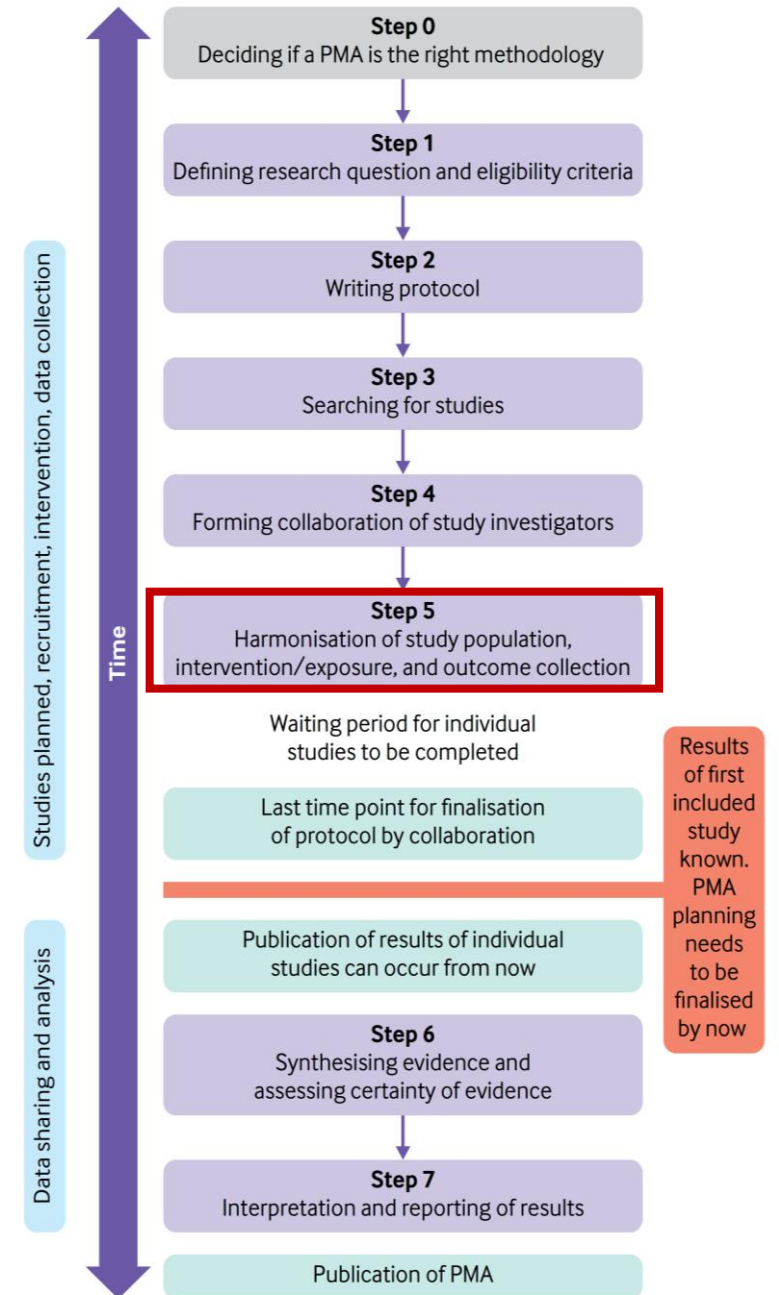
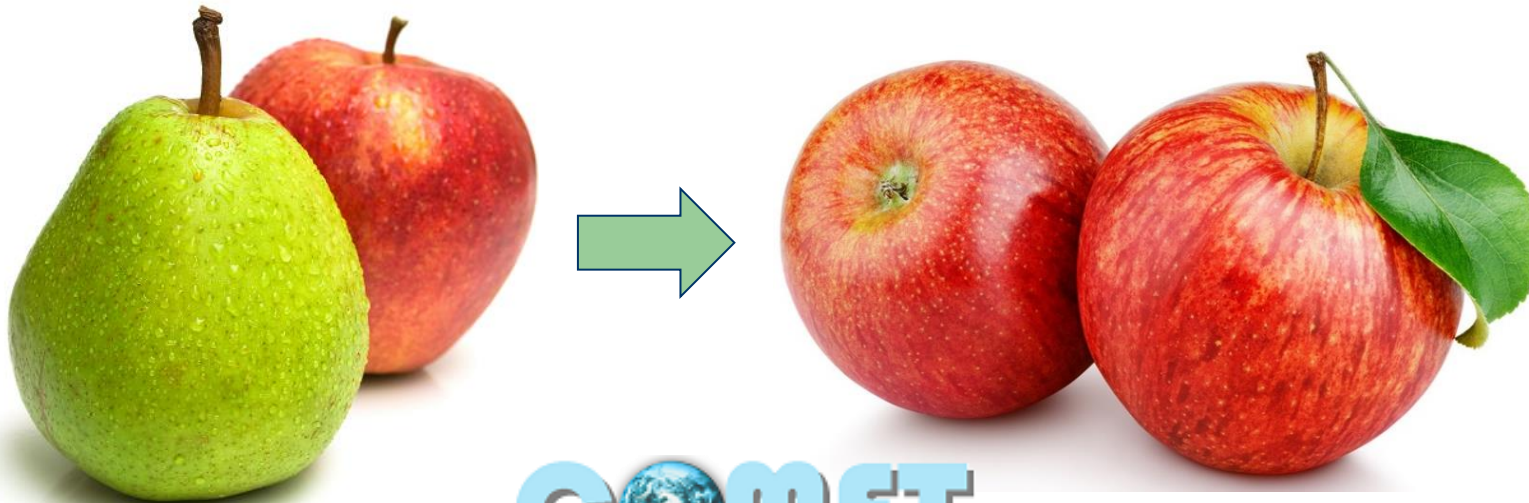


What is your favourite aspect of collaboration?

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PMAAs allow for harmonisation common CORE outcome sets

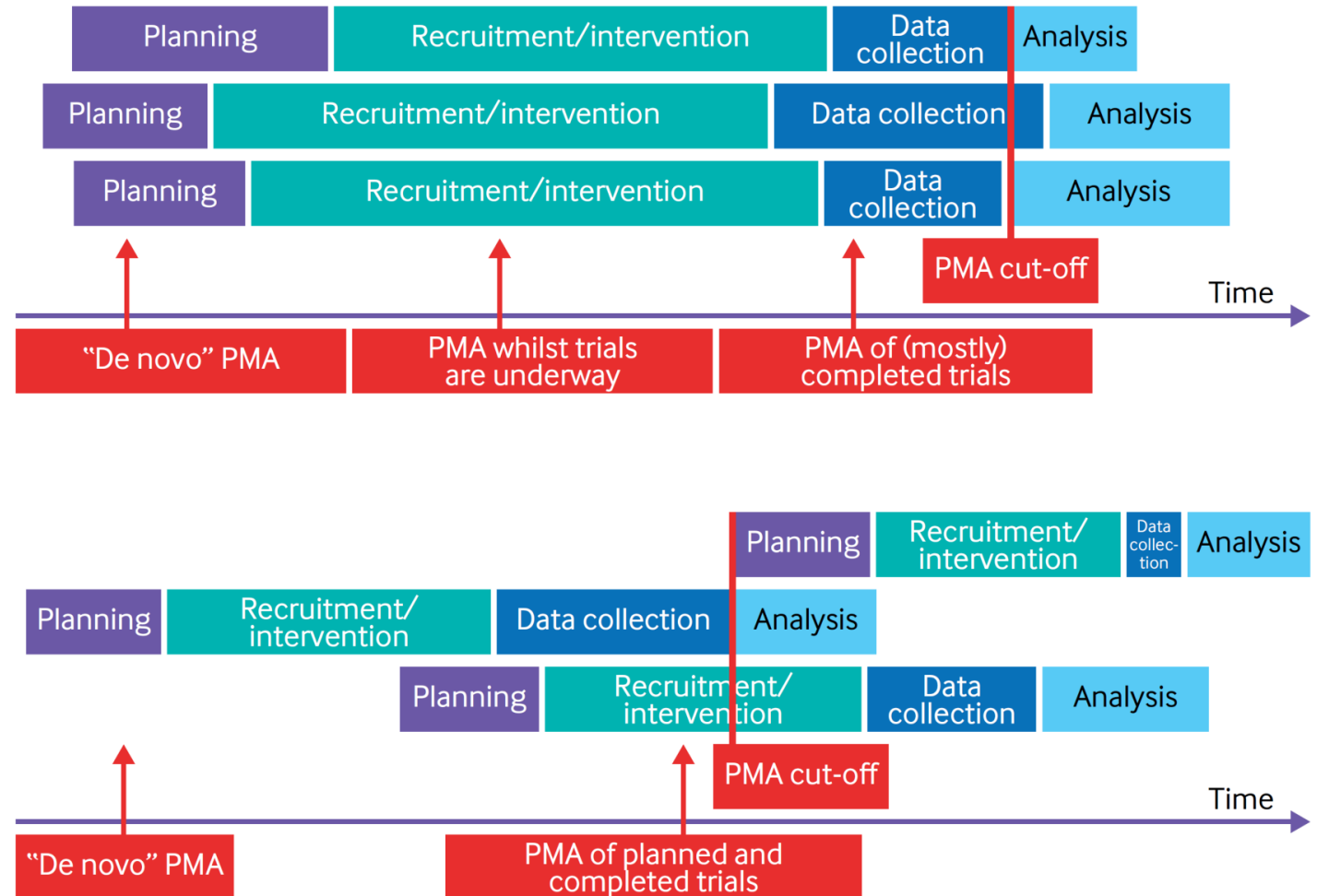
- Same **CORE** outcomes, same instruments & time points
- Enables collection of rare adverse side effects (combined power)
- Harmonisation does *not* require exactly the same protocol



Ability to harmonise depends on stage at which studies are included

Once a collaboration is formed, collaboration members can work together to harmonise:

- Populations
- Interventions/ exposures
- Common **core** outcomes



Early Prevention of Obesity in Childhood (EPOCH) PMA



The Early Prevention of Obesity in Childhood (EPOCH)

Collaboration: Lisa Askie, Louise Baur, Karen Campbell, Lynne Daniels, David Espinoza, Kylie Hesketh, Kylie Hunter, Anthea Magarey, Andrew Martin, Chris Rissel, Barry Taylor, Rachael Taylor, Li Ming Wen

Funding: Australian National Health & Medical Research Council, NZ Health Research Council, Meat & Livestock Association

- ▶ The first prospective meta-analysis in very early childhood obesity prevention
- ▶ 4 trials with a total of 2,196 mother-children dyads included
- ▶ All trials tested very early parent-focused interventions to prevent childhood obesity
- ▶ Early interventions led to a BMI z-score reduction of -0.12 standard deviations at 1.5-2 years

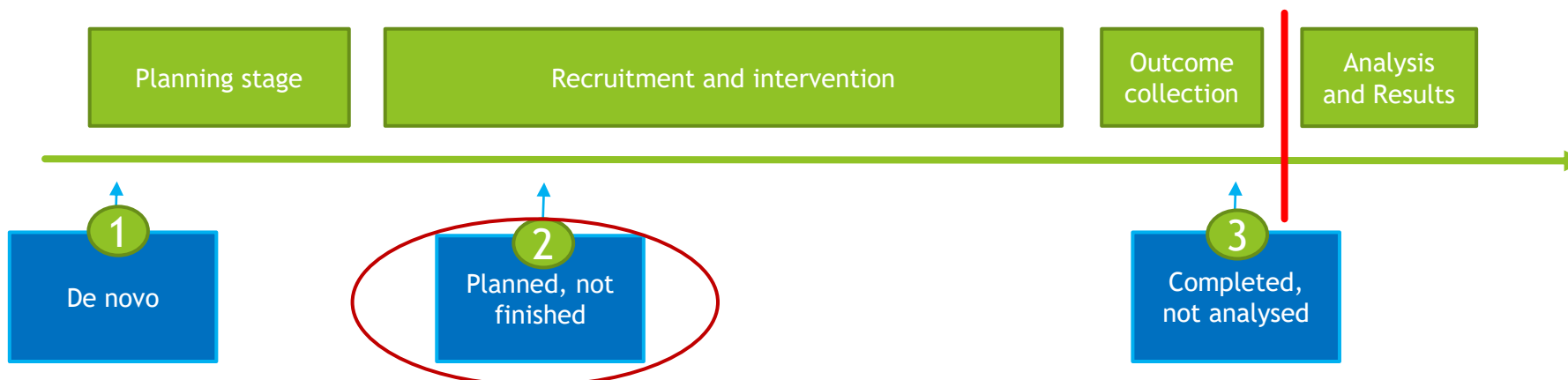
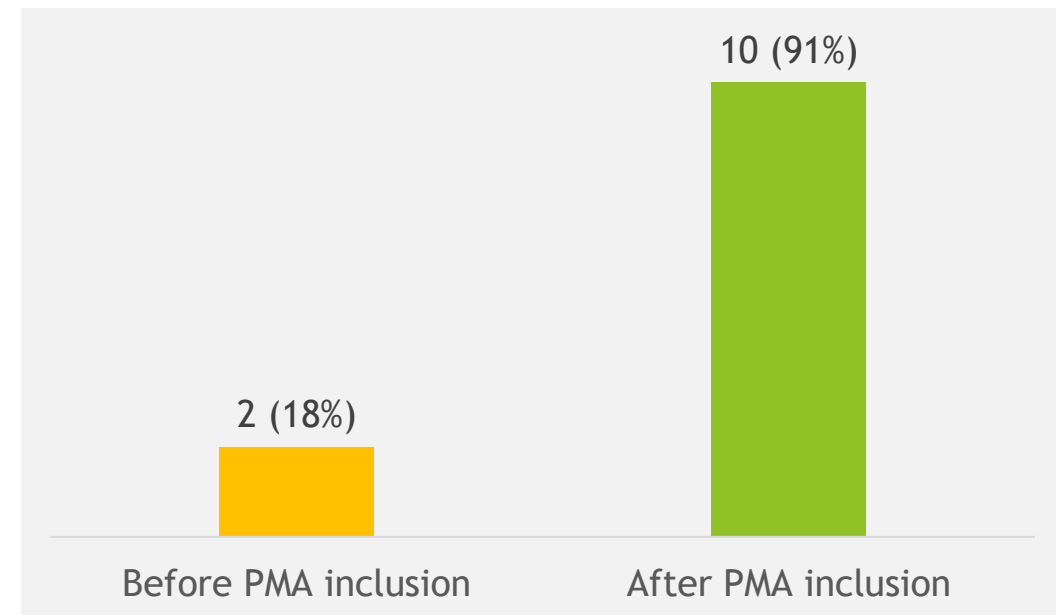


Figure. Different study stages PMA can be formed at

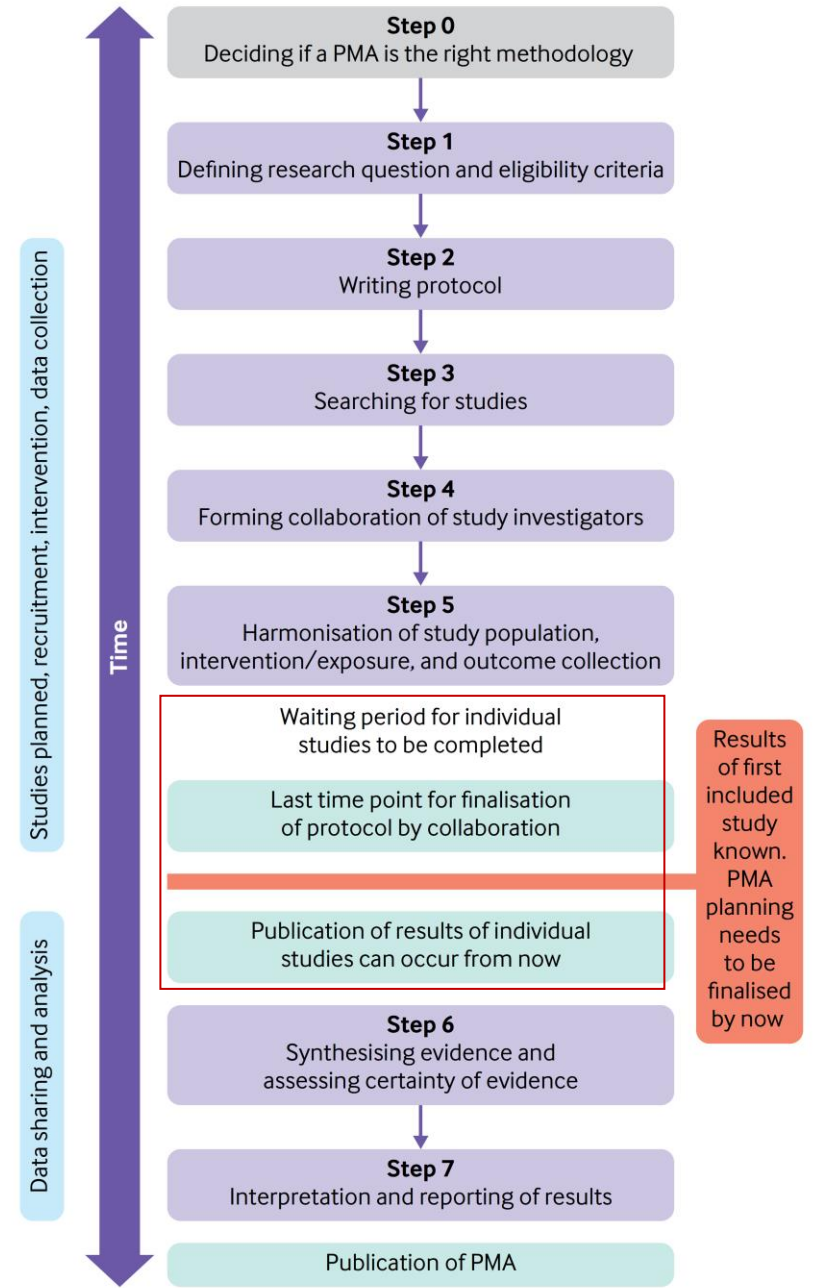
Harmonisation example: EPOCH PMA - early childhood obesity prevention

Inclusion in PMA strongly increased harmonisation of core outcome categories!

Outcome category	No. of trials (out of 4) included outcome category before PMA was planned	No. of trials (out of 4) included outcome category after PMA was planned
Child's BMI/ Anthropometric Measures	4	4
Child's Dietary Intake	4	4
Breastfeeding	3	4
Child's Feeding Behaviour	2	4
Child's TV/ Sedentary Behaviour	3	4
Child's Sleep	1	4
Child's Physical Activity	3	4
Parents' Diet	2	3
Parents' Physical Activity	2	4
Parents' BMI	2	4
Parenting Style	2	4



Waiting period...



Step 6: Evidence synthesis

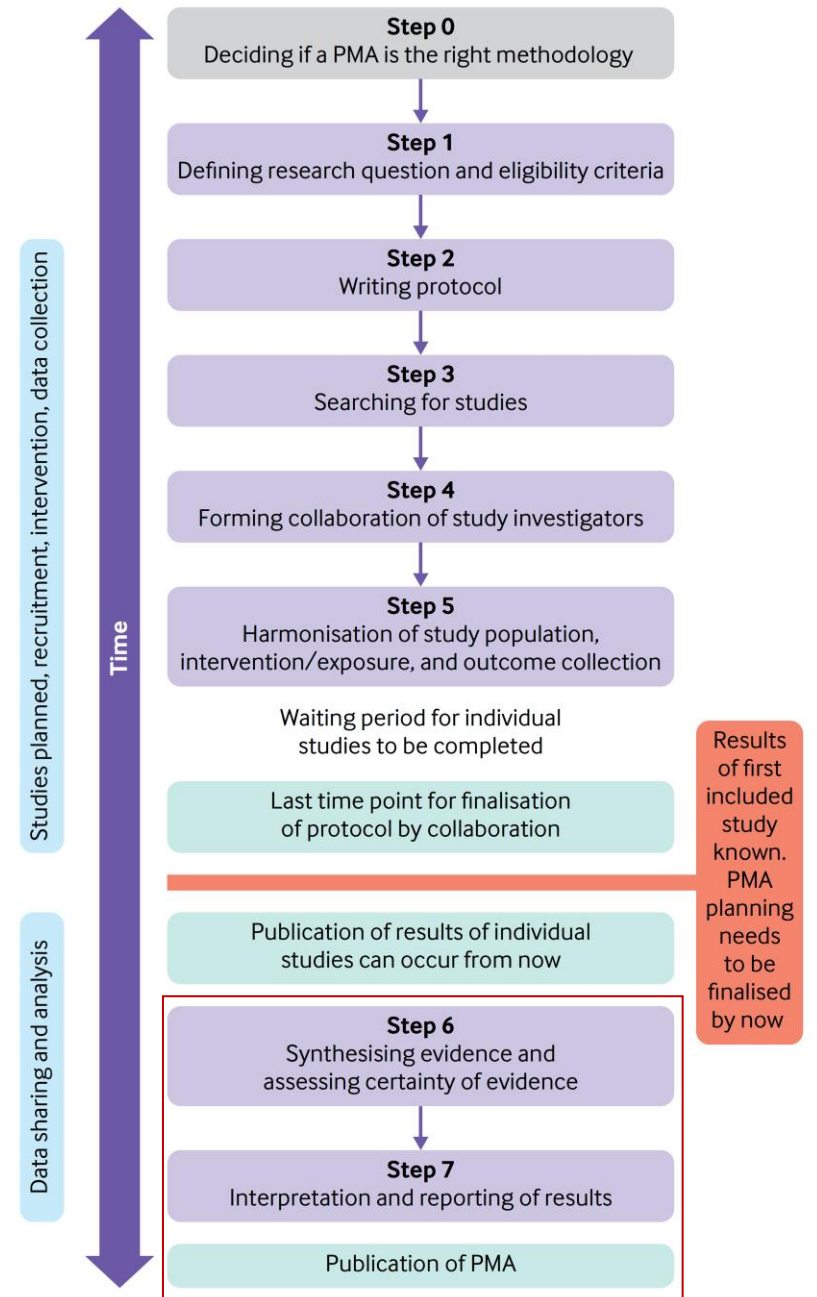
Step 7: Interpretation & reporting

Evidence synthesis & assessing certainty of evidence

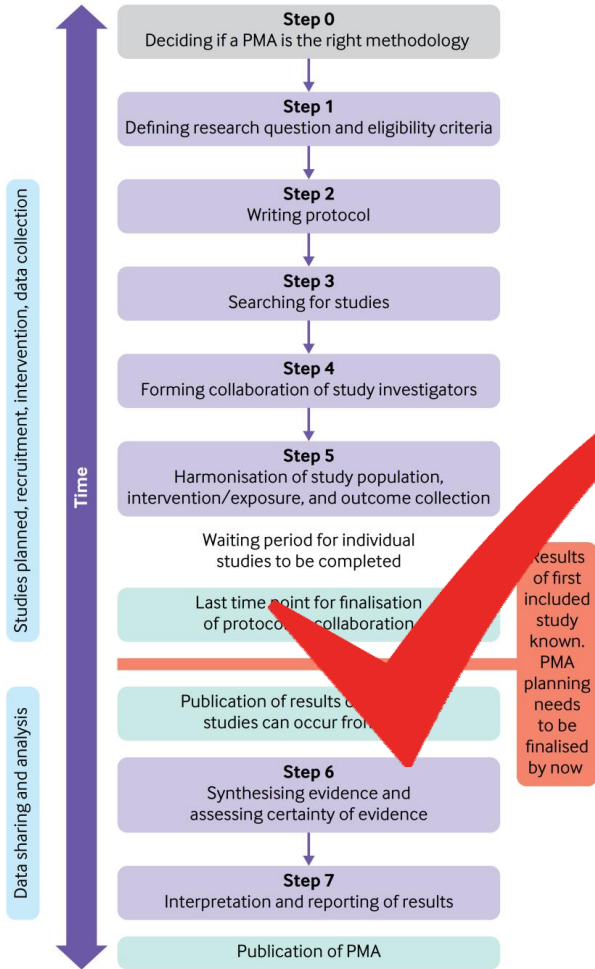
- Individual participant data or aggregate data
- Harmonised outcomes and analyses
- Often easier than for retrospective meta-analysis

Interpretation and reporting

- Reporting guidelines in development
- Involve robust discussions within collaboration



Congratulations – you have made it through all 7 steps!



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Join the quiz!



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PMA compared to multi-centre-studies

SYSTEMATIC SEARCH

- For planned and ongoing studies

EFFICIENT

- Minimisation research waste. Combining and adapting currently planned trials to answer additional research questions

FLEXIBLE

- Study-specific protocol variations and outcomes that are locally relevant

GENERALISABLE

- Higher external validity due to variation in individual study design

PMA compared to retrospective meta-analyses

LESS BIASED

- Reduced risk of publication/ selective outcome reporting bias

COLLABORATIVE

- Researchers working together instead of competing

HARMONIOUS

- Harmonisation of outcomes, interventions and populations possible

POWERFUL

- Core outcome sets & ability to include rare outcomes

Neonatal Oxygenation Prospective Meta-analysis (NeOProm) Collaboration

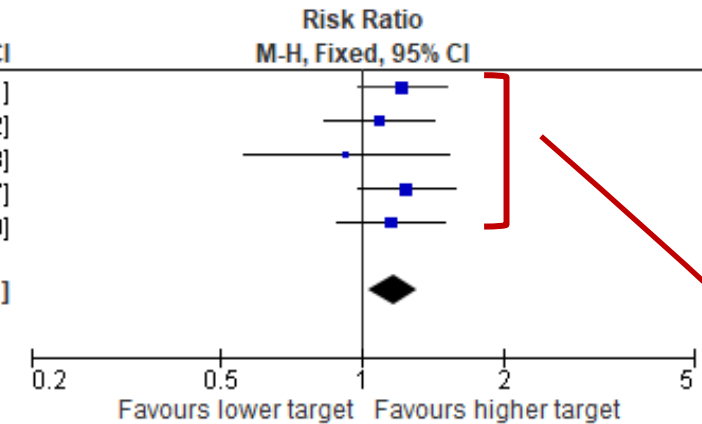
- Aim: to determine best range to target oxygen levels in preterm infants
- Large sample size needed, but too expensive to fund
- 5 trials formed NeOProm, individual funding contingent on contributing to PMA

Trial	Sample size
SUPPORT (USA)	1316
COT (Canada)	1201
BOOST NZ (NZ)	340
BOOST II UK (UK)	973
BOOST II (Australia)	1135
Total	4965



Death by 18-24 months corrected age

Study or Subgroup	Lower oxygen saturation		Higher oxygen saturation		Weight	Risk Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Vaucher 2012	140	633	118	648	27.9%	1.21 [0.98, 1.51]
Schmidt 2013	97	585	88	577	21.2%	1.09 [0.83, 1.42]
BOOST NZ 2014	25	170	27	170	6.5%	0.93 [0.56, 1.53]
BOOST-II UK 2016	122	484	98	483	23.5%	1.24 [0.98, 1.57]
BOOST-II Australia 2016	100	561	87	562	20.8%	1.15 [0.89, 1.50]
Total (95% CI)		2433		2440	100.0%	1.16 [1.03, 1.31]
Total events	484		418			
Heterogeneity: Chi ² = 1.51, df = 4 (P = 0.83); I ² = 0%						
Test for overall effect: Z = 2.50 (P = 0.01)						



No trial alone found a significant difference in death – all CIs crossed 1

JAMA | Original Investigation

Association Between Oxygen Saturation Targeting and Death or Disability in Extremely Preterm Infants in the Neonatal Oxygenation Prospective Meta-analysis Collaboration

Lisa M. Askie, PhD; Brian A. Darlow, MD; Neil Finer, MD; Barbara Schmidt, MD; Ben Stenson, MD; William Tarnow-Mordi, MBChB; Peter G. Davis, MD; Waldemar A. Carlo, MD; Peter Brocklehurst, MBChB; Lucy C. Davies, MSc; Abhik Das, PhD; Wade Rich, BSHS; Marie G. Gantz, PhD; Robin S. Roberts, MSc; Robin K. Whyte, MB; Lorrie Costantini, BA; Christian Poets, MD; Elizabeth Asztalos, MD; Malcolm Battin, MD; Henry L. Halliday, MD; Neil Marlow, DM; Win Tin, MBBS; Andrew King, BA; Edmund Juszcak, MSc; Colin J. Morley, MD; Lex W. Doyle, MD; Val Gebski, MSc; Kylie E. Hunter, MPH; Robert J. Simes, MD; for the Neonatal Oxygenation Prospective Meta-analysis (NeOProm) Collaboration

Cholesterol Treatment Trialists' (CTT) Collaboration

- **30 trials** evaluating statins
- ~175,000 participants
- Statins produced a **13% reduction in relative risk** of major vascular events and are safe
- Led to worldwide uptake of statins and prevention of millions of deaths



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Name some advantages of PMA

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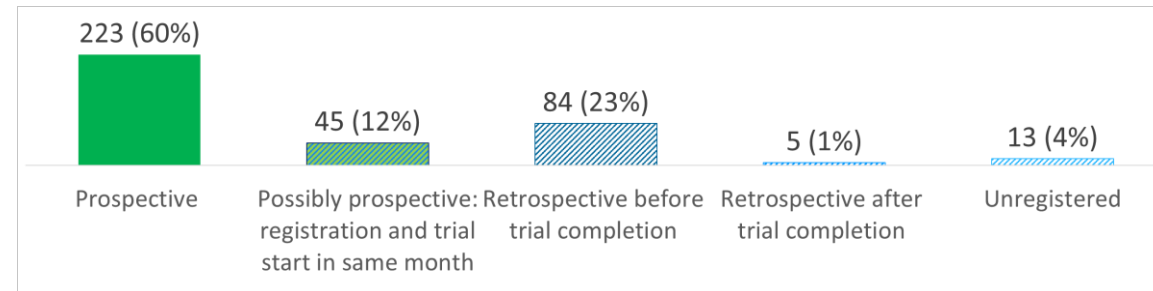


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New horizons for prospective meta-analyses

- Increased trial registration
 - 95% of trials registered before trial completion
 - ICMJE statement 2005
 - Ability to identify planned and ongoing trials
- Improved collaboration & data sharing abilities
 - New technologies
 - Journals and registries enforce data sharing



Tan AC, Jiang I, Askie L, Hunter K, Simes RJ, Seidler AL. Prevalence of trial registration varies by study characteristics and risk of bias. *J Clin Epidemiol* 2019;113:64-74. doi:10.1016/j.jclinepi.2019.05.009



Combining PMA with other (next generation) systematic review methodology: IPD-MA

Individual participant data (IPD) PMA

- Row-by-row, individual participant data
- IPD 'gold standard' of meta-analysis: Allow additional analyses, in particular subgroup analyses
- IPD and PMA are both **collaborative** approaches: involve forming a collaboration between eligible studies

	Patient characteristics at trial entry					Maternal outcomes						Infant outcomes				
PatientID	GArand	TreatGp	RandDBP	ChronicHT	PrevSGA	MaxSBP	MaxDBP	Prot	TrialistsPE	Delivery	APH	SGA	BirthGA	BW	Sex	SCU
10007932	28	2	60	1	0	145	100	1	1	0	0	1	40	2135	2	0
10007933	11	1	80	0	1	140	90	0	0	4	0	0	41	3700	1	1
10007934	20	2	70	0	0	140	88	0	0	2	0	0	41	3250	2	0

Combining PMA with other (next generation) systematic review methodology

- Nested PMAs
 - Combining retrospective with prospective evidence
- Living systematic reviews for PMAs
 - Systematically adding newly identified planned and ongoing studies to a PMA until research question is answered
- Network PMA? PMA of prognostic models?

Design priority programs of research as prospective meta-analyses

Cochrane's role in embracing PMA and other NextGen approaches

 @LeneSeidler
@KylieEHunter

Cochrane's future: innovation and agility with NextGen Methods?
Cochrane and the methods community need to work together:
facilitate appraisal and uptake of novel methods



The screenshot shows the Cochrane Library website interface. At the top left is the Cochrane Library logo with the tagline "Trusted evidence. Informed decisions. Better health." To the right of the logo is a search box containing the text "Title Abstr:". Below the logo is a purple navigation bar with the following menu items: "Cochrane Reviews", "Trials", "Clinical Answers", "About", and "Help". The main content area displays the article title "Prospective meta-analyses and Cochrane's role in embracing next-generation methodologies" under the heading "Cochrane Database of Systematic Reviews | Editorial". Below the title, the authors are listed as "Anna Lene Seidler, Kylie E Hunter, Saskia Cheyne, Jesse A Berlin, Davina Gherzi, Lisa M Askie" with a link to "Authors' declarations of interest". The publication date is "Version published: 30 October 2020" and the DOI is "https://doi.org/10.1002/14651858.ED000145".

Why COVID-19 is a prime example for the need for PMA

- No previous direct evidence
- Unpredictable case numbers within one centre/ country
- Urgency to collect the same outcomes using the same measures (including rare adverse side effects of treatments)
- Urgency to combine data rapidly

 Collaboration instead of competition to overcome this global pandemic

Landscape of COVID-19 trials in Australia

How well did researchers listen to calls for collaboration in Australia?

Findings

- Impressive research scale up
- Only 21% of COVID-19 trials plan to share data upon completion
- Small sample sizes: Median (IQR) = 150 (33-395)
- Lack of collection of common core outcomes → precludes evidence synthesis

Research design no sufficiently strategic or collaborative
Taxpayer-funded research waste?

Coordinated efforts required to address COVID-19

Little gain as millions spent on virus studies

Liam Mannix
Science reporter

Prospective meta-analyses and COVID-19

Journal List › Elsevier Public Health Emergency Collection › PMC7237904

Elsevier Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Trends Pharmacol Sci. 2020 May 20

PMCID: PMC7237904

doi: [10.1016/j.tips.2020.05.002](https://doi.org/10.1016/j.tips.2020.05.002) [Epub ahead of print]

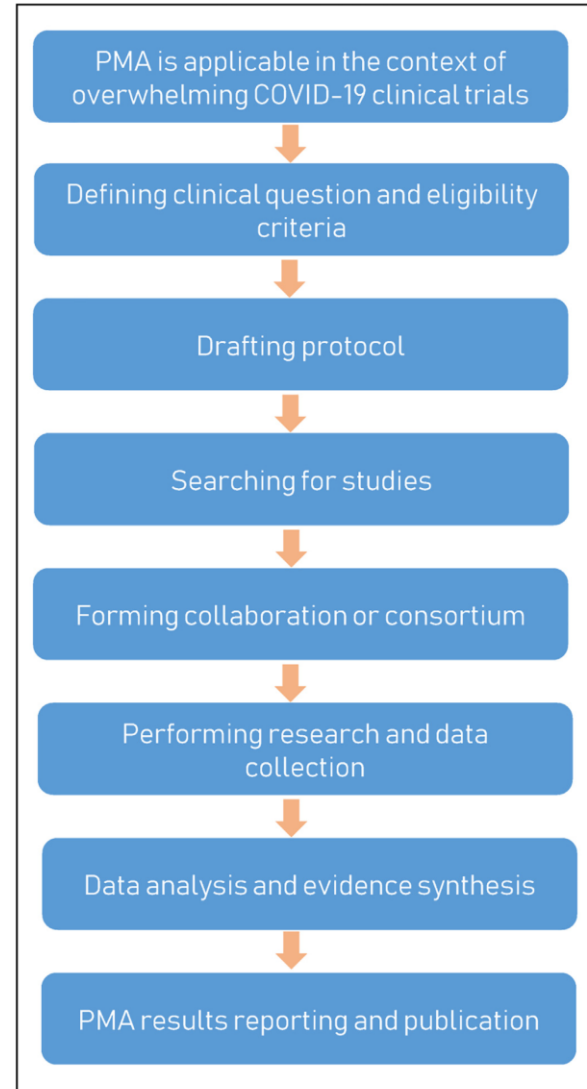
PMID: [32471655](https://pubmed.ncbi.nlm.nih.gov/32471655/)

Overwhelming COVID-19 Clinical Trials: Call for Prospective Meta-Analyses

[Zhongren Ma](#),¹ [Jiaye Liu](#),² and [Qiuwei Pan](#)^{1,2,*}

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PMA improving treatment of COVID-19

Research

JAMA | **Original Investigation** | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies

CONCLUSIONS AND RELEVANCE In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

- Rapid aggregate data PMA
- PMA collaboration management:
 - Trial registry search
 - Weekly calls to harmonise studies
 - Trials shared summary outcome data for pre-specified outcome & subgroup analyses
- Article published online <2 months after final data collection!

Take home messages

PMA reduce research waste, and are adaptive, efficient and collaborative

- Questions to ask yourself when starting a new study:
 - Is anyone else doing this? How can we collaborate?
- The beauty of collaboration: More expertise and statistical power = more influential research



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Thank you. Questions?

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For more information:

Seidler AL, Hunter KE, Cheyne S, Gherzi D, Berlin JA, Askie L. A guide to prospective meta-analysis. *BMJ*. 2019;367:l5342.

Key resources

- Seidler AL, Hunter KE, Cheyne S, Gherzi D, Berlin JA, Askie L. A guide to prospective meta-analysis. *BMJ*. 2019;367:l5342.
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- Seidler AL, Hunter KE, Espinoza D, Mahrshahi S, Askie LM, on behalf of the EPOCH Collaboration: Quantifying the advantages of conducting a prospective meta-analysis (PMA): a case study of early childhood obesity prevention. *Trials* 2021, 22(1):78.
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