An introduction to prospective meta-analysis (PMA)

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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
What is your professional background?

Start presenting to display the poll results on this slide.
Why did you join the webinar today?

Start presenting to display the poll results on this slide.
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

Source: Trials registered on primary WHO trial registries and ClinicalTrials.gov, accumulated on https://covid.inato.com/
The problem: Majority of trials underpowered to detect differences in important clinical outcomes

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

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Death rate control group</th>
<th>Death rate intervention group</th>
<th>Absolute risk difference</th>
<th>Required sample size</th>
<th>Required sample size subgroup differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>25%</td>
<td>20%</td>
<td>5%</td>
<td>2,188</td>
<td>~10,000</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>30%</td>
<td>27%</td>
<td>3%</td>
<td>7,106</td>
<td>~30,000</td>
</tr>
</tbody>
</table>

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

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 target sample sizes we have...
But: many trials are addressing the same research question

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine and hydroxychloroquine</td>
<td>230</td>
</tr>
<tr>
<td>Antiviral</td>
<td></td>
</tr>
<tr>
<td>Blood therapy</td>
<td>69</td>
</tr>
<tr>
<td>Traditional Chinese medicine</td>
<td>69</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>69</td>
</tr>
<tr>
<td>Interleukin inhibitor</td>
<td>43</td>
</tr>
<tr>
<td>Interferon</td>
<td>42</td>
</tr>
<tr>
<td>Cell therapy</td>
<td>32</td>
</tr>
<tr>
<td>Vaccine</td>
<td>28</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>28</td>
</tr>
<tr>
<td>JAK inhibitor</td>
<td>26</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>26</td>
</tr>
<tr>
<td>ACE2</td>
<td>14</td>
</tr>
<tr>
<td>Nitric Oxide</td>
<td>13</td>
</tr>
<tr>
<td>Colchicine</td>
<td>13</td>
</tr>
<tr>
<td>BCG vaccine</td>
<td>12</td>
</tr>
<tr>
<td>Interleukin 1 inhibitor</td>
<td>11</td>
</tr>
<tr>
<td>Anesthetic agent</td>
<td>6</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>5</td>
</tr>
</tbody>
</table>

**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/](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.
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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath</td>
<td>6 (18%)</td>
<td>28 (82%)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>21 (62%)</td>
<td>13 (38%)</td>
</tr>
<tr>
<td>Recovery</td>
<td>16 (47%)</td>
<td>18 (53%)</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>6 (18%)</td>
<td>28 (82%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>18 (53%)</td>
<td>16 (47%)</td>
</tr>
</tbody>
</table>

(Seidler et al. MJA 2021)
### Variation in what is being measured, and how…..

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

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

- **Anthropometric measures**
  - Height, weight, BMI
  - Body comp. (DEXA scan)
  - BMI z-score
  - BMI, waist circumf.

- **Physical activity**
  - Accelerometer

- **Dietary intake**
  - Food Freq checklist

- **Sleep**
  - Bedtime self report

- **Feeding**
  - CFP Questionnaire
  - FPS Questionnaire
  - Hours slept self report
Solution

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.”

**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.

Have you ever conducted a prospective meta-analysis?
Prospective meta-analysis: scoping review

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

Definition, methodology, and reporting of previous PMAs vary greatly

- Cardiovascular disease 37%
- Cancer 21%
- Reproductive health and childbirth 16%
- Public health 8%
- Diet and nutrition 5%
- Infection 8%
- Other 8%

Seidler et al BMJ 2019
A guide to prospective meta-analysis

Anna Lene Seidler,1 Kylie E Hunter,1 Saskia Cheyne,1 Davina Ghersi,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:
- Intervenational or observational studies
- Individual participant data (IPD) or aggregate data
- For aggregate data: FAME (Tierney et al 2021)
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*
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!
What is your favourite aspect of collaboration?
PMAs 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 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


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

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!

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

Inclusion in PMA strongly increased harmonisation of core outcome categories! Before PMA inclusion 2 (18%) After PMA inclusion 10 (91%)
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!
Join the quiz!

1. Start presenting to display the poll results on this slide.
Join the quiz!

Start presenting to display the poll results on this slide.
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**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUPPORT (USA)</td>
<td>1316</td>
</tr>
<tr>
<td>COT (Canada)</td>
<td>1201</td>
</tr>
<tr>
<td>BOOST NZ (NZ)</td>
<td>340</td>
</tr>
<tr>
<td>BOOST II UK (UK)</td>
<td>973</td>
</tr>
<tr>
<td>BOOST II (Australia)</td>
<td>1135</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>4965</strong></td>
</tr>
</tbody>
</table>
Death by 18-24 months corrected age

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Lower oxygen saturation</th>
<th>Higher oxygen saturation</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Vaucher 2012</td>
<td>140</td>
<td>633</td>
<td>116</td>
</tr>
<tr>
<td>Schmidt 2013</td>
<td>97</td>
<td>585</td>
<td>88</td>
</tr>
<tr>
<td>BOOST NZ 2014</td>
<td>25</td>
<td>170</td>
<td>27</td>
</tr>
<tr>
<td>BOOST-UK UK 2016</td>
<td>122</td>
<td>484</td>
<td>98</td>
</tr>
<tr>
<td>BOOST II Australia 2016</td>
<td>100</td>
<td>561</td>
<td>67</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>484</td>
<td>2433</td>
<td>416</td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 15.1, df = 4 (P = 0.03); I² = 0%
Test for overall effect: Z = 2.56 (P = 0.01)

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

Name some advantages of PMA
Join the quiz!
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

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
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

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
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

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

Zhongren Ma, 1 Jiaye Liu, 2 and Qiuwei Pan 1, 2,*

Author information • Article notes • Copyright and License information

Trends Pharmacol Sci. 2020 May 20
doi: 10.1016/j.tips.2020.05.002 [Epub ahead of print]
PMA improving treatment of COVID-19

- 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
Acknowledgement

Angela Webster, Jesse Berlin, Davina Ghersi, Kylie Hunter, Anna Lene Seidler, Saskia Cheyne, Lisa Askie (left to right, top to bottom)
Thank you. Questions?

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For more information:
Key resources


