How can FAME be used to improve the quality of Cochrane reviews?

Jayne Tierney & Sarah Burdett
Why do we need it?
(Retrospective) meta-analysis of aggregate data

Start when some or all eligible trials are published
  • Methods influenced by knowledge of trial results

Based on published information and results
  • Limits data & analyses
  • Potential for reporting biases
  • Variable outcome and subgroup definitions
  • Limits knowledge of trials for RoB & interpretation
  • Results not always placed in context of all evidence

Quick, but not always reliable
(Retrospective) meta-analysis of IPD

Start when some or all eligible trials are published
  • Methods influenced by knowledge trial results

Collaborate with trialists to
  • Obtain IPD from all trials, participants, outcomes
  • Request or derive harmonised outcome definitions
  • More detailed and flexible analyses
  • Better knowledge of trials for RoB, interpretation etc.
  • Usually interpreted in context of all evidence

Impactful, but resource-intensive and slow
Prospective meta-analysis of IPD

Start before trials have produced results
  • Methods not influenced by trial results

Collaborate with trialists to
  • Get all the gains of the IPD approach!!

Impactful, but resource-intensive and slow
Framework for Adaptive MEnta-analysis of aggregate data

FAME
Principles of FAME

Start early, whilst trials are ongoing or yet to report

Liaise with trialists to get more info on trials

Predict earliest timing of reliable meta-analysis

Develop protocol and collect detailed data

Interpret meta-analysis taking account of available & unavailable data
FAME 1. Start whilst trials ongoing/yet to report

- **Trial 1**: Recruitment (500 participants) → Data collection/follow-up
- **Trial 2**: Recruitment (800 participants planned)
- **Trial 3**: Recruitment (1400 participants) → Data collection/follow-up
- **Trial 4**: Recruitment (100 participants planned)
- **Trial 5**: Recruitment (300 participants planned)

- Trials 1 and 5 in follow-up
- Trials 2, 4 & 5 trials ongoing
FAME 2. Liaise with trialists to get more info

- Trials 1, 2 & 3 will complete and report 2015
- Trials 4 & 5 still ongoing and will report years later
FAME 3. Predict earliest timing of reliable meta-analysis

- Trials 1 to 3 recruit 2,700 pts
- Trials 4 & 5 still aiming for 400

<table>
<thead>
<tr>
<th>Trial</th>
<th>Recruitment</th>
<th>Yearly Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>(500 pts)</td>
<td>2010-2013: Data collection/follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014: Planned reporting</td>
</tr>
<tr>
<td>Trial 2</td>
<td>(800 pts)</td>
<td>2010-2013: Data collection/follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014: Planned reporting</td>
</tr>
<tr>
<td>Trial 3</td>
<td>(1400 pts)</td>
<td>2010-2013: Data collection/follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014: Planned reporting</td>
</tr>
<tr>
<td>Trial 4</td>
<td>(100 pts)</td>
<td>2011-2013: Data collection/follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014: Planned reporting</td>
</tr>
<tr>
<td>Trial 5</td>
<td>(300 pts)</td>
<td>2011-2013: Data collection/follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2014: Planned reporting</td>
</tr>
</tbody>
</table>
Predicting earliest timing of reliable meta-analysis

Pogue & Yusuf (Controlled Clin Trials 1997;18:580-593)

“calculate prospectively the amount of information that would be needed had a well-designed trial been planned. We define this as the optimal information size”

Backed up by our IPD vs AD results (PloS Med 2019;17(1):e1003019)
FAME 3. Predict earliest timing of reliable meta-analysis

- 2,700 pts from trials 1 to 3 would provide sufficient power
- And represent ~87% of eligible participants
- Plan meta-analysis of these trials, not wait for 4 & 5
FAME 4. Develop protocol and collect data

- **Baseline and RoB information**
- **For all trials, outcomes, participant**
FAME 5. Interpret meta-analysis taking account of available & unavailable data

- No clear treatment effect
- Trials 4 & 5 recruit 150 fewer participants
- Results based on 92% of eligible participants, so little value in collecting more AD (or IPD)

### Trial 1
- Recruitment: 500 participants
- Data collection/follow-up
- Planned reporting

### Trial 2
- Recruitment: 800 participants planned
- Data collection/follow-up
- Planned reporting

### Trial 3
- Recruitment: 1400 participants
- Data collection/follow-up
- Planned reporting

### Trial 4
- Recruitment: 50 participants
- Data collection/follow-up

### Trial 5
- Recruitment: 200 participants planned
- Data collection/follow-up
Applying all the principles of
Predict earliest timing of reliable meta-analysis
Abiraterone for advanced prostate cancer (Eur J Cancer 2017)

In 2016, identified 3 eligible trials
  • 2 with results due in 2017
    • Both individually, and together well powered
    • >70% of men randomised
  • 1 with results not due until 2022
Collect detailed and harmonised data
Abiraterone for advanced prostate cancer (Eur J Cancer 2017)

<table>
<thead>
<tr>
<th>Survival</th>
<th>Abi+SC events/pts.</th>
<th>SC events/pts.</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAMPEDE</td>
<td>150/500</td>
<td>218/502</td>
<td>0.61 (0.49, 0.75)</td>
</tr>
<tr>
<td>LATITUDE</td>
<td>169/597</td>
<td>237/602</td>
<td>0.62 (0.51, 0.76)</td>
</tr>
</tbody>
</table>
| Overall   | 319/1097           | 455/1104       | 0.62 (0.53, 0.71)    | P<0.001
Collect detailed and harmonised data
Abiraterone for advanced prostate cancer (Eur J Cancer 2017)
Predict earliest timing of reliable meta-analysis
Prostate radiotherapy for advanced prostate cancer (Eur Urol 2019)

In early 2018, identified 3 eligible trials
- 2 with results due later in 2018
  - Provide adequate power
  - 90% of men randomised
- 1 with results not due until 2022
Collect detailed and harmonised data
Prostate radiotherapy for advanced prostate cancer (Eur Urol 2019)

Survival benefit confined to men with <5 bone metastases
• 7% absolute improvement in 3-year survival

<table>
<thead>
<tr>
<th>Overall survival</th>
<th>STAMPEDE</th>
<th>HORRERAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;5 bone mets</td>
<td>&gt;=5 bone mets</td>
</tr>
<tr>
<td></td>
<td>105/399</td>
<td>130/404</td>
</tr>
<tr>
<td></td>
<td>218/393</td>
<td>207/397</td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR (95% CI)
1.44 (1.05, 1.98)
1.55 (0.89, 2.70)
1.47 (1.11, 1.94)
Benefits to ongoing trials
Immediate vs salvage radiotherapy for early prostate cancer (Lancet 2020)

- Motivated continuation of recruitment (evidence to IDMC)
- Justified applications to extend funding / amend protocols
- Forum to discuss / resolve issues with other trialists
- Opportunity to more reliably answer key questions
Align trials and meta-analysis publications
Immediate vs salvage radiotherapy for early prostate cancer (Lancet 2020)

Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data

Claire L. Vale, David Fisher, Andrew Kneebone, Christopher Parker, Maria Pearce, Pierre Richard, Paul Sargent, Matthew R Sydes, Christopher Bruce, Mayeem Brashoum, Andrew Cook, Skiria Forcet, Carol Fraser-Browne, Igor Lutovraff, Mahesh K B Parmar, Joyce F Timoney, for the ARTISTIC Meta-analysis Group

THE LANCET
All published 28 Sept 2020
Additional gains of FAME

Obtain harmonised & additional results (e.g. subgroups, toxicity)

Gain access to pre-publication results

Align publication of trials and meta-analyses

Assist the completion and reporting of included trials
in other contexts
From prostate cancer to a pandemic

- Effects of anti-IL6 agents for patients hospitalised with COVID-19
  - Data from 27 trials from 28 countries
  - 10,930 participants (~95% of all eligible)

- 18/27 trials supplied results pre-publication
  - Baseline and information for RoB
  - Overall results for 11 outcomes
  - Results by 7 subgroups for main outcomes

= many detailed spreadsheets !!
E.g. for 28-day mortality by subgroup

<table>
<thead>
<tr>
<th>Mortality at 28 days</th>
<th>Total randomised to receive control</th>
<th>Total events in patients randomised to receive control</th>
<th>Total randomised to receive Anti-IL-6</th>
<th>Total events in patients randomised to receive Anti-IL-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (all patients randomised)</td>
<td>2094</td>
<td>729</td>
<td>2022</td>
<td>621</td>
</tr>
<tr>
<td><strong>Patient subgroups:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Receipt of corticosteroids</strong> and respiratory support at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids AND NOT supplemental O2 therapy</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroids AND supplemental O2 therapy (O2 ≤ 15 l/min)</td>
<td>765</td>
<td>173</td>
<td>766</td>
<td>125</td>
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<tr>
<td>Corticosteroids AND NIV (O2 flow &gt;15 l/min)</td>
<td>733</td>
<td>300</td>
<td>711</td>
<td>259</td>
</tr>
<tr>
<td>Corticosteroids AND IMV (including ECMO)</td>
<td>221</td>
<td>127</td>
<td>184</td>
<td>97</td>
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<tr>
<td>No corticosteroids AND NOT supplemental O2 therapy</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>No corticosteroids AND supplemental O2 therapy (O2 ≤ 15 l/min)</td>
<td>162</td>
<td>41</td>
<td>165</td>
<td>53</td>
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<tr>
<td>No corticosteroids AND NIV (O2 flow &gt;15 l/min)</td>
<td>130</td>
<td>65</td>
<td>107</td>
<td>54</td>
</tr>
<tr>
<td>No corticosteroids AND IMV (including ECMO)</td>
<td>72</td>
<td>21</td>
<td>84</td>
<td>34</td>
</tr>
<tr>
<td>Unknown</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>0</td>
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<tr>
<td><strong>Acute organ support at baseline:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVV support; cardiovascular system support (vasoactive medication); NIV; non-invasive ventilation (including ECMO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No respiratory support or O2 ≤ 15 l/min only AND NOT CVV support</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No respiratory support or O2 ≤ 15 l/min only AND CVV support</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NIV (O2 flow &gt;15 l/min) or IMV (including ECMO) AND NOT CVV support</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NIV (O2 flow &gt;15 l/min) or IMV (including ECMO) AND CVV support</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unknown</td>
<td>2094</td>
<td>729</td>
<td>2022</td>
<td>621</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years</td>
<td>1355</td>
<td>309</td>
<td>1331</td>
<td>273</td>
</tr>
<tr>
<td>≥70 years</td>
<td>739</td>
<td>420</td>
<td>691</td>
<td>348</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1437</td>
<td>539</td>
<td>1337</td>
<td>417</td>
</tr>
<tr>
<td>Female</td>
<td>657</td>
<td>209</td>
<td>685</td>
<td>204</td>
</tr>
<tr>
<td>Unknown / other</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
A tremendous collaborative effort

- Anti-IL6 agents reduced 28-day mortality
  - Particularly when given with corticosteroids
  - Effect consistent across most outcomes and subgroups

- All results used in living NMA and WHO guideline
- PMA and guideline published on the same day
...is it feasible?!
Use as many principles as you can: FAME-lite

Start early, whilst trials are ongoing or yet to report

Liaise with trialists to get more info on trials

Interpret meta-analysis taking account of available & unavailable data
Use as many principles as you can: **FAME-lite**

Develop and register/publish protocol before trials produce results, and seek detailed and harmonised aggregate data.
lite in action...
NRG RTOG 9601 (n = 760)

GETUG-AFU-16 (n = 743)

RADICALS-HD (n = 2839)

NRG-RTOG-0534 (n = 1142)

FAME-lite
Hormone duration for early prostate cancer (ongoing)
Collect detailed and harmonized data

- Information to inform RoB
- Extra outcomes and harmonised definitions
  - Overall survival
  - Metastases-free survival
  - Prostate cancer specific survival
- Unpublished subgroup results
- Pre-publication results
### Published vs collected outcome results

**Published results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GETUG16</th>
<th>RTOG9601</th>
<th>RTOG0534</th>
<th>RADICALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td>[Green]</td>
</tr>
<tr>
<td>MFS</td>
<td>[Green]</td>
<td></td>
<td></td>
<td>[Red]</td>
</tr>
<tr>
<td>PCSS</td>
<td>[Red]</td>
<td></td>
<td></td>
<td>[Red]</td>
</tr>
</tbody>
</table>

**Collected results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GETUG16</th>
<th>RTOG9601</th>
<th>RTOG0534</th>
<th>RADICALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>[Green]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MFS</td>
<td>[Green]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCSS</td>
<td>[Green]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Definitions:**
- **OS** - Overall survival
- **MFS** - Metastases-free survival
- **PCSS** - Prostate cancer specific survival
### Published vs collected subgroup results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>GETUG16</th>
<th>RTOG9601</th>
<th>RTOG0534</th>
<th>RADICALS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-surgical PSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seminal vesicle involved</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical margin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPRA-S risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA level pre-RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac comorbidity</td>
<td></td>
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</tr>
</tbody>
</table>

### Published subgroup results for survival

### Collected subgroup results for survival
Final thoughts

• FAME aims to produce a single, timely, reliable and thorough meta-analysis

• It may not be feasible for every Cochrane Review

• But FAME-lite could improve the quality of many Cochrane reviews

• Workshop to explore the barriers and enable reviewers coming soon

• See you at the Colloquium!
  • **Session:** Living evidence and PMA
  • **Data and time:** Wed 6 Sep 2023, 2.00 to 3.30 pm
Use FAME(-lite) for...