MRC Clinical Trials Unit

UCL

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

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Cochrane Web Clinic, August 2023

Smarter Studies
Global Impact
Better Health

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 awlays 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

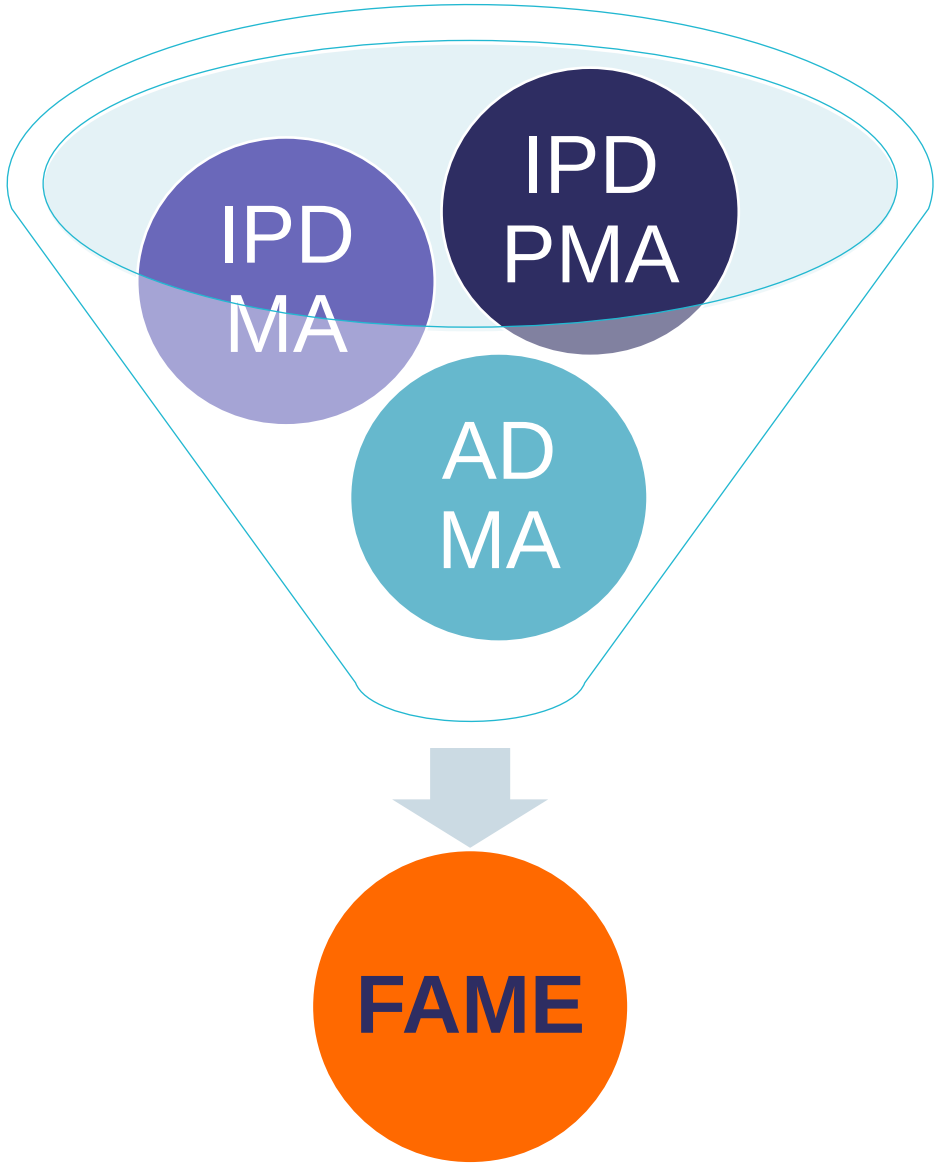
Collaborate with trialists to

- Get all the gains of the IPD approach!!

Impactful, but resource-intensive and slow

Framework for
Adaptive
MEta-analysis of
aggregate data

FAME



Principles of FAME

Start early, whilst trials are ongoing or yet to report

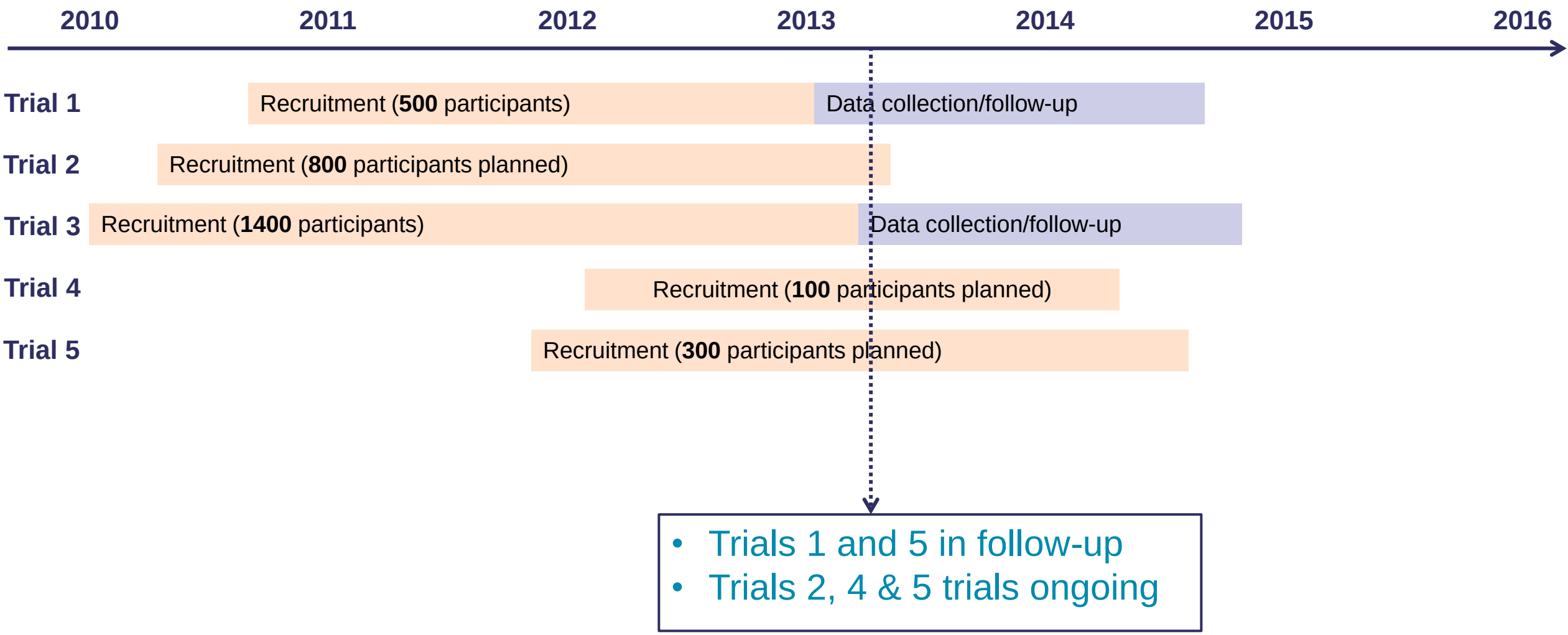
Liaise with trialists to get more info on trials

Predict earliest timing of reliable meta-analysis

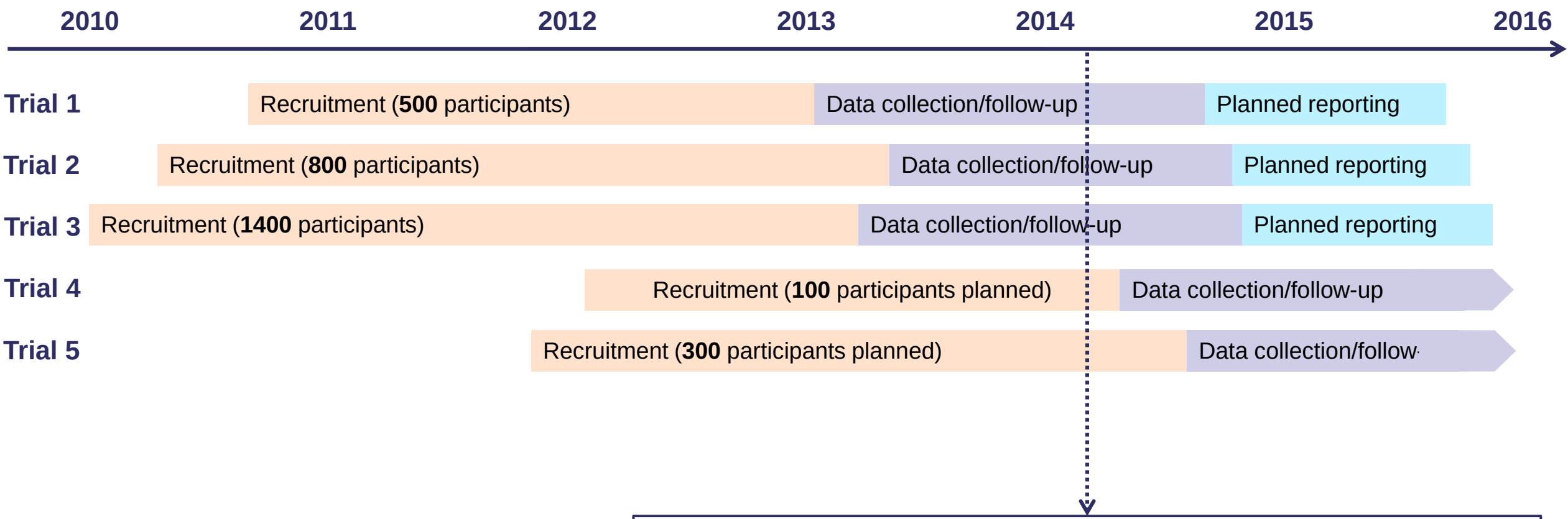
Develop protocol and collect detailed data

Interpret meta-analysis taking account of available & unavailable data

FAME 1. Start whilst trials ongoing/yet to report

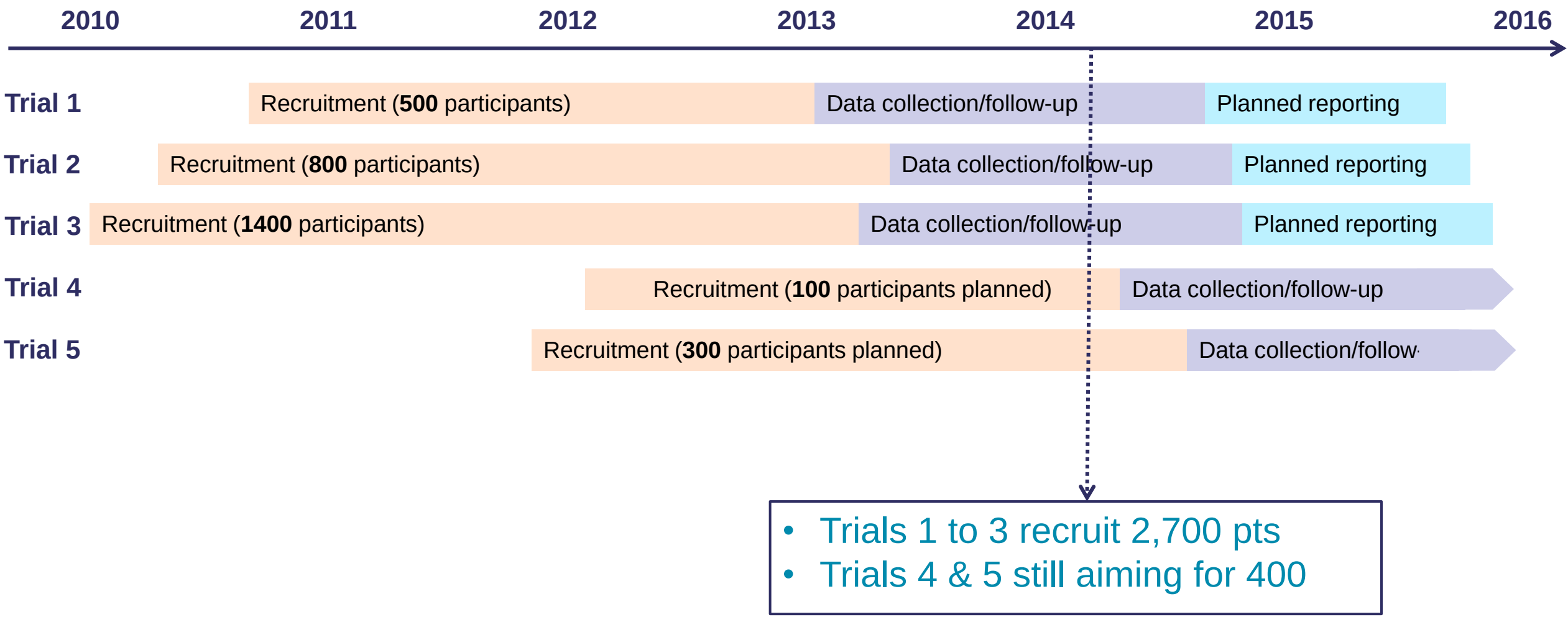


FAME 2. Liaise with trialists to get more info



- 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

Predicting earliest timing of reliable meta-analysis

Pogue & Yusuf

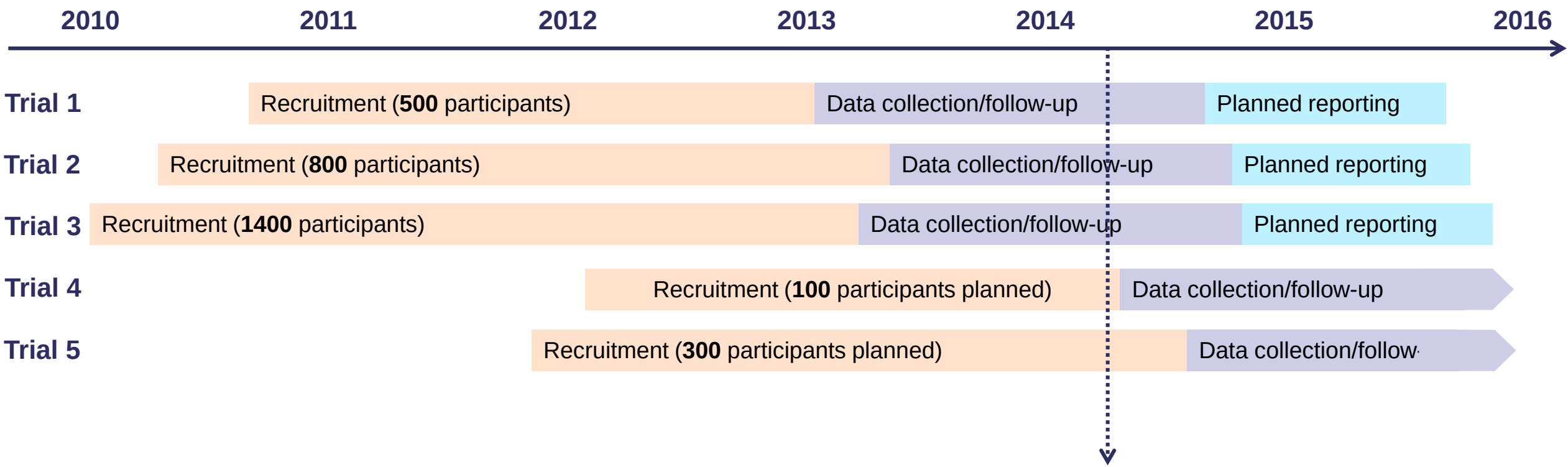
(Controlled Clin Trials1997;18:580-593)

> *“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

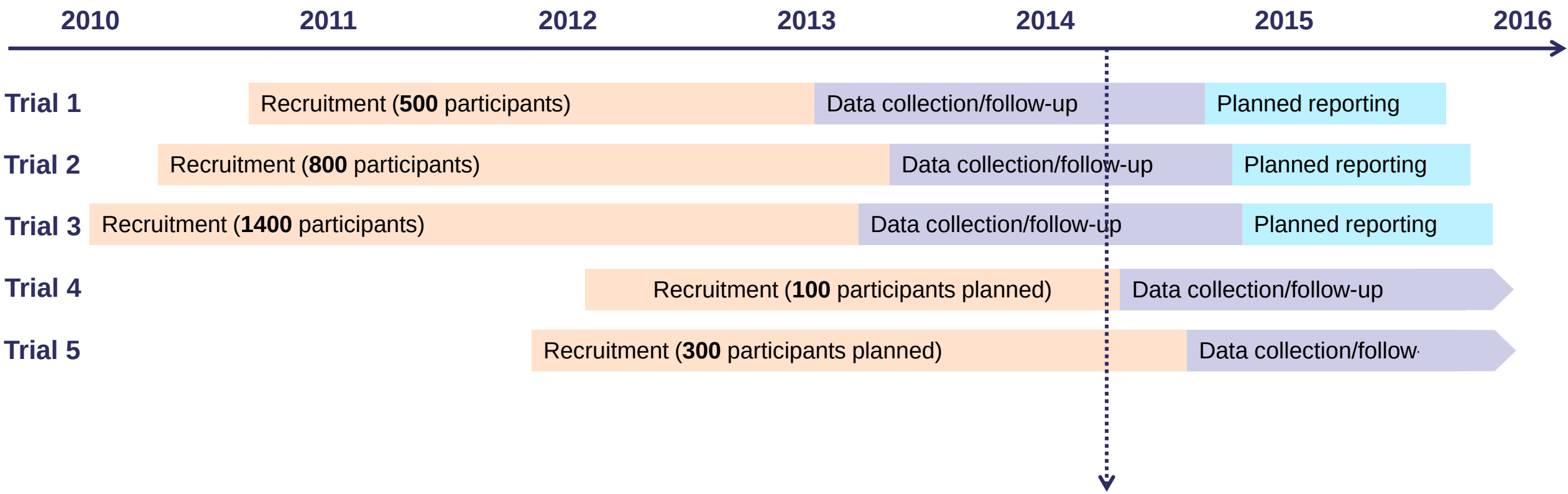
(PloS Med 2019;17(1):e1003019)

FAME 3. Predict earliest timing of reliable meta-analysis



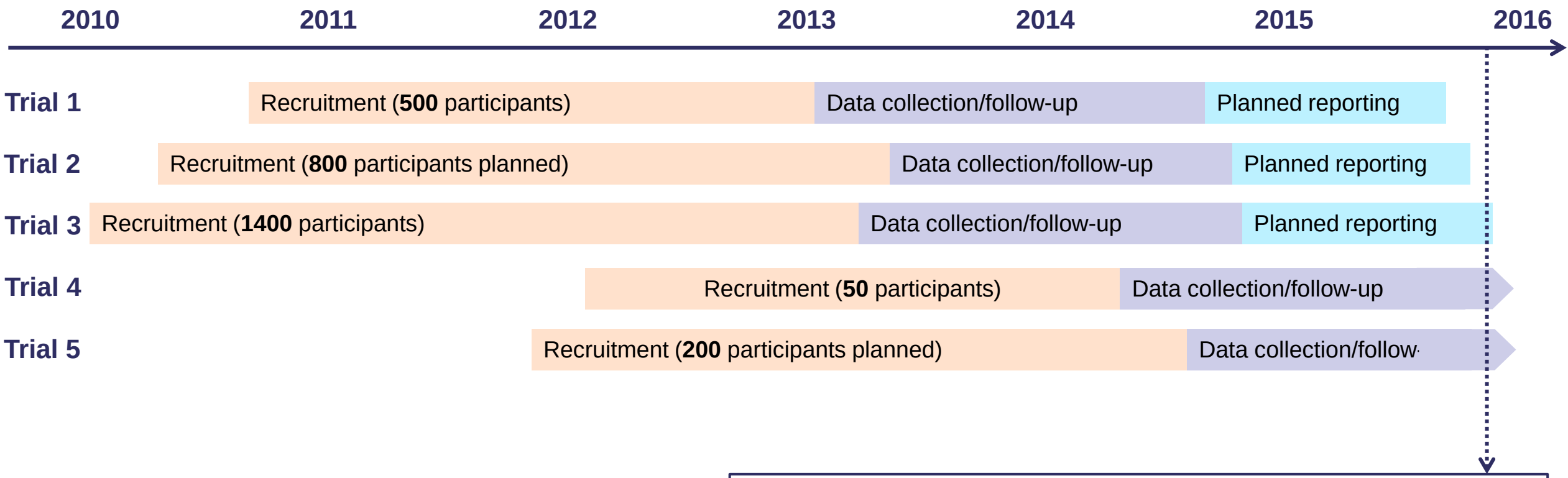
- 2,700 pts from trials 1 to 3 would provide sufficient power
- And represent ~87% of eligible participants
- Plan meta-analysis of these trials, not wait for 4 & 5

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)

Applying all the principles of

Predict earliest timing of reliable meta-analysis

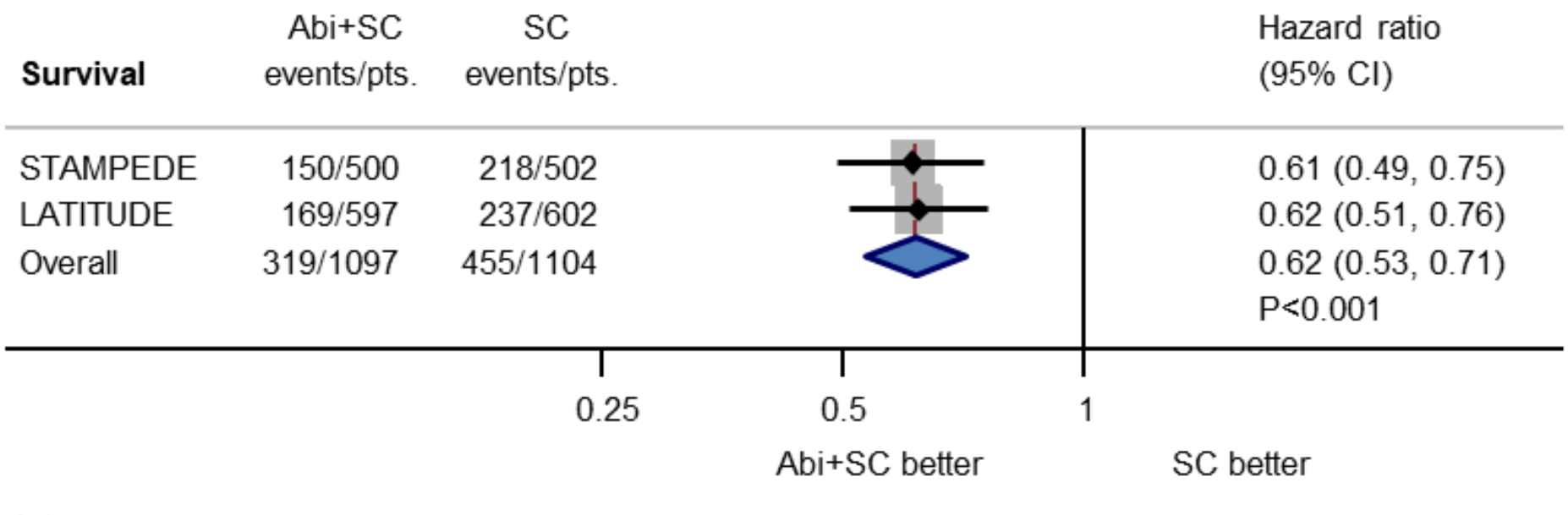
Abiraterone for advanced prostate cancer (Eur J Cancer 2017)

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

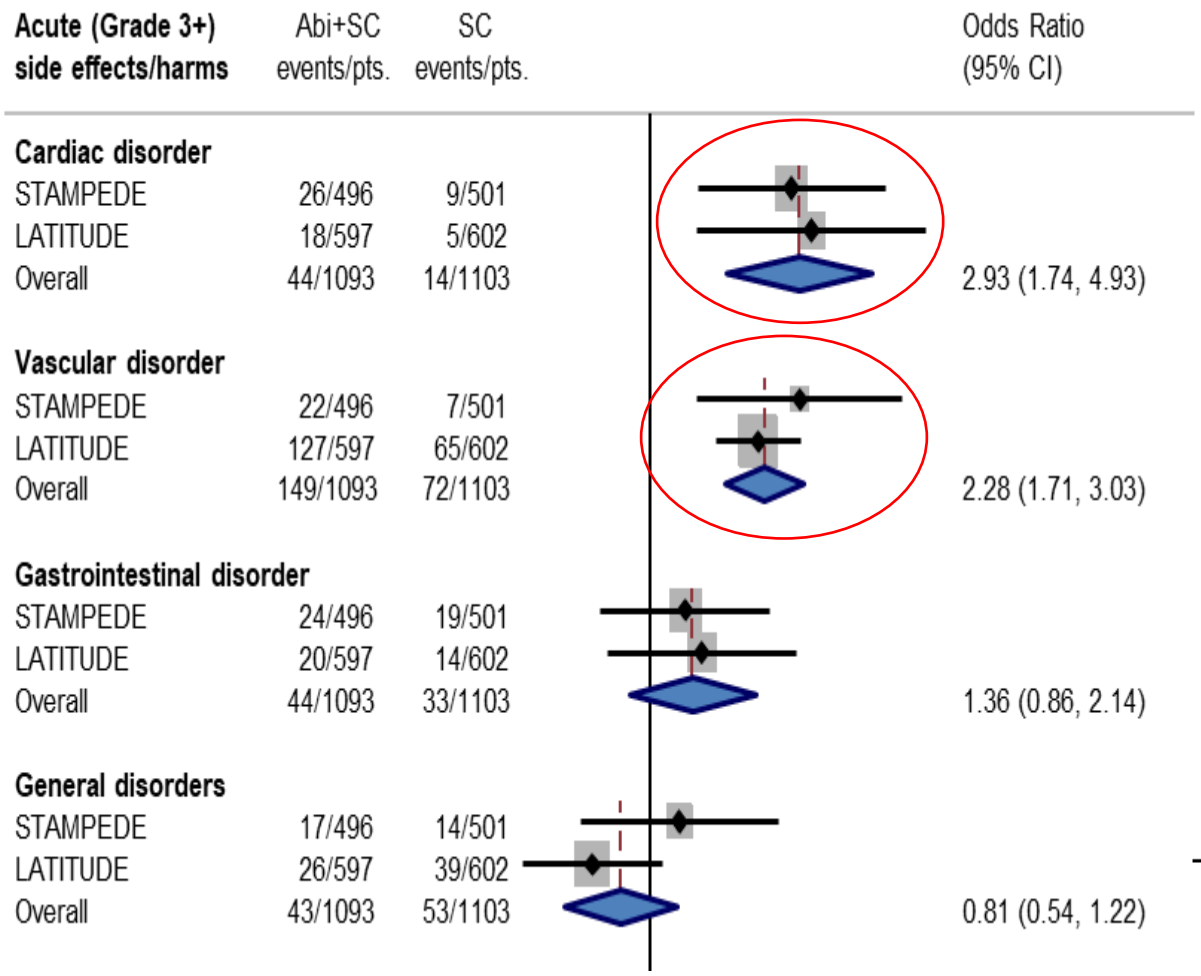
Collect detailed and harmonised data

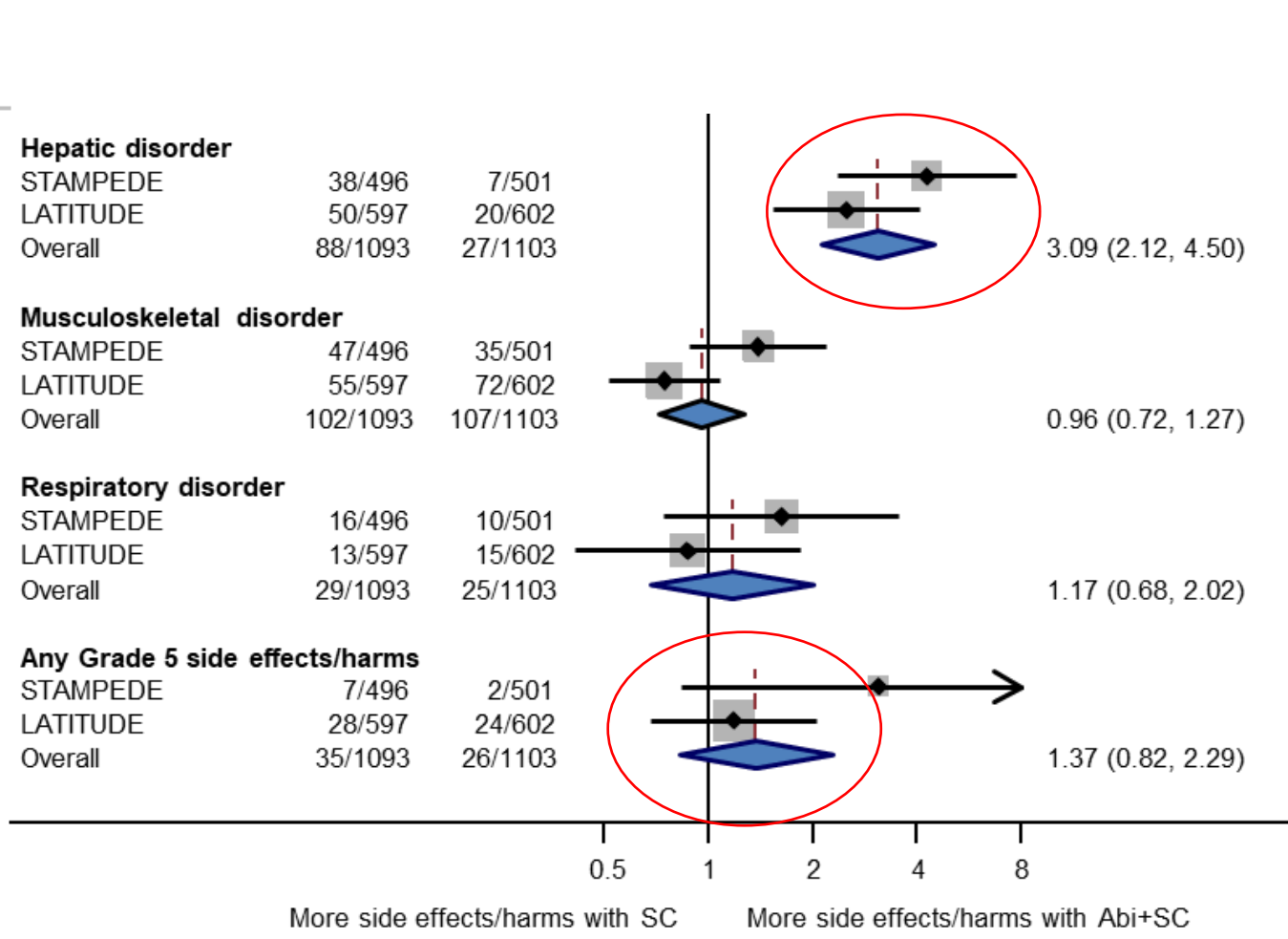
Abiraterone for advanced prostate cancer (Eur J Cancer 2017)



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

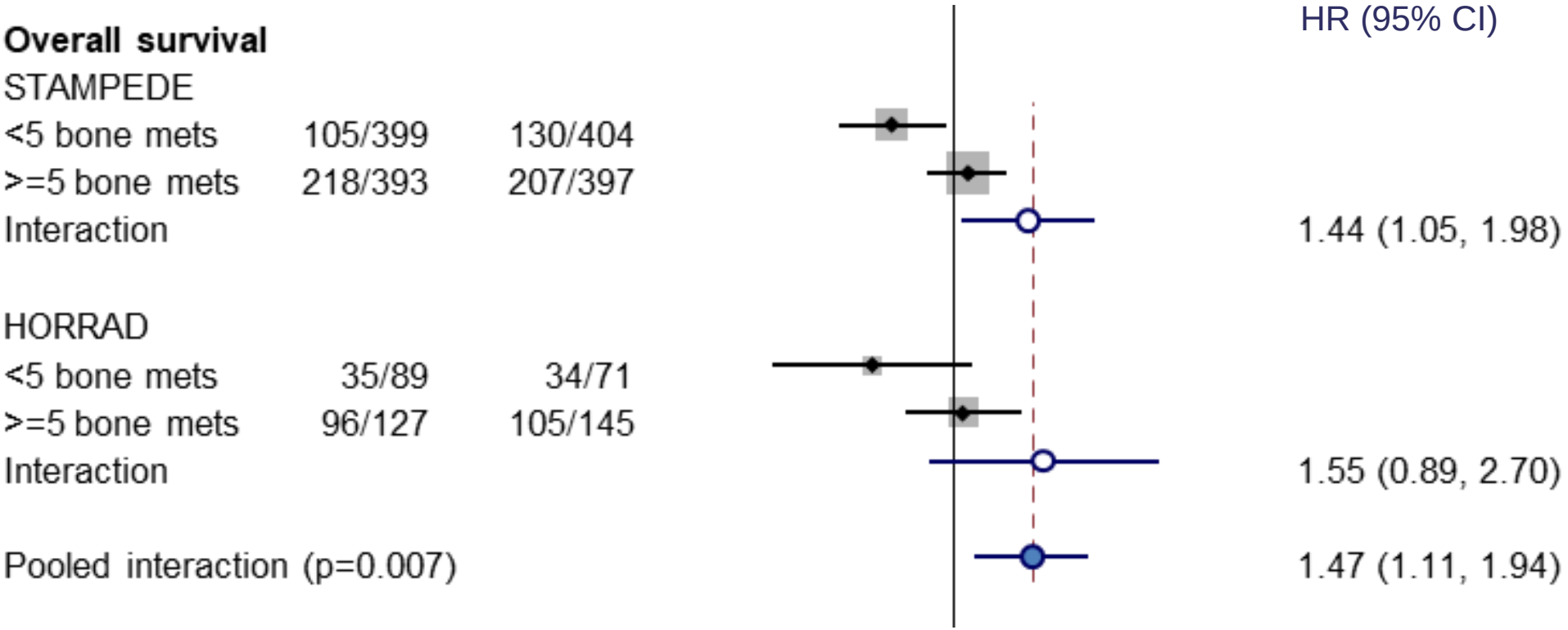
- 2 with results due later in 2018
  - Provide adequate power
  - 90% of men randomised
- 1 with results not due until 2022

Collect detailed and harmonised data

Prostate radiotherapy for advanced prostate cancer (Eur Urol 2019)

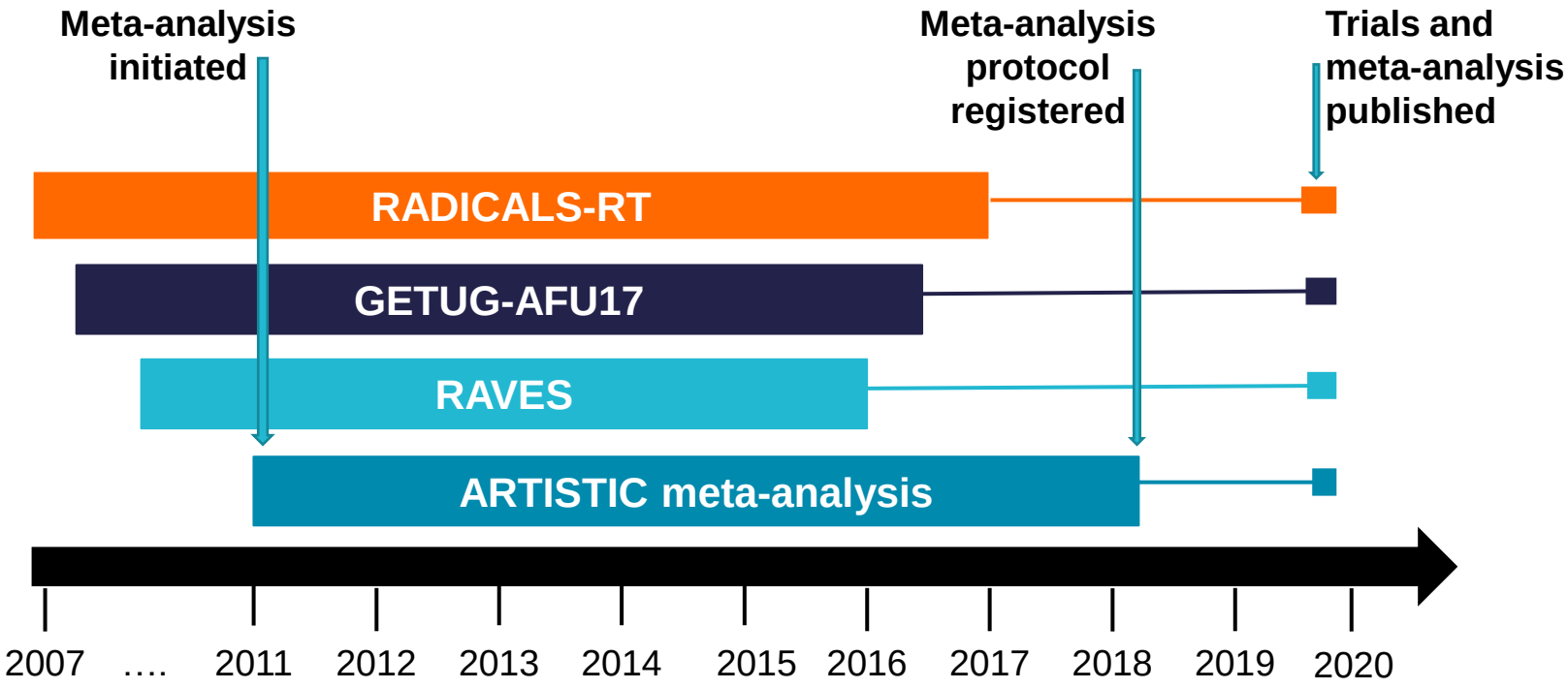
Survival benefit confined to men with <5 bone metastases

- 7% absolute improvement in 3-year survival



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 Pearse, Pierre Richaud, Paul Sargos, Matthew R Sydes, Christopher Brawley, Meryem Brihoum, Chris Brown, Sylvie Chabaud, Adrian Cook, Silvia Forcat, Carol Fraser-Browne, Igor Latorzeff, Mahesh K B Parmar, Jayne F Tierney, for the ARTISTIC Meta-analysis Group

THE LANCET

Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial

Andrew Kneebone, Carol Fraser-Browne, Gillian M Duchesne, Richard Fisher, Mark Frydenberg, Alan Herschtal, Scott G Williams, Chris Brown, Warick Delprado, Annette Haworth, David J Joseph, Jarad M Martin, John H L Matthews, Jeremy L Millar, Mark Sidhom, Nigel Spry, Colin I Tang, Sandra Turner, Kirsty L Wiltshire, Henry H Woo, Ian D Davis, Tee S Lim, Maria Pearse

All published 28 Sept 2020

THE LANCET Oncology

Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial

Christopher C Parker, Noel W Clarke, Adrian D Cook, Howard G Kynaston, Peter Meidahl Petersen, Charles Catton, William Cross, John Logue, Wendy Parulekar, Heather Payne, Rajendra Persad, Holly Pickering, Fred Saad, Juliette Anderson, Amit Bahl, David Bottomley, Klaus Brasso, Rohit Chahal, Peter W Cooke, Ben Eddy, Stephanie Gibbs, Chee Goh, Sandeep Gujral, Catherine Heath, Alastair Henderson, Ramasamy Jaganathan, Henrik Jakobsen, Nicholas D James, Subramanian Kanaga Sundaram, Kathryn Lees, Jason Lester, Henriette Lindberg, Julian Money-Kyrle, Stephen Morris, Joe O'Sullivan, Peter Ostler, Lisa Owen, Prashant Patel, Alvan Pope, Richard Popert, Rakesh Raman, Martin Andreas Røder, Ian Sayers, Matthew Simms, Jim Wilson, Anjali Zarkar, Mahesh K B Parmar, Matthew R Sydes

Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial

Paul Sargos, Sylvie Chabaud, Igor Latorzeff, Nicolas Magné, Ahmed Benyoucef, Stéphane Supiot, David Pasquier, Menouar Samir Abdiche, Olivier Gilliot, Pierre Graff-Cailleaud, Marlon Silva, Philippe Bergerot, Pierre Baumann, Yazid Belkacemi, David Azria, Meryem Brihoum, Michel Soulié, Pierre Richaud

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

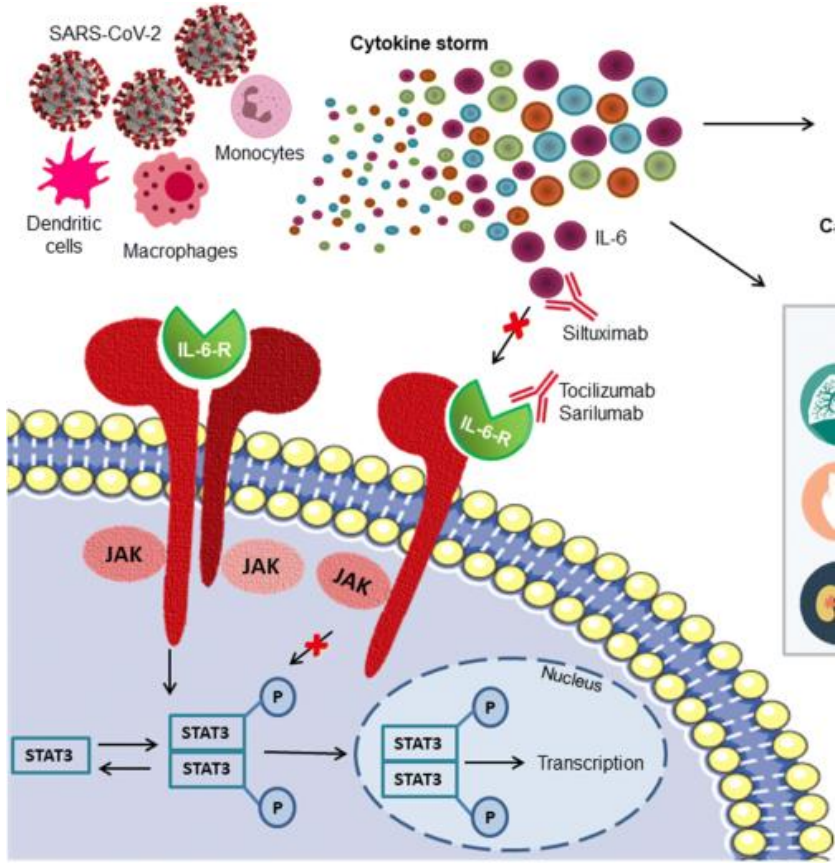
Assist the completion and reporting of included trials

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

	Mortality at 28 days	Total randomised to receive control	Total events in patients randomised to receive control	Total randomised to receive Anti IL-6	Total events in patients randomised to receive Anti IL-6
2	**Overall (all patients randomised)**	2094	729	2022	621
3	**Patient subgroups:**				
4	**Receipt of corticosteroids* and respiratory support** at baseline**				
5	Corticosteroids AND NOT supplemental O2 therapy	2	0	3	1
6	Corticosteroids AND supplemental O2 therapy (O2 ≤ 15l/min)	765	173	766	125
7	Corticosteroids AND NIV (O2 flow >15l/min)	733	300	711	259
8	Corticosteroids AND IMV (including ECMO)	221	127	184	97
9	No corticosteroids AND NOT supplemental O2 therapy	3	0	1	1
10	No corticosteroids AND supplemental O2 therapy(O2 ≤ 15l/min)	162	41	165	53
11	No corticosteroids AND NIV (O2 flow >15l/min)	130	65	107	51
12	No corticosteroids AND IMV (including ECMO)	72	21	84	34
13	Unknown	6	2	1	0
14	**Acute organ support at baseline (CVS support: cardiovascular system support (vasoactive medication); NIV: non-invasive ventilation (including HFNC); IMV: invasive mechanical ventilation including ECMO)**				
15	No respiratory support or O2≤ 15l/min only AND NOT CVS support	0	0	0	0
16	No respiratory support or O2 ≤ 15l/min only AND CVS support	0	0	0	0
17	NIV (O2 flow >15l/min) or IMV (including ECMO) AND NOT CVS support	0	0	0	0
18	NIV (O2 flow >15l/min) or IMV (including ECMO) AND CVS support	0	0	0	0
19	~~Unknown~~	~~2094~~	~~729~~	~~2022~~	~~621~~
20	**Age**				
21	<70 years	1355	309	1331	273
22	>=70 years	739	420	691	348
23	Unknown	0	0	0	0
24	**Sex**				
25	Male	1437	529	1337	417
26	Female	657	200	685	204
27	Unknown / other	0	0	0	0

Overall

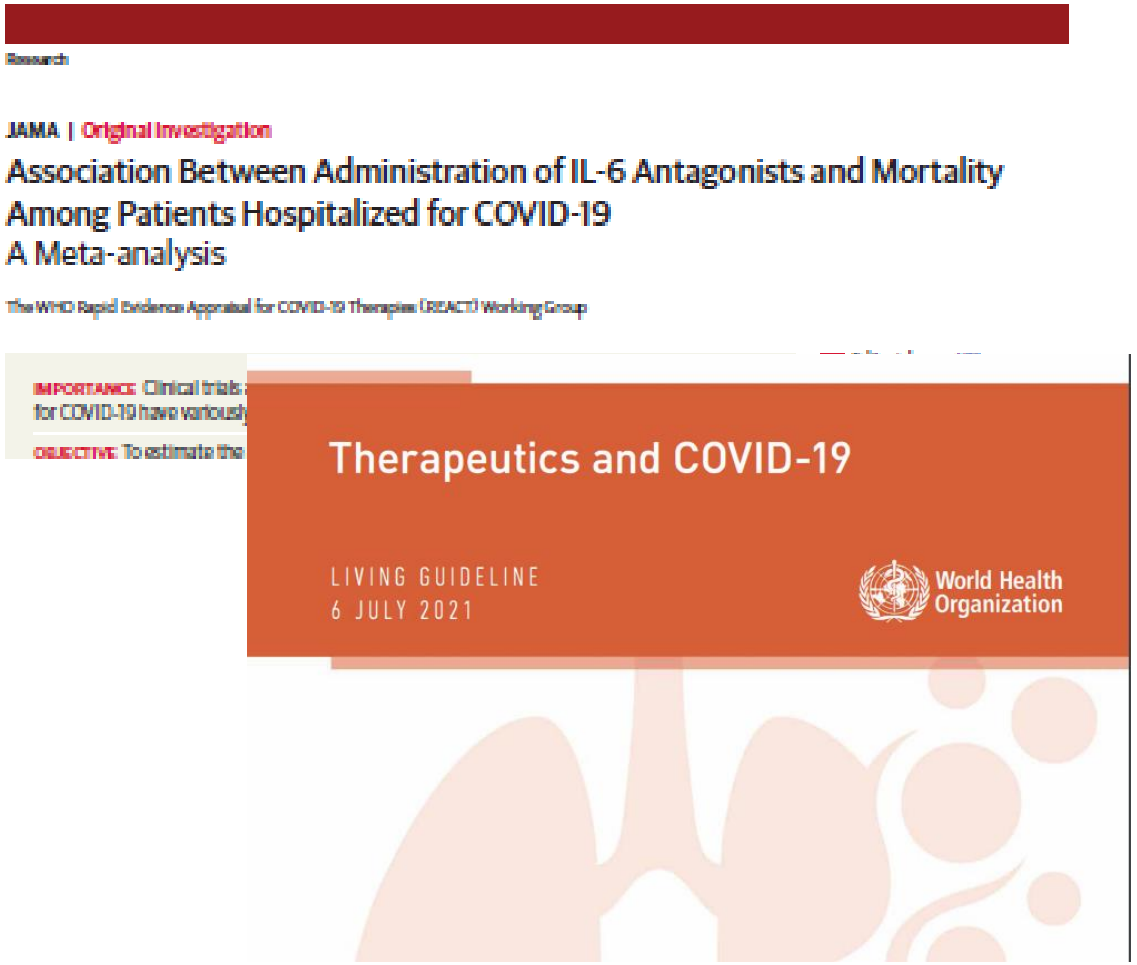
More complex subgroup

Simple binary subgroup

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

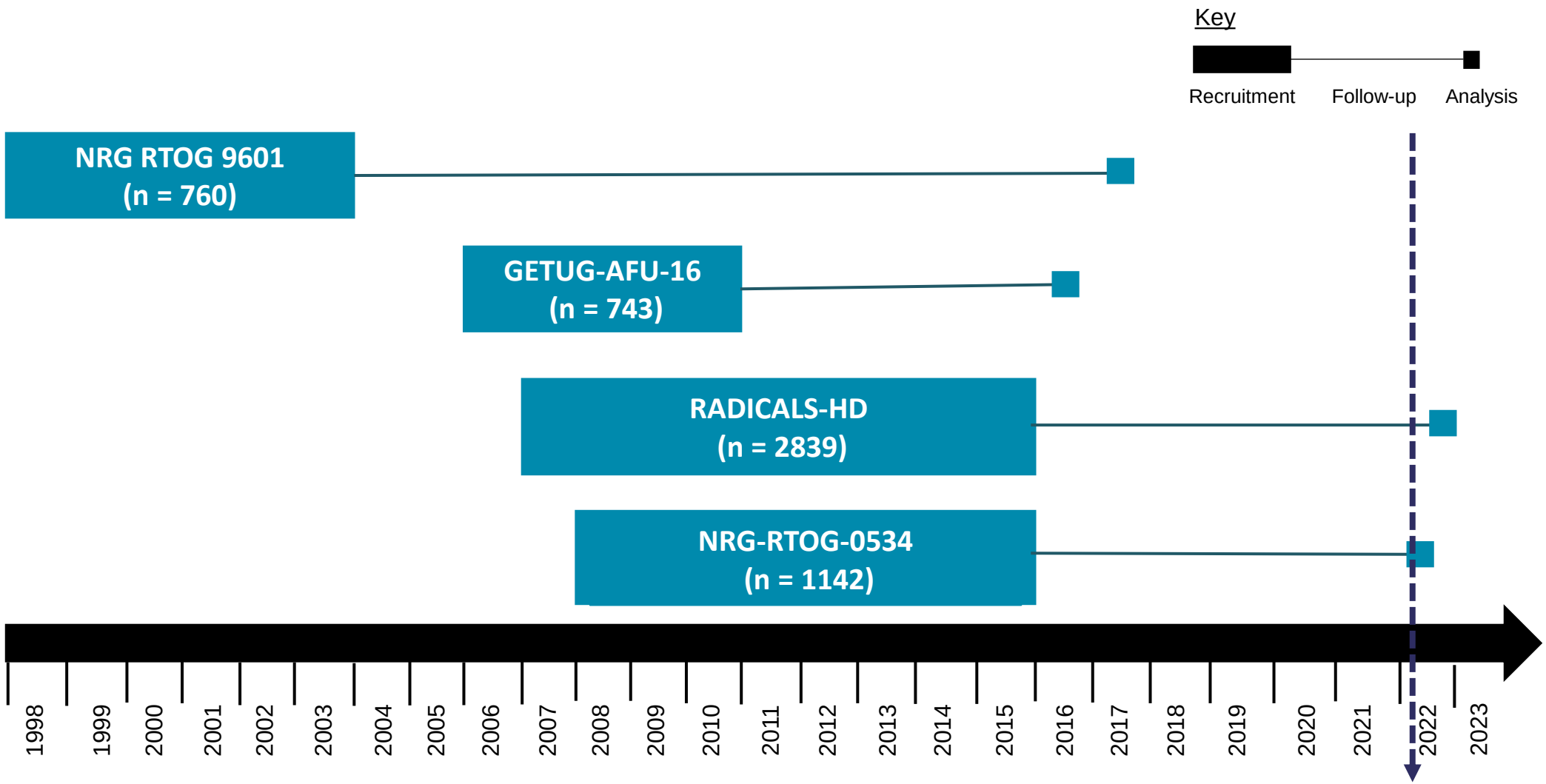
Use as many principles as you can: FAME-lite

Develop and register/publish protocol before trials produce results, and seek detailed and harmonised aggregate data

-lite in action…

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

Outcome	GETUG16	RTOG9601	RTOG0534	RADICALS
OS				
MFS				
PCSS				

- Collected results

Outcome	GETUG16	RTOG9601	RTOG0534	RADICALS
OS				
MFS				
PCSS				

OS - Overall survival;
MFS - Metastases-free survival
PCSS - Prostate cancer specific survival

Published vs collected subgroup results

- Published subgroup results for survival

Subgroup	GETUG16	RTOG9601	RTOG0534	RADICALS
Pre-surgical PSA				
Gleason score				
Seminal vesicle involved				
Surgical margin				
CAPRA-S risk group				
PSA level pre-RT				
Cardiac comorbidity				

- Collected subgroup results for survival

Subgroup	GETUG16	RTOG9601	RTOG0534	RADICALS
Pre-surgical PSA				
Gleason score				
Seminal vesicle involved				
Surgical margin				
CAPRA-S risk group				
PSA level pre-RT				
Cardiac comorbidity				

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…

Cochrane

Trusted evidence.
Informed decisions.
Better health.