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

MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, University College London, United Kingdom

* jayne.tierney@ucl.ac.uk

Abstract

Background

The vast majority of systematic reviews are planned retrospectively, once most eligible trials have completed and reported, and are based on aggregate data that can be extracted from publications. Prior knowledge of trial results can introduce bias into both review and meta-analysis methods, and the omission of unpublished data can lead to reporting biases. We present a collaborative framework for prospective, adaptive meta-analysis (FAME) of aggregate data to provide results that are less prone to bias. Also, with FAME, we monitor how evidence from trials is accumulating, to anticipate the earliest opportunity for a potentially definitive meta-analysis.

Methodology

We developed and piloted FAME alongside 4 systematic reviews in prostate cancer, which allowed us to refine the key principles. These are to: (1) start the systematic review process early, while trials are ongoing or yet to report; (2) liaise with trial investigators to develop a detailed picture of all eligible trials; (3) prospectively assess the earliest possible timing for reliable meta-analysis based on the accumulating aggregate data; (4) develop and register (or publish) the systematic review protocol before trials produce results and seek appropriate aggregate data; (5) interpret meta-analysis results taking account of both available and unavailable data; and (6) assess the value of updating the systematic review and meta-analysis. These principles are illustrated via a hypothetical review and their application to 3 published systematic reviews.

Conclusions

FAME can reduce the potential for bias, and produce more timely, thorough and reliable systematic reviews of aggregate data.
Background

The vast majority of systematic reviews are planned retrospectively, once most eligible trials have completed and reported, and are based on aggregate data extracted from publications. However, prior knowledge of trial results can introduce bias into both review and meta-analysis methods (Table 1), and the omission of unpublished data can introduce reporting biases [1]. Often unpublished and ongoing trials are overlooked [2,3], meaning results may not be interpreted in the context of all the potential evidence, and updating is considered separately [4]. A central tenet of randomised controlled trials is that they are designed prospectively, with methods specified prior to data analysis, in order to preserve objectivity and avoid bias, yet paradoxically, retrospective systematic reviews are often considered a higher level of evidence. Prospective meta-analysis (PMA) has been proposed as a “next generation” solution to the limitations [5].

In PMA, all methods are planned before results of included trials are known, thereby limiting bias [6]. If a PMA is designed when eligible trials are ongoing, or being planned, investigators can work together to harmonise their trial designs, data collection, and other processes [6]. Even if a PMA is initiated when trials are near completion, bias can still be reduced, e.g., by standardising data definitions and analyses. To date, most PMAs have been based on individual participant data (IPD), which brings additional advantages, such as the ability to include more outcomes, standardise their definitions, and carry out more in-depth analyses, including investigation of subgroup effects [7,8]. However, the time lag between trial completion and

| Aspect of conventional retrospective review | Potential Bias |
|-------------------------------------------|----------------|
| Timing of systematic review or meta-analysis | Systematic differences between trial results available at the time of the review or meta-analysis, and the remaining eligible trials. This can occur, for example, if the review or meta-analysis coincides with the publication of striking trial results, and these are published first. |
| Choice of objective and trial eligibility criteria | Systematic differences between results of trials that are, and are not, selected for inclusion. This might arise if the objective and eligibility criteria selected are narrow, thereby excluding trials with particular results, for example, those that that don’t fit with prior beliefs. |
| Choice of participant eligibility criteria | Systematic differences between results for participants that are, and are not, selected for inclusion. This can be an issue, for example, if a treatment is (or appears to be) beneficial only in certain participant subgroups. |
| Choice of main outcome(s) | Systematic differences between results for outcomes that are, and are not, selected for inclusion. This can lead to bias, for example, if treatment benefits or harms are apparent for some outcomes and not others. |
| Assessment of risk of bias | Systematic differences in risk of bias assessment according to results. This can occur, for example, if trials with unexpected or discordant results are regarded as being at higher risk of bias. |
| Methods of analyses including:  
  • Choice of model  
  • Choice of subgroup analyses by trial or participant characteristics  
  • Choice of sensitivity analysis by trial characteristics, risk of bias or results | Systematic differences between meta-analysis results according to methods of analysis. This could arise if, for example:  
  • a random effects model is selected, giving larger weight to small trials with more pronounced effects;  
  • the selection of participant subgroup variables or subgroup analyses is driven by subgroup interactions already observed in one or more trials;  
  • a sensitivity analysis excludes trials with extreme results, but without other justification. |

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availability of IPD precludes rapid evidence synthesis. Therefore, we have developed a Framework for Adaptive Meta-analysis (FAME) [9,10] that is prospective and collaborative in nature but uses aggregate data to provide results that are timelier and less prone to bias. Unlike “living” systematic reviews [11] that incorporate new trial evidence as it emerges, with FAME, we monitor how evidence from trials is accumulating, to anticipate the earliest opportunity for a potentially definitive meta-analysis. This paper outlines FAME and illustrates its application to systematic reviews in prostate cancer.

Methodology

Piloting FAME

In 2015, recognising that a number of trials investigating the effects of docetaxel and zoledronic acid for hormone-sensitive prostate cancer were due to produce results, we wanted to find a way to synthesise these in a timely and unbiased way, to quickly inform clinical practice and an ongoing, adaptive trial [12]. By engaging with investigators, we learned more about the design, conduct, analysis, and dissemination plans of the eligible trials. This allowed us to develop systematic review methods prior to most trial results being known (PROSPERO protocol CRD42015020059), and gauge how soon reliable meta-analyses might be possible. For example, we showed definitively that adding docetaxel to standard therapy improves the survival of men with advanced prostate cancer, whereas adding zoledronic acid does not, ahead of all trial results being available [13]. An unanticipated benefit was gaining access to trial results prepublication, speeding up the review process further. This pilot prompted us to be entirely prospective in the planning of subsequent reviews, and to routinely seek extra results from investigators to improve the quality and consistency of the analyses.

The refined principles of FAME are detailed below, summarised in Fig 1, and illustrated via a hypothetical review of 5 randomised trials (Fig 2).

FAME key principles

1. **Start the systematic review process early, while trials are ongoing or yet to report**
   As for any PMA, the review process should be initiated when eligible trials are ongoing, or before their final analyses, to avoid the methods being biased by prior knowledge of trial results. Acquaintance with the healthcare area is advantageous for identifying unpublished and ongoing trials, but must be backed up by a comprehensive search [14]; with registers, regulatory agencies, and investigator networks being particularly crucial sources of trials. As depicted in Fig 2, at initiation of the hypothetical review, all 5 trials are ongoing.

2. **Liaise with trial investigators to develop a detailed picture of all eligible trials**
   Engagement with trial investigators is critical to obtaining the information needed for review planning, prioritisation and conduct. They can clarify aspects of trial design and conduct, which improves eligibility screening and the accuracy of risk of bias assessments [15]. Also, importantly, they can provide accurate and up-to-date information on accrual, data maturity, analysis, and dissemination plans without compromising the individual trials. Collaborating investigators become co-contributors to the review and coauthors on the final publication. For the hypothetical review, contact with investigators helps clarify that each trial is eligible and at low risk of bias.

3. **Prospectively assess the earliest possible timing for reliable meta-analysis based on the accumulating aggregate data**
   Evidence suggests that more reliable results for overall treatment effects are obtained when
the total number of participants or events (“absolute information size”) and the proportion of eligible participants or events (“relative information size”) included in aggregate data meta-analyses are large [16]. Knowledge garnered from trial investigators can be used to estimate the absolute and relative information size of the accumulating aggregate data, and therefore anticipate when there will be enough for a reliable meta-analysis. Such reliable evidence synthesis may be achieved months or years before all eligible trial results are available.

Firstly, there is a need to determine if, and when, the accumulating absolute information would likely provide sufficient power to detect realistic and clinically meaningful effects of the intervention under investigation. Provided care is taken to minimise potential heterogeneity when specifying the objective and eligibility criteria, the meta-analysis can be regarded like a single prospective trial, in which the accumulating information is monitored to determine the optimum timing of the final analysis, blinded to the results. As such, standard sample size methods and typical control-group event rates for the particular population are used, and these target magnitudes of effect not larger than those being targeted in the included trials. From our experience in cancer, relative risk reductions of around 20% to 25% (or absolute differences of 5% to 10%) are both realistic and worthwhile, but may be adapted for other healthcare areas. For binary and time-to-event and outcomes, the
absolute information size will relate to the number of participants and events and, for continuous outcomes, to the number of participants. Additionally, for time-to-event outcomes, the follow-up will need to be sufficient for the population being studied.

Secondly, there is a need to assess when the anticipated number of participants or events would comprise a large proportion of those potentially available from all eligible trials (whether completed or not). This is to ensure that conclusions are unlikely to be overturned later. For active trials, the potential number of participants may need to be estimated from current or planned accrual figures.

Clearly, striking a balance between maximising the absolute and relative information size and producing a sufficiently timely review is an important consideration. For example, in the hypothetical review, the 3 largest trials (which are due to complete first) will likely provide sufficient power to detect an effect on the main outcome and constitute a substantial proportion of all potentially eligible participants (Fig 2). Thus, a meta-analysis of these 3 trials is planned to provide both an early and reliable synthesis.

4. Develop and register (or publish) the systematic review protocol before trials produce results and seek appropriate aggregate data

To avoid bias, the objectives, eligibility criteria, outcomes, and planned analyses must be outlined in a publicly available protocol, before results of all (or most) eligible trials are known [6]. The FAME estimates of absolute information size, power and relative information size, and the associated decision on meta-analysis timing should be included. Rather than be bound by the planned individual trial analyses, there is the opportunity to agree with investigators, for example, new outcome and subgroup definitions and additional analyses, then collect aggregate data accordingly. This can improve the quality, reliability, and interpretability of meta-analysis results.

If possible, review completion should be timed to coincide with the emergence of included trial results to provide the greatest potential for it to impact expeditiously on clinical practice and on related ongoing or planned trials. In the hypothetical review, the manuscripts for the meta-analysis and the largest trial are prepared in tandem, with a view to co-publication (Fig 2).
5. **Interpret meta-analysis results taking account of both available and unavailable data**

Added to standard considerations such as the direction and precision of the overall effect, and any unanticipated heterogeneity, it is important to assess the potential impact of trials that were not included on the interpretation of the meta-analysis results. This relies on obtaining updated information on all eligible trials from investigators, reestimating the absolute information size, and from that, the relative information size represented by the data. The hypothetical review is based on a larger proportion of the evidence than originally anticipated, because the later trials did not recruit to target (Fig 2), and the results show no clear overall effect of treatment.

6. **Assess the value of updating the systematic review and meta-analysis**

Considering all the potential trial evidence, whether included or not, also makes it possible to ascertain whether there is likely to be value in updating the meta-analysis with further aggregate data, or if IPD might be required for a more reliable or detailed synthesis [16]. This will depend, for example, on the direction and precision of the existing meta-analysis result, which trial results have yet to emerge, how quickly an answer is needed and the resources available. With little trial evidence still to emerge in the hypothetical review, updating the meta-analysis is considered to be of limited value.

**Implementation of FAME**

We illustrate the application of FAME to 3 published reviews in prostate cancer:

1. **Effects of adding abiraterone to standard care in metastatic prostate cancer**

In 2016, we identified 3 trials evaluating the addition of abiraterone to standard hormone therapy for metastatic prostate cancer, none of which had reported results. We found that one trial (PEACE 1, NCT0195743), employing a factorial design, and also examining the effects of prostate radiotherapy, was not due to complete and publish for some years. The other 2 trials had completed recruitment, were due to report in 2017 [17,18], and each was large and individually adequately powered. Together, therefore, they would provide a large absolute information size. Based on accrual figures available at the time, we estimated they would represent 90% of all men randomised to abiraterone, and 70% of men randomised to abiraterone with or without docetaxel, also providing a large relative information size. Hence, rather than waiting for PEACE 1 results, we planned a potentially definitive meta-analysis of the 2 trials to coincide with the emergence of their results (PROSPERO protocol CRD42017058300). With information from trial protocols and investigators, we judged both trials at low risk of bias [19] for randomisation sequence generation, allocation concealment, blinding, completeness of outcome data, and selective provision of outcomes [20]. Collaborating trialists provided aggregate data in advance of publishing their own results [17,18], allowing us to complete and publish the systematic review in a similar time frame [20].

The meta-analysis showed a substantial and convincing improvement in overall survival with the addition of abiraterone (Fig 3), equivalent to an absolute improvement of 14% at 3 years. Although the results of the included trials were conclusive in their own right, we were able to confine the meta-analysis to men with metastatic disease, making the results easier to interpret, and demonstrate remarkable consistency of effects across the trials. Also, we obtained extra results that allowed us to show that the effects of abiraterone did not vary across most predefined subgroups, and that although abiraterone increases some serious harms, it does not appear to be associated with excess mortality (Fig 3) [20].
a) Survival

| Study       | Abi+SC events/pts. | SC events/pts. | Hazard ratio (95% CI) |
|-------------|--------------------|----------------|-----------------------|
| STAMPEDE    | 150/500            | 218/502        | 0.61 (0.49, 0.75)     |
| LATITUDE    | 169/597            | 237/602        | 0.62 (0.51, 0.76)     |
| Overall     | 319/1097           | 455/1104       | 0.62 (0.53, 0.71)     |
|             |                    |                | **p<0.001**           |

b) Acute (Grade 3+) side effects/harms

| Disorder                          | Abi+SC events/pts. | SC events/pts. | Odds Ratio (95% CI) |
|-----------------------------------|--------------------|----------------|---------------------|
| Cardiac disorder                  |                    |                |                     |
| STAMPEDE                          | 26/496             | 9/501          | 2.93 (1.74, 4.93)   |
| LATITUDE                          | 18/597             | 5/602          |                     |
| Overall                           | 44/1093            | 14/1103        |                     |
| Vascular disorder                 |                    |                |                     |
| STAMPEDE                          | 22/496             | 7/501          | 2.28 (1.71, 3.03)   |
| LATITUDE                          | 127/597            | 65/602         |                     |
| Overall                           | 149/1093           | 72/1103        |                     |
| Gastrointestinal disorder         |                    |                |                     |
| STAMPEDE                          | 24/496             | 19/501         | 1.36 (0.86, 2.14)   |
| LATITUDE                          | 20/597             | 14/602         |                     |
| Overall                           | 44/1093            | 33/1103        |                     |
| General disorders                 |                    |                |                     |
| STAMPEDE                          | 17/496             | 14/501         | 0.81 (0.54, 1.22)   |
| LATITUDE                          | 26/597             | 39/602         |                     |
| Overall                           | 43/1093            | 53/1103        |                     |
| Hepatic disorder                  |                    |                |                     |
| STAMPEDE                          | 38/496             | 7/501          | 3.09 (2.12, 4.50)   |
| LATITUDE                          | 50/597             | 20/602         |                     |
| Overall                           | 88/1093            | 27/1103        |                     |
| Musculoskeletal disorder          |                    |                |                     |
| STAMPEDE                          | 47/496             | 35/501         | 0.96 (0.72, 1.27)   |
| LATITUDE                          | 55/597             | 72/602         |                     |
| Overall                           | 102/1093           | 107/1103       |                     |
| Respiratory disorder              |                    |                |                     |
| STAMPEDE                          | 16/496             | 10/501         | 1.17 (0.68, 2.02)   |
| LATITUDE                          | 13/597             | 15/602         |                     |
| Overall                           | 29/1093            | 25/1103        |                     |
| Any Grade 5 side effects/harms    |                    |                |                     |
| STAMPEDE                          | 7/496              | 2/501          | 1.37 (0.82, 2.29)   |
| LATITUDE                          | 28/597             | 24/602         |                     |
| Overall                           | 35/1093            | 26/1103        |                     |
Ultimately, fewer men than planned were recruited to PEACE 1, meaning the meta-analysis results were based on 82% of eligible men rather than the 70% anticipated [20]. This higher relative information size, paired with a robust meta-analysis, gave us confidence that the inclusion of PEACE 1 could not alter the direction or magnitude of the meta-analysis effect (although precision or heterogeneity might change by a small degree). Thus, instead of updating the aggregate data meta-analysis, we are collecting IPD to explore more thoroughly potential effect modifiers, and to compare reliably the effects of abiraterone with other treatments using network meta-analysis.

2. Effects of adding prostate radiotherapy to standard care in metastatic prostate cancer

In early 2016, we identified 3 trials investigating the addition of prostate radiotherapy to standard care for metastatic prostate cancer. One was still recruiting and not due to report for some time (PEACE 1, NCT01957436). The other two were due to report in late 2018, and we estimated that together they would comprise approximately 90% of eligible men and would provide 66% or 99% power to detect 5% (hazard ratio (HR) = 0.85) or 10% (HR = 0.72) absolute differences in 3-year survival, respectively. Thus, the anticipated absolute and relative information from the 2 trials was deemed sufficient for a definitive meta-analysis (PROSPERO protocol CRD42018096108). Both trials were judged to have low risk of bias for randomisation sequence generation, allocation concealment, completeness of outcome data, and provision of outcome data [21].

Adding prostate radiotherapy to standard care led to substantial improvements in biochemical progression and failure-free survival (Fig 4) [21]. While there was no clear evidence that prostate radiotherapy improved survival or progression-free survival in the overall population, these effects were influenced by the number of bone metastases (Fig 4) [21]. For men with few bone metastases, we found a 7% absolute improvement in survival at 3 years. Prospectively planning the subgroup analyses, obtaining the results necessary to conduct these, and demonstrating an interaction that was consistent across trials and outcomes and therefore unlikely to have arisen by chance, was a major strength.

3. Effects of immediate adjuvant versus early salvage prostate radiotherapy in localised prostate cancer

In 2014, we identified 3 ongoing trials of immediate adjuvant versus early salvage prostate radiotherapy for localised prostate cancer. As none were individually powered for survival, we initiated a PMA of IPD that might allow us to detect an effect on this outcome. However, recognising that it would be many years before data would mature and IPD would become available, we began planning a series of prospective aggregate data meta-analyses, each synthesising the results of an intermediate outcome when the required absolute information size was reached, starting with event-free survival.

We agreed a standardised definition of event-free survival with the trial investigators that would be applicable across the somewhat different trial designs. We anticipated that by
a) Overall survival

|               | RT+SC events/pts. | SC events/pts. | Hazard ratio (95% CI) |
|---------------|-------------------|----------------|-----------------------|
| STAMPEDE     | 342/849           | 357/845        | 0.93 (0.80, 1.08)     |
| HORRAD       | 131/216           | 139/216        | 0.89 (0.70, 1.13)     |
| Overall      | 473/1065          | 496/1061       | 0.92 (0.81, 1.04)     |

p=0.195

b) Progression-free survival

|               | RT+SC events/pts. | SC events/pts. | Hazard ratio (95% CI) |
|---------------|-------------------|----------------|-----------------------|
| STAMPEDE     | 509/849           | 514/845        | 0.95 (0.84, 1.08)     |
| HORRAD       | 137/216           | 145/216        | 0.89 (0.70, 1.12)     |
| Overall      | 646/1065          | 659/1061       | 0.94 (0.84, 1.05)     |

p=0.238

Overall survival

- STAMPEDE
  - <5 bone mets: 105/399 vs. 130/404
  - >=5 bone mets: 218/393 vs. 207/397
  - Interaction: 1.44 (1.05, 1.98)
- HORRAD
  - <5 bone mets: 35/89 vs. 34/71
  - >=5 bone mets: 96/127 vs. 105/145
  - Interaction: 1.55 (0.89, 2.70)
  - Pooled interaction (p=0.007): 1.47 (1.11, 1.94)

Progression-free survival

- STAMPEDE
  - <5 bone mets: 184/399 vs. 200/404
  - >=5 bone mets: 299/393 vs. 288/397
  - Interaction: 1.29 (0.99, 1.67)
- HORRAD
  - <5 bone mets: 38/89 vs. 35/71
  - >=5 bone mets: 99/127 vs. 110/145
  - Interaction: 1.47 (0.86, 2.52)
  - Pooled interaction (p=0.021): 1.32 (1.04, 1.67)

Greater effect of RT+SC in men with more bone metastases

Greater effect of RT+SC in men with fewer bone metastases
autumn 2019, approximately 240 events would have occurred across the 3 trials, giving at least 90% power to detect a 5% difference in 5-year event-free survival (HR = 0.57). This, and the ability to obtain results based on 100% of eligible men, prompted us to plan a meta-analysis of this outcome (PROSPERO protocol CRD42019132669). The 3 trials were assessed to be at low risk of bias [22] for the randomisation process, and by obtaining extra results, we were able to limit biases associated with deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result [23].

Based on more events than predicted (270), the meta-analysis showed that immediate radiotherapy does not provide superior event-free survival (1% absolute difference at 5 years) [23]. As it is highly unlikely that such a small difference would translate to a later survival benefit, we could recommend an early salvage treatment policy and spare many men the side effects associated with immediate radiotherapy. The results of the meta-analysis were published [23] contemporarily with the results of the 3 trials [24–26].

Discussion

We have demonstrated that planning aggregate data meta-analysis prospectively and collaboratively using FAME produced timely evaluations of treatment effects that were less prone to bias than standard approaches. Working with trial investigators gave access to better quality aggregate data, allowing more consistent, reliable, and thorough analyses than are usually possible. It also enabled the meta-analysis results to be published in the same time frame as included trials, potentially increasing the visibility and impact of each.

FAME is suited to situations where quick and robust answers are needed, but prospective IPD meta-analysis would be too protracted. Nevertheless, the collaborative nature of FAME brings advantages more often associated with the IPD approach [6–8], such as inclusion of unreported results, harmonisation of outcomes, analysis of participant subgroup effects and wider endorsement and dissemination of results, as well as better identification of trials. If trial searches can be extended to a broad topic area, they can provide an overview of all interventions that have and will be evaluated. This allows strategic and prospective planning of multiple FAME reviews, which can be reprioritised as the status of trials change, and their analysis and dissemination plans evolve. If ongoing trials are identified after the initiation of a FAME review, they can be factored into meta-analysis planning, provided results of all or most eligible trials remain unknown, and any found later can be accounted for in the interpretation of meta-analysis results. If a definitive meta-analysis result is obtained, it can be used by trial investigators and independent data monitoring committees to inform decisions about continuing or adapting such ongoing trials.

As FAME makes use of aggregate data, it is best suited to synthesising overall effects of interventions and variations in effects across a number of predefined subgroups. IPD may be required for a more thorough investigation of potential effect modifiers, other detailed or complex analyses [8], or to ensure reliable estimates of effect [16]. However, a FAME review can
help to justify the IPD approach, indicate which trials are most critical to include, and establish collaborations with investigators that will expedite subsequent data collection.

Predicting information size and determining the precise timing of reliable meta-analysis may be more challenging if eligible trials are numerous, cover a broad time span, are of short duration, or information on them is limited. This further emphasises the need to engage with trialists at an early stage, and to work closely with them to plan and conduct the meta-analysis, taking trial developments into account. Systematic reviewers may be concerned about the feasibility of liaising with investigators and the resource implications of FAME compared to a standard review. Certainly, it necessitates greater preplanning, as well as careful management, in order to avoid jeopardising individual trials, respect their publication timelines, and recognise the contribution of trial teams through coauthorship. Also, Trial Steering Committees may need to sanction participation, and nondisclosure or data sharing agreements may be required to protect information and results. However, we believe that all of this is achievable with a broadly similar level of funding and personnel. While involvement of trial investigators can hamper the objectivity of retrospective systematic reviews, it should not affect a prospective FAME approach, particularly if the systematic review team leads the design and conduct.

Pinpointing the timing of reliable meta-analysis based on information size and taking account of all trials whether they are included or not are key features of FAME. Although it has already been proposed that (absolute) information size should be optimised to ensure robust meta-analysis conclusions [27], and that it could be used to monitor accumulating evidence and account for multiple testing in cumulative pairwise [27,28] and network meta-analyses [29], these approaches seem to have been applied only to existing, retrospectively-planned systematic reviews (e.g., [28–30]).

To our knowledge, FAME represents the first prospective and collaborative approach to aggregate data meta-analysis. Similar PMAs are being employed to balance speed with rigour in the evaluation of COVID-19 therapies [31] (e.g., corticosteroids [32]). Using FAME to anticipate when enough information has accrued could add value in such settings, where many trials are being conducted quickly, and timeliness is vital. Instead, “living” systematic reviews [11] and “living” network meta-analyses [33] aim to incorporate new trial evidence as it emerges, but this means there is a risk that the information size of particular treatment comparisons is limited, and the results potentially unreliable. That said, living network meta-analysis has produced a snapshot of the available evidence on COVID 19 treatments [34], closely aligned to “living” guideline development [35]. Therefore, it could be advantageous to link with clinical guideline developers during the planning and conduct of FAME reviews.

Conclusions
FAME can reduce the potential for bias, and produce more timely, thorough and reliable systematic reviews of aggregate data.

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

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