Cochrane Scientific Call for agenda items – CSC decisions

Thirteen submissions received – reviewed by Ana, Philippe and David

The following six items were discussed at the CSC meeting on 18th October 2017 and with decisions recorded below.

	Submitted by and title	Aims and objectives	Key features and elaboration
1.	Nicole Skoetz Inclusion of results from searching study registries in Cochrane reviews: completed but not published studies	To give authors guidance how to include completed but not published studies identified in study registries	Currently, there is one section in the Cochrane review called "ongoing trials", but what about all the completed trials authors identified in trial registries? Especially those without any published results, where to report them? Still in the ongoing section? This name is misleading, as some might not be ongoing any more. How do review authors search in trial registries? For the "status" ongoing only? Then they will not identify completed, but not published results. Should review authors include completed but not published trials in "included trials" section? Should review authors impute data for these unpublished trials?
	DT, AM, PR commentary	Advice required on how to proceed Another related question of interest is, in what situations where there are published reports/journal articles as well as data in trial registries, should authors be expected to examine all sources related to a study and comment on inconsistencies? How best to capture data from multiple sources? Also track changes with trials overtime e.g. outcomes How best to manage and to account for discrepancies that occur between sources and approach systematically? Problems with subsequently imputing data, if inconsistent. This covers a broad topic and improved guidance required.	
	CSC decision: Nicole reiterated her key point that "ongoing trials" was not the right classification for trials identified in trial registries that were unpublished but completed. So how should they be classified? JH noted that clearer guidance may assist authors in classifying these appropriately as either awaiting classification (awaiting results) or included studies but with no data. Nicole made a further point, as to whether one should impute data (but no results) to shame authors who leave their work unpublished. In addition, trial registries may also provide data not in the published study report. Therefore, further guidance on managing multiple sources of data required. This is not a matter for the CSC.		

2.	Donna Gilles Meta-analyses of prevalence and risk	To broaden the scope of Cochrane reviews to include the best meta-analytic methods of studies of prevalence and risk	Meta-analysis of prevalence and risk - specific types of reviews. Cochrane does not support meta-analysis of prevalence and risk. This is a growing field and high-quality methods need to be developed. In addition, supporting reviews of prevalence and risk could cover many of the areas which users of Cochrane have identified as gaps in our product.
	DT, AM, PR commentary	Advise on whether a paper outlining challenges and benefits of including this review type should be presented in consultation with the prognosis Methods Group New review type in terms of resourcing requires serious consideration.	
	CSC decision: Cochrane (EiC and the Governing Board) need to decide whether Cochrane should include additional research questions such as prevalence and risk. It becomes a question for the CSC as to whether the methods are ready for application in Cochrane. DT indicated that this could be considered within the Content strategy in development (and whether this would require a Methods Group, if agreed). These research questions are background information rather than directly related to clinical care, although they may become more relevant as personalised medicine becomes a more prevalent focus in health care decision making. This is not currently matter for the CSC and will be considered further in Cochrane's Content Strategy.		
3.	Donna Gilles Meta-regression	To support meta-regression in order to improve the quality of analytic methods particularly in relation to continuous study variables and potentially confounding variables	Meta-regression - all reviews. Because of the lack of available meta-regression software and support, analyses of many large-scale Cochrane reviews inadequately address continuous factors such as dosage and longitudinal follow-up, as well as potential covariates.
	DT, AM, PR commentary	It would help to have a collective view on the importance of this method to encourage its application especially for updates. Meta-regression should be done Currently, RevMan does not support meta-regression. However, should we encourage use of other software, such as R.	
	CSC decision: DG's request addressed the need for better guidance and especially with access to external software e.g. R. Currently there are delays to updating RevMan analysis functions but previously Cochrane did not want to make these complex methods widely available to inexperienced authors. Although, Gert (Information & Knowledge Management) is creating an underlying data structure that should make incorporating statistical methods easier. DG's point is that we should actively encourage the appropriate application of meta-regression for sub group analyses, also needed in network meta-analysis. This is an implementation issue because meta-regression is uncontroversial, however, its		

	application is an implementation issue and if we require it done we should identify the necessary statistical support. So, this is a matter for the Editorial Board (possibly Governing Board if it impacts on budgets). This is not a matter for the CSC.		
4.	Jayne Tierney Timely and Reliable Evaluation of the Effects of Interventions: A Framework for Adaptive Meta-analysis (FAME)	Aims to develop a prospective approach to Aggregated Data (AD) systematic review that takes all relevant trials into account and allows us to quickly respond and adapt to emerging trial results. The novel Framework for Adaptive Meta-analysis (FAME) allows us to anticipate the earliest opportunity for reliable AD meta-analysis, often years in advance of all trial results being available.	Most systematic reviews of efficacy are retrospective and based aggregate data (AD) from trial reports, meaning they can lag behind therapeutic developments and fail to influence ongoing or new trials. As unpublished and particularly ongoing trials are often overlooked, this can lead to reporting biases, hamper interpretation of meta-analysis results, and means updating is often inefficiently regarded as a separate process. Against this backdrop, unplanned duplication of systematic reviews has flourished. Further information available in Dropbox
	DT, AM, PR commentary	CSC are asked to review this proposal for future agenda discussion. Need to agree the scope of the review as changes.	
	CSC decision: This is a variant on prospective MA. The Handbook chapter is undergoing a revamp to incorporate additional material on "Living systematic Reviews" and IPD. This approach is about keeping on top of accumulating evidence. Jayne will be asked to share this work with colleagues leading on this chapter. JH thinks this is uncontentious and can be incorporated into the Handbook. This is not a matter for the CSC.		
5.	Jayne Tierney Determining when meta-analyses of published time-to-event outcomes reliable enough to form robust clinical conclusions. An evidence-based approach	Currently, it is not clear when meta-analyses of published time-to-event outcomes are reliable enough to form robust clinical conclusions. We aim to provide substantial and systematic empirical evidence on the reliability of meta-analyses based on HRs from published AD in comparison to those from IPD, so as to inform when IPD might be required.	Effects of treatments on time-to-event outcomes are usually measured using a hazard ratio (HR). If HRs are not explicitly reported, they can be calculated or estimated indirectly from other published statistics, or from data extracted from Kaplan-Meier (KM) curves. Each require assumptions that may affect the reliability of aggregate data (AD) meta-analyses including HRs. Further, AD meta-analyses of HRs are at risk of reporting biases, including follow-up bias, which the collection of individual participant data (IPD) may overcome. However, the IPD approach is lengthy, not always feasible and still rare. Therefore, when an answer is needed quickly or until IPD becomes more readily available, we will continue to rely on meta-analysis of published HRs. We aimed to provide

			substantial and systematic empirical evidence on the reliability of HRs derived from published AD and IPD, so as to inform when IPD may be required. Based on an unselected cohort of 18 IPD systematic reviews (238 unique trials), we compared HRs from AD with their IPD equivalents at the trial and meta-analysis level. The IPD represent >80% of eligible trials and ~90% of eligible patients, often with updated follow-up, providing a 'gold standard' with which to compare HRs from AD. Additional information available.
	DT, AM, PR commentary	<u>CSC asked whether leads should submit a paper on providing recommendations as to how to implement and when.</u> It is now possible to calculate data extracted from Kaplan-Meir curves.	
	CSC decision: Authors do not know how to pool time to event data within aggregated datasets. Authors get the direction of effect wrong and don't consider censoring in one arm results in high risk of bias. More advanced guidance is required. NS asked to add a section to the "Collecting data" chapter of the Handbook. This is not a matter for the CSC.		
6.	<u>Rebecca Turner</u> Data-based predictive distributions for between-study heterogeneity	Many meta-analyses contain only a small number of studies, which makes it difficult to estimate the extent of between-study heterogeneity. Bayesian meta-analysis allows incorporation of external evidence on heterogeneity and offers advantages over conventional random effects meta-analysis (Higgins and Whitehead 1996). To assist with implementation of Bayesian meta-analysis, we have provided empirical evidence on the likely extent of heterogeneity in particular areas of healthcare.	Meta-analyses from the Cochrane Database of Systematic Reviews (Issue 1, 2008) were classified according to the type of outcome, type of intervention comparison and medical specialty. The impact of meta-analysis characteristics on the underlying between-study heterogeneity variance was investigated by modelling the study data from all meta-analyses simultaneously. Predictive distributions were obtained for the heterogeneity expected in future meta-analyses. These can be used directly as data-based informative prior distributions for heterogeneity in Bayesian meta-analyses. Between-study heterogeneity was found to be strongly associated with the type of outcome measured in the meta-analysis and somewhat associated with the types of interventions compared. We have published predictive distributions for heterogeneity in meta-analyses of binary

			outcomes (Turner et al. 2012; Turner et al. 2015) and for heterogeneity in meta-analyses of continuous outcomes (Rhodes et al. 2015). In addition, we have proposed accessible methods for implementing Bayesian meta-analysis with informative priors, avoiding the need for specialist Bayesian software (Turner et al. 2015; Rhodes et al. 2016). Using informative priors for heterogeneity would be beneficial in meta-analyses including few studies. These methods could be applied in standard Cochrane reviews.
	DT, AM, PR commentary	Seek a view from the CSC as to whether this should be mandatory or discretionary, and therefore consider the implementation implications.	
	CSC decision: JH conflicted (lead author). Using Bayesian approaches to add prior information provides a better estimate using the random effects MA model and is more robust. Important in DTA reviews with a low number of studies. Specialist approaches will require statistician support. Request paper and presentation for future meeting.		