Suggestions for standard EBCTCG text on PRISMA-IPD items relevant to methods and funding, to be made available on EBCTCG website and referred to when completing a PRISMA or PRISMA-IPD checklist.

Item	No.	Task	EBCTCG text
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	The methods used in the systematic reviews produced by the EBCTCG have developed over the last 30 years, and a formal protocol has not been produced that would cover this wide range of reviews. The methods used have been summarized in the various reports of the reviews and the most complete description of the methods was included in: Early Breast Cancer Trialists' Collaborative Group Treatment of Early Breast Cancer. Volume 1. Worldwide Evidence 1985-1990. Oxford University Press: Oxford, 1990. Available from http://www.ctsu.ox.ac.uk/research/meta-trials/ebctcg/original-methods-for-ebctcg-meta-analyses The EBCTCG overview began before there were any opportunities to register research such as this, but the intention of conducting the initial reviews was announced before the collection of individual participant data: Anon. Review of mortality results in randomized trials in early breast cancer. Lancet 1984; ii: 1205.
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider	In describing the general eligibility criteria used across the EBCTCG systematic reviews, it is worth noting the omnibus nature and history of this project,* which involves the collaboration of hundreds of research groups from around the world. Over the last 30 and more years, we have identified more than 600 randomised trials of treatments for women with operable breast cancer, and collected IPD from ~500 of these, on more than 600,000 women. In the early 1990s, we routinely sought IPD from every randomized trial that had compared treatments for women who had been diagnosed with operable breast cancer (or breast cancer which might become operable through the use of neo-adjuvant therapy), in which recurrence or death was a principal outcome; regardless of other factors such as age, tumour characteristics, other interventions or place of

		population than specified by the review inclusion criteria. The rationale for criteria should be stated.	treatment. As the scale of the task of collecting, processing and analyzing IPD for every trial grew, our efforts became more focused. This includes engagement with members of the EBCTCG, principally through its Steering Committee to prioritise work on comparisons of specific treatments, followed by concerted efforts to gather the IPD for these comparisons, and to prepare, discuss and publish the associated meta-analyses. The comparisons being tackled in the last decade, and continuing, relate to hormonal therapy (principally, ovarian ablation and suppression, tamoxifen and aromatase inhibitors), chemotherapy (including taxanes, anthracyclines and dose dense therapy), other systematic therapies (including bisphosphonates and biological therapies such as trastuzumab and bevacizumab) and local therapy (including radiotherapy and surgery and more general question such as the management of the axilla). Alongside the research into the main effects of treatments on recurrence, mortality and breast cancer mortality; we also study the effects on second cancers, non-breast-cancer mortality and cardiovascular disease. * Darby S, Davies C, McGale P. The Early Breast Cancer Trialists' Collaborative Group: a brief history of results to date. In Davison AC, Dodge Y, Wermuth N (editors). Celebrating statistics. Oxford University Press, Oxford, 2005 pp.185-198.
Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open	In describing the extensive methods used to identify studies for the EBCTCG systematic reviews, it is important to consider its development over the last 30 and more years.* Briefly, when the overview began with the establishment of the EBCTCG in the early 1980s the focus was on the effects of chemotherapy and hormonal therapy (in particular, tamoxifen) on recurrence and death. Relevant randomised trials were sought through literature searches, contact with research groups around the world who might have done relevant studies and pharmaceutical companies. In the late 1980s, as part of the second cycle of the overview, the scope was expanded to cover all treatments for women with early breast cancer. The searching was also expanded to include a wider range of databases, including registers of trial protocols, conference proceedings, and specific

		adverts and surveys. Give the date of last search or elicitation.	efforts to ask researchers to provide information on trials that they had conducted or knew about. Over the subsequent decades, this approach to searching has continued, with regular searches of bibliographic databases including MEDLINE, Embase and the Cochrane Library and the checking of abstracts presented at the San Antonio Breast Cancer Congress, and conferences of the American Society of Clinical Oncology, European Cancer Organisation and European Society of Medical Oncology. This has led to the compilation of a database of more than 39,500 articles of relevance to the EBCTCG overview (as of November 2022), which continues to be populated on a regular basis, with additional targeted updates for any meta-analyses prior to submission for publication. As such, the date of last search or elicitation for each systematic review is likely to be close to the data on which the relevant analyses were finalized. * Darby S, Davies C, McGale P. The Early Breast Cancer Trialists' Collaborative Group: a brief history of results to date. In Davison AC, Dodge Y, Wermuth N (editors). Celebrating statistics. Oxford University Press, Oxford, 2005 pp.185-198.
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Search strategy for MEDLINE** 1 random$.af. 2 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).af. 3 (phase III or phase 3 or phase IV or phase 4).af. 4 controlled clinical trial$.af. 5 placebo$.af. 6 (meta?analys$ or (meta adj1 analys$)).af. 7 1 or 2 or 3 or 4 or 5 or 6 8 exp breast neoplasms/ 9 (breast$ adj5 (neoplas$ or carcinom$ or cancer$ or tumor$ or tumour$)).af. 10 (advanced or metastatic or inoperable).ti. 11 locally advanced.af. or (neoadjuvant or adjuvant or early or operable).ti.

			12 10 not 11 13 (8 or 9) not 12 14 7 and 13 15 Human$/ 16 Animal$/ 17 16 not (15 and 16) 18 14 not 17 19 18
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	The eligibility of each study for a specific EBCTCG systematic review is determined initially by the EBCTCG Secretariat, and confirmed in consultation with the EBCTCG Steering Committee and the broader membership of the EBTCG through the presentation and discussion of the findings of the review.
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study).	The EBCTCG Secretariat requests IPD from the principal investigator or the relevant research group for each eligible study for each review. This request includes the standard data format, describing each variable and suggesting coding scheme. However, the necessary data are accepted in any format. The IPD are processed by the Secretariat to check for internal consistency, missing data and to confirm that the randomization process appears to have been conducted appropriate. Queries are raised and, where possible, resolved by correspondence with the responsible researchers. The results to be used for each study are shared with the responsible researchers in advance of their inclusion in the published reports.
		If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and	The published EBCTCG meta-analyses are usually restricted to the IPD and are not supplemented by aggregate data from trials for which IPD are not available. This is partly because it is not possible to incorporate such data into all the analyses, which might lead to inconsistencies in the results. Details of the identified trials for which IPD were not available are provided and, in some circumstances, illustrative analyses might be performed (in particular for discussion at the meetings of the EBCTCG, or the Steering Committee) in which aggregate data from the trials without

		confirming these data with investigators.	IPD would be included. These aggregate data would usually have been extracted from published reports of the relevant trials.
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	The variables to be requested as part of the IPD are chosen in consultation between the EBCTCG Secretariat and the Steering Committee. The lists of variables for each cycle of the overview are made available on the EBCTCG website and include a mixture of baseline and follow-up information. The variable list is provided to the responsible trialists along with the data request, and includes the coding used by the EBCTCG Secretariat to store the IPD to be analysed. Some trialists submit the data in this format, using the EBCTCG codes, but most submit it using their own coding or data structure and this is then processed, with appropriate rules for each variable, to create a standardised dataset for each trial.
IPD integrity	**A1**	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	The IPD are first checked for consistency against published reports or the trial to confirm, for example, that the number of patients and events is consistent with reports of the trial. The IPD are then processed to create standardized dataset, which are then subject to a series of checks relating to the sequence that patients were randomized, the balance of variables within the group, range checks on the variables to identify outliers or invalid values, and cross tabulations to determine consistency in related variables. Some of these checks might not be possible because of the provision of data on for example, the interval between events (such as randomisation and recurrence), rather than the actual dates of the events.
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	Where possible, risk of bias is assessed through checks of the randomization sequence, and the balance of baseline variables and follow-up dates across the intervention groups. If substantial problems are identified with a trial, it is excluded from the analyses until these problems have been resolved (if they can be).

Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	The treatment comparisons are described in detail in each report. The principal analyses are usually time-to-event analyses of the time to the outcome of interest, and the principal measure of this is the odds ratio.
Synthesis methods	14	Describe the meta-analysis methods used to synthesise IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): Use of a one-stage or two-stage approach. How effect estimates were generated separately within each study and combined across studies (where applicable). Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. Use of fixed or random effects models and any other model assumptions, such as proportional hazards. How (summary) survival curves were generated (where applicable).	The methods used in the standard analyses for the EBCTCG meta-analyses are those described in the mid 1970s,* and rely on the use of time to event data to calculate the log-rank statistic for each contributing trial, analyzed separately. The analyses are stratified by trial, age, ER status and nodal status . These statistics for each trial are then combined to estimate the relative effects of the interventions and the associated confidence intervals for the meta-analyses. . If a log-rank statistic (o − e) has variance v, then, defining $z = (o - e) / \sqrt{v}$ and $b = (o - e) / v$, the event rate ratio (RR, newer treatment *vs* control) is estimated as exp(*b*) with standard error SE = (RR − 1) / *z*. Either RR and its SE are cited, or confidence limits for RR are derived from those for *b* (by normal approximations). 2p indicates two-sided significance. An estimate of the absolute effects of the intervention and survival curves are calculated and plotted using methods described in detail in: Early Breast Cancer Trialists' Collaborative Group Treatment of Early Breast Cancer. Volume 1. Worldwide Evidence 1985-1990. Oxford University Press: Oxford, 1990. Available from https://www.ctsu.ox.ac.uk/research/ebctcg/further-information/original-methods-for-ebctcg-meta-analyses

		Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). How studies providing IPD and not providing IPD were analysed together (where applicable). How missing data within the IPD were dealt with (where applicable).	Since the mid 1990s,† the effects of treatments on breast cancer mortality have been calculated using log-rank subtraction, in which the log-rank statistics for mortality without recurrence [ie, censored at recurrence] are subtracted from those for overall mortality to estimate breast cancer mortality. * Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. British Journal of Cancer 1977; 35(1): 1-39. † Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomised trials. New England Journal of Medicine 1995; 333: 1444–1455.
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	Subgroup analyses are undertaken for baseline variables, as relevant to each meta-analysis and these are described in the specific reports of each review. Tests for interaction are done across the effects estimates for the subgroups.
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	Risk of bias across the studies is not assessed formally, but issues relating to the non-availability of IPD (for example, because it is not supplied for unpublished studies) is discussed as necessary in each report.
Additional analyses	16	Describe methods of any additional analyses, including sensitivity	Sensitivity analyses, if conducted, are described in the specific reports of each review.

		analyses. State which of these were pre-specified.	

Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	The EBCTCG receives no funding support from the pharmaceutical industry. It is supported by grants from Cancer Research UK and the UK Medical Research Council. Neither funder has any role in study design, conduct, or reporting. The decision to publish is taken by the writing committee for the specific report of each review.