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The role of meta-analyses in assessing cancer treatments

R. Sylvester *, L. Collette, L. Duchateau

European Organization for Research and Treatment of Cancer (EORTC) Data Center, Avenue E. Mounier 83, Bte 11, 1200 Brussels, Belgium

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Abstract

The results of individual phase III cancer clinical trials are often inconclusive due to the overly optimistic size of treatment differences that are sought. Increased power and precision can generally be obtained if the data from several different trials studying the same or similar questions are analysed together. Individual patient data meta-analyses, which combine together the quantitative results from all properly randomised studies, provide an overall estimate of the size of treatment differences. Individual patient data meta-analyses have played an especially important role in breast and gastrointestinal tract cancers where many important questions have been addressed. Although meta-analyses have been subject to considerable criticism, individual patient data meta-analyses provide the best overall evidence of treatment effect in the absence of large-scale trials and have been instrumental in providing objective data that can be used in the design of new studies. © 2000 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Large randomised phase III trials are the method of choice to detect small but medically important treatment differences. Unfortunately individual cancer clinical trials are often designed based on overly optimistic assumptions concerning the size of the treatment difference. Hence individual trials are often not powerful enough to detect smaller, more realistic differences. They are thus unable to provide a definitive answer to the question of interest since too few patients have been entered in the trial. As a result, many trials may conclude that there is no difference in treatment efficacy when in fact the results are inconclusive: an important difference may have been missed simply due to a lack of power.

Data may however be available from several different trials that have studied the same or a similar question. A meta-analysis (or overview or systematic review) is the process whereby the quantitative results of separate but similar studies are combined together using formal statistical techniques [1]. Due to the larger sample size, this usually provides a more powerful test for treatment differences and an increased precision of the estimated treatment effect. Meta-analyses are often carried out if the individual trials addressing a given question of interest are inconclusive or if there are conflicting results from the different studies [1]. They provide an estimate of the overall treatment effect and its precision based on data from all available properly randomised trials.

2. Types of meta-analyses

There are three different types of meta-analyses according to whether they are based on the literature (MAL), summary data (MAS) or individual patient data (MAP or IPD meta-analysis).

In a MAL a literature search is undertaken to find all relevant publications. The results from these publications are then combined together based on the information available in the publications. In a MAS all relevant publications are also identified but now a summary of the relevant statistics is obtained from the authors of the publication. With an IPD meta-analysis a search is not only done in the literature for all relevant published trials, but also in the scientific community for

* Corresponding author. Tel.: +32-2-774-1613; fax: +32-2-772-3545.

E-mail address: rsy@eortc.be (R. Sylvester).

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unpublished trials. For all trials, whether published or not, individual patient data on the endpoint of interest are obtained from the investigator, for example, each patient's exact date of death or censoring, along with additional information on the patient's treatment and prognostic factors.

Performing a MAL in the field of cancer is difficult since the time to an event, generally the duration of survival or time to progression, is the main endpoint in most phase III trials in oncology [2]. The information that can be obtained from the different publications does not, in most cases, allow one to perform a genuine time to event analysis [3,4]. MAS shares weaknesses similar to MAL.

There are two important sources of bias in both MAL and MAS but not in IPD meta-analysis [5]:

1. Publication bias [6–9], which is caused by the fact that trials with statistically significant treatment differences are more likely to be published than 'negative' or inconclusive trials, thus leading to an overestimation of the size of the treatment effect when only published trials are included. In conducting a meta-analysis it is important to identify all relevant randomised trials that have been carried out, whether published or unpublished. *MEDLINE* by itself will not identify all the relevant trials, thus the consultation of other databases, trial registers, hand searching of the literature, and personal contacts are important to identify all appropriate trials [10,11].
2. Selection bias [12,13], that may occur when patients are excluded from the published analysis for reasons that are treatment related. These patients are not included in a MAL or MAS, whereas an IPD meta-analysis is generally based on an intent to treat analysis including all randomised patients.

IPD meta-analyses present many other advantages compared with MAL and MAS studies [10,14]:

1. Quality control of the individual patient data can be carried out. Trials which were not properly randomised, and which could thus be biased, can be excluded from the MAP.
2. Updated follow-up data can be obtained from the investigator, thus leading to a more powerful analysis compared with MAL.
3. Subgroup and prognostic factor analyses can be carried out.
4. Time to event analyses, estimation of hazard ratios and calculation of survival curves can be made.
5. They provide databases for future research.

IPD meta-analysis is the only type of meta-analysis that can be recommended in oncology when time to event endpoints are used, even though it is much more time consuming than the two other types of meta-analyses.

3. Statistical techniques for IPD meta-analyses

The statistical methodology for conducting meta-analyses has been the subject of a number of workshops [15,16] and reviews [17].

For phase III trials in oncology the most common measures of treatment effect used in meta-analyses are the hazard ratio for time to event analyses and the odds ratio for the analysis of binary data (response rate). In combining the results from different trials, data should not just be pooled and an analysis done on the pooled data, rather a statistic that compares the treatment and control groups within each trial must be calculated. This is generally done by calculating,

O = the observed number of events on the experimental treatment
E = the expected number of events on the experimental treatment under the null hypothesis
V = the variance of O−E

within in each trial and then summing them across trials. In this way the within trial statistics O and E are combined, weighting them by their precision V, in order to obtain an overall estimate. The principle of comparing like to like is followed: patients are only compared with other patients within the same trial and are never compared with patients in other trials. All analyses are thus retrospectively stratified by study [1,18].

Since the trials that contribute to a meta-analysis are based on different protocols, there may be differences between the trials with respect to the treatment regimens, the patient population, the endpoint assessment and the size of the treatment effect. It is thus important to investigate whether the results in the different trials or groups of trials are similar and to try to identify the reasons for any such differences [19]. For this purpose tests for heterogeneity of results between trials or for interactions between groups of trials are carried out.

A graphical summary of the data can be presented in a forest plot [1,20]. This provides for each trial an estimate of the size of the treatment effect (odds ratio or hazards ratio) and its precision (confidence interval) along with an estimate of the overall odds ratio or hazards ratio, its confidence interval and a test of significance.

4. The contribution of IPD meta-analyses to cancer research

The use of meta-analyses in oncology has become well known thanks to the pioneering efforts of the Early Breast Cancer Trialists Collaborative Group [18]. In addition to the Imperial Cancer Research Fund (ICRF) Clinical Trial Service Unit in Oxford, UK, the following groups have all been instrumental in carrying out IPD

meta-analyses in Europe: the Medical Research Council (MRC) Clinical Trials Office in London (formerly the MRC Cancer Trials Office in Cambridge), the Meta-Analysis Unit of the European Organization for Research and Treatment of Cancer (EORTC) Data Center in Brussels, Belgium, the Meta-Analysis Group in Cancer (MAGIC) and the Department of Biostatistics and Epidemiology at the Institut Gustave Roussy in Villejuif, France.

The Cochrane Cancer Network, founded in 1997, facilitates the development of Collaborative Review Groups that carry out cancer specific systematic reviews [21]. The Cochrane Collaboration also produces a Cochrane Cancer Library, available on CD-ROM and the Internet, that includes a register of randomised cancer clinical trials and a database of systematic reviews [22]. More information is available at *http://www.update-software.com/ccweb/cochrane/cdsr.htm* and *http://www.cochrane.org/*

In 1998 Clarke and colleagues [2] published a comprehensive list of IPD meta-analyses in oncology. In order to indicate the areas where cancer meta-analyses have been carried out, the following summary of published IPD meta-analyses includes these plus other more recent meta-analyses which were not included in this reference.

4.1. Breast cancer

4.1.1. Early stage disease

4.1.1.1. Primary treatment. Four randomised trials were carried out comparing radical mastectomy without radiotherapy to simple mastectomy with radiotherapy [23]. A meta-analysis of these four trials showed no significant difference in overall survival ($P = 0.07$).

4.1.1.2. Adjuvant radiotherapy. A meta-analysis studied the effect of postoperative adjuvant radiotherapy on survival in operable breast cancer patients that underwent either simple or radical mastectomy [24]. No significant differences were detected ($P = 0.18$).

In operable breast cancer patients who were randomised to postoperative or no postoperative radiotherapy, differences in cause-specific mortality of long-term survivors were assessed [25]. Although there was no significant treatment effect for overall survival, the postoperative radiotherapy arm was associated with an excess of cardiac deaths ($P < 0.001$) but had fewer deaths attributed to breast cancer.

The effect of postoperative radiotherapy in early breast cancer was assessed in another meta-analysis [26]. The type of surgery, a stratification factor, was divided into mastectomy alone, mastectomy with axillary sampling, mastectomy with axillary clearance and breast conservation with axillary clearance. No treatment effect was found for survival ($P = 0.3$) but the difference in time to local recurrence was significant ($P < 0.0001$) in favour of the postoperative radiotherapy arm.

4.1.1.3. Systemic treatment. In an overview of 61 trials, the effect of different treatment strategies on the survival of early breast cancer patients with or without regional lymph node involvement was studied [27]. Mortality was significantly reduced for patients on tamoxifen compared with those not treated with tamoxifen ($P < 0.0001$) and patients treated with cytotoxic therapy also had a longer survival than untreated patients ($P = 0.003$). Finally, polychemotherapy prolonged survival compared with single-agent therapy ($P = 0.001$).

In an extensive meta-analysis, the value of different types of adjuvant systemic treatment in early breast cancer was assessed [28]. Tamoxifen improved both recurrence-free survival ($P < 0.00001$) and survival ($P < 0.00001$). Polychemotherapy also had a beneficial effect on recurrence-free survival ($P < 0.00001$) and survival ($P < 0.00001$). However, no significant treatment effect could be shown for immunotherapy. Ovarian ablation for women below 50 years of age prolonged recurrence-free survival ($P = 0.00007$) and survival ($P = 0.0004$), whereas this was not the case for older women.

In an update of the meta-analysis of the study in [28], the value of adjuvant polychemotherapy [29] and tamoxifen [30] in early breast cancer were assessed. Polychemotherapy prolonged both time to recurrence ($P < 0.00001$) and overall survival ($P < 0.00001$) as did tamoxifen for both recurrence-free survival ($P < 0.00001$) and overall survival ($P < 0.00001$).

The value of adding adjuvant chemotherapy to tamoxifen in postmenopausal patients with node-positive breast cancer was addressed in a meta-analysis [31] of quality adjusted survival based on Q-TWIST (quality adjusted time without symptoms or toxicity). With 7 years of follow-up, there was no difference in quality adjusted survival between the two treatment regimens.

A meta-analysis was done in early-stage breast cancer patients to investigate whether peri-operative polychemotherapy prolongs overall and disease-free survival [32]. Although no significant treatment effect was found for overall survival ($P > 0.1$) perioperative polychemotherapy significantly prolonged disease-free survival ($P = 0.02$).

The survival of early breast cancer patients that did or did not undergo ovarian ablation was compared in a meta-analysis [33]. With 15 years of follow-up, this meta-analysis demonstrated a benefit for both survival ($P = 0.001$) and recurrence-free survival ($P = 0.0007$) for the ovarian ablation group.

4.1.2. Advanced disease

Ovarian ablation (surgery or irradiation) was compared with tamoxifen in a meta-analysis of premeno-

pausal metastatic breast cancer patients with positive or unknown oestrogen receptor (ER) status [34]. There was no significant difference for either progression-free survival ($P = 0.32$) or overall survival ($P = 0.72$).

The goal of a meta-analysis including toremifene and tamoxifen as treatment regimens in postmenopausal women with positive or unknown ER status and advanced breast cancer was to show non-inferiority of toremifene for the response rate, time to treatment failure and survival [35]. For the response rate, the null hypothesis of a difference larger than or equal to 10% was rejected, and for time to treatment failure and survival the null hypothesis of a hazard ratio greater than or equal to 1.25 was also rejected.

4.2. Gastro-intestinal tract

4.2.1. Adjuvant colorectal cancer

Continuous postoperative portal vein infusion (PVI) of 5-fluorouracil (5-FU)-based chemotherapy into the liver was compared with no further treatment in 10 trials comprising 3499 colorectal cancer patients [36]. The difference in survival was significant in favour of PVI ($P = 0.006$) with an absolute difference of 4.7% at 5 years.

4960 patients from three trials were included in a meta-analysis of adjuvant oral fluoropyrimidines after curative resection for colorectal cancer [37]. Compared with surgery alone, there was a significant prolongation of disease-free survival. There also appeared to be a survival improvement in rectal cancer and Dukes' C colorectal cancer patients.

Two meta-analyses studying the value of adjuvant chemotherapy for colon cancer yielded conflicting results.

The first studied the relative efficacy of adjuvant chemotherapy in Dukes' B and C patients in four sequential National Surgical Adjuvant Breast and Bowel Project (NSABP) trials [38]. Two trials comprising 1409 patients compared adjuvant chemotherapy with MOF (semustine, vincristine, 5-FU) or perioperative 5-FU PVI to observation while two other adjuvant trials with 2411 patients compared 5-FU + folinic acid (leucovorin, LV) with either MOF or 5-FU + levamisole. The authors concluded that there was a significant treatment effect for overall, disease-free and event-free survival with the difference being at least as large for Dukes' B patients (mortality reduction of 30%) as for Dukes' C patients (mortality reduction of 18%).

The second meta-analysis compared adjuvant 5-FU + LV to observation after potentially curative resection of B2 colon cancer in 1016 patients from five different trials [39]. Contrary to the previous meta-analysis, no significant differences in either event-free or overall survival were observed.

4.2.2. Advanced colorectal cancer

A meta-analysis of nine randomised trials with 1381 patients compared 5-FU with 5-FU + LV in advanced colorectal cancer [40,41]. The combination showed a significantly higher response rate but there was no improvement in survival ($P = 0.57$). Excluding the four trials that allowed a crossover to 5-FU + LV after progression on 5-FU alone did not change the conclusions.

Continuous intravenous infusion (CI) of 5-FU was compared with a bolus administration of 5-FU in a meta-analysis of six randomised trials which included 1219 patients with advanced colorectal cancer [42]. Patients treated with CI 5-FU had a significantly higher response rate and a slightly longer survival ($P = 0.04$) than patients receiving the bolus. Grade 3 or 4 haematological toxicity, especially neutropenia, was more frequent on the bolus whilst hand–foot syndrome was more frequent on CI 5-FU. Prognostic factors for toxicity were also identified [43].

Another meta-analysis compared 5-FU with 5-FU + methotrexate (MTX) in a total of 1178 patients from eight trials [44]. The combination yielded a significantly higher response rate and a small but statistically significant increase in survival ($P = 0.024$).

4.2.3. Non-resectable colorectal liver metastases

Hepatic arterial infusion (HAI) of fluoropyrimidines was compared with systemic administration of fluoropyrimidines or supportive care in seven trials [45]. HAI with floxuridine (FUDR) was compared with intravenous (i.v.) FUDR in three trials, i.v. 5-FU in two trials and an *ad libitum* control group (i.v. chemotherapy or no treatment) in two trials. HAI FUDR yielded a significantly higher response rate when compared with i.v. FUDR and i.v. 5-FU, but no survival advantage was seen based on 391 patients from these five trials ($P = 0.14$). The difference in survival was, however, significant when based on all 654 patients from the seven trials ($P = 0.0009$). It was also concluded that the cost-effectiveness of HAI with fluoropyrimidines was within the range of accepted treatments for serious medical conditions [46].

The duration of survival of bolus i.v. fluoropyrimidines was compared with experimental fluoropyrimidines (5-FU + LV, 5-FU + MTX, CI 5-FU, HAI FUDR) in a meta-analysis of 1458 patients from 22 trials [47]. The experimental group showed a small but borderline significant prolongation of survival, $P = 0.037$ ($P = 0.058$ after adjustment for performance status).

4.2.4. Oesophageal cancer

A meta-analysis of five randomised trials with 1147 patients studied the value of preoperative radiotherapy in the treatment of patients with potentially resectable oesophageal carcinoma [48]. There was a small non-

significant reduction in the risk of death of 11% which corresponds to an absolute long-term survival benefit of only approximately 3–4% ($P = 0.06$).

4.3. Genito-urinary tract

4.3.1. Bladder cancer

Two meta-analyses have been carried out, one in superficial disease and one in locally advanced disease.

A combined analysis of all EORTC and MRC prophylactic, randomised phase III trials in patients with primary or recurrent, stage Ta, T1 transitional cell carcinoma that compared immediate adjuvant prophylactic treatment with no adjuvant treatment after transurethral resection (TUR) was carried out [49]. Four EORTC and two MRC trials using intravesical chemotherapy or oral agents which included a total of 2535 patients were included. Whilst adjuvant treatment significantly prolonged the disease-free interval, there was no benefit of immediate treatment on long-term endpoints such as time to progression to invasive disease, progression-free survival, time to distant metastases or the duration of survival.

The Advanced Bladder Cancer Overview Collaboration carried out a meta-analysis based on 804 patients from five trials to determine whether neoadjuvant or concurrent platinum-based chemotherapy improved survival in patients with locally advanced bladder cancer [50]. Four trials with individual patient data on 479 patients studied single-agent cisplatin and one trial with summary data on 325 patients investigated cisplatin plus doxorubicin. Although there was no significant difference in survival, it was concluded that there was insufficient information to draw definitive conclusions based on only 301 deaths.

4.3.2. Prostate

A systematic overview of all available evidence from trials comparing maximal androgen blockade (MAB) with castration in advanced prostate cancer [51] showed no statistically significant benefit of MAB in terms of overall survival ($P > 0.1$).

The combination of nilutamide plus orchiectomy in advanced non-pretreated prostate cancer [52] showed a benefit over castration alone in terms of complete or partial regression of the disease ($P < 0.001$), improvement of bone pain and marker levels ($P < 0.01$) and time to disease progression ($P = 0.05$), but no benefit in terms of overall survival ($P > 0.1$).

4.4. Head and neck

The addition of chemotherapy to the loco-regional treatment of patients with non-metastatic squamous cell head and neck cancer significantly improved overall survival ($P < 0.0001$) in the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) [53]. There was no significant difference in overall survival between neoadjuvant chemotherapy followed by radiotherapy and concomitant or alternating radiochemotherapy. For patients with laryngeal cancer, no statistically significant difference was seen between a larynx preserving approach using neoadjuvant chemotherapy and the standard mutilating approach.

4.5. Leukaemia

The acute myeloid leukaemia (AML) Collaborative Group compared induction chemotherapy regimens with idarubicin versus daunorubicin or other anthracyclines in patients with newly diagnosed acute myeloid leukaemia [54]. The analysis showed an increased complete remission rate with idarubicin ($P = 0.02$) and an improved overall survival ($P = 0.03$). The benefit in terms of complete remission tended to be less in the older age groups ($P = 0.006$).

A meta-analysis of maintenance chemotherapy for childhood acute lymphoblastic leukaemia (ALL) [55] showed that survival in first remission was significantly increased by a longer duration of maintenance, by the addition of periodic pulses of vincristine and prednisone and by intensive re-induction treatment. However, only the use of intensive re-induction treatment resulted in an improved overall survival.

A recent meta-analysis [56] by the chronic lymphocytic leukaemia (CLL) collaborative group concluded that there was no statistically significant survival advantage of immediate chemotherapy over delayed chemotherapy in patients with early stage CLL. It also failed to demonstrate any survival benefit of combination chemotherapy over single-agent chlorambucil first-line chemotherapy for patients with more advanced disease.

For patients with chronic myeloid leukaemia and Philadelphia chromosomal abnormalities, the chronic myeloid leukaemia (CML) Trialist's collaborative group meta-analysis [57] showed that the inclusion of interferon-alpha as the main drug in the therapeutic regimen led to a significantly improved survival compared with standard chemotherapy treatment involving either hydroxyurea ($P = 0.001$) or busulphan alone ($P = 0.00007$).

4.6. Lung

4.6.1. Small cell

A meta-analysis of the effect of thoracic radiotherapy in patients with limited small cell lung cancer treated with chemotherapy [58] indicated a 14% reduction in the risk of death with the combined treatment modality ($P = 0.001$). This benefit was larger in patients aged 55 years or less.

In patients with small cell lung cancer in complete remission, prophylactic cranial irradiation improved overall survival ($P = 0.01$) as well as disease-free survival

($P < 0.001$) and decreased the incidence of brain metastases ($P < 0.001$) [59]. The effect on overall survival did not differ significantly according to the dose.

4.6.2. Non-small cell

A meta-analysis of chemotherapy in non-small cell lung cancer [60] revealed that in early and advanced disease settings, older trials using long-term alkylating agents tended to show a detrimental effect of the chemotherapy, especially in adjuvant surgical trials ($P = 0.05$). In all comparisons, the results of modern chemotherapy regimens containing cisplatin favoured chemotherapy. These were significant in the locally advanced ($P = 0.006$) and supportive care ($P < 0.0001$) settings.

The postoperative radiotherapy (PORT) meta-analysis group studied the role of postoperative radiotherapy in patients with completely resected non-small cell lung cancer [61]. Postoperative radiotherapy was shown to have a detrimental effect on survival ($P = 0.001$), particularly in patients with stage I and stage II disease. There was no clear evidence that it was detrimental in patients with stage III N2 disease.

4.7. Lymphoma

For patients with early-stage Hodgkin's disease [62], extensive radiotherapy reduced the risk of resistant or recurrent disease compared with less extensive radiotherapy ($P < 0.00001$) with no apparent improvement in overall survival. Adjuvant chemotherapy added to primary radiotherapy significantly reduced the risk of treatment failure ($P < 0.0001$) without significantly affecting overall survival.

The combination of radiotherapy and chemotherapy was compared with chemotherapy alone in patients with advanced and intermediate stage Hodgkin's disease [63]. When given during an appropriate number of cycles, it led to a significantly worse overall survival ($P = 0.045$) despite its effectiveness in local control.

4.8. Ovarian cancer

In advanced ovarian cancer, a meta-analysis of chemotherapy regimens [64] showed that in terms of overall survival platinum-based chemotherapy is better than non-platinum therapy ($P = 0.02$), there was a trend in favour of platinum combinations over single-agent platinum ($P = 0.07$) and suggested that cisplatin and carboplatin are equally effective.

A meta-analysis comparing the combination of cyclophosphamide, cisplatin and doxorubicin (CAP) to cyclophosphamide and cisplatin (CP) in advanced ovarian cancer [65] showed an improved survival with CAP ($P = 0.02$). However, as the dose-intensity of CAP was higher than that of CP, it is unknown whether the benefit is associated with the addition of doxorubicin or to the higher dose intensity.

4.9. Soft tissue sarcoma

In adult patients with localised resectable soft tissue sarcoma, a meta-analysis [66] showed that adjuvant doxorubicin-based chemotherapy significantly improved the time to local recurrence, distant recurrence and overall recurrence-free survival ($P = 0.016$, $P = 0.0003$ and $P = 0.0001$, respectively). There was also a trend towards improved overall survival ($P = 0.12$).

5. Conclusions

Today a number of these meta-analyses are no longer relevant due to recent advances in oncology. For example, there has been the introduction of taxanes in breast cancer and ovarian cancer and the publication of results from a large randomised trial of neoadjuvant chemotherapy in locally advanced bladder cancer that was not available at the time the meta-analysis was carried out [50,67]. However, these meta-analyses addressed questions that were important at the time that they were designed and have provided objective data that can be used in the design of new trials, both with respect to the choice of the control group and the size of plausible treatment differences. Meta-analyses have been instrumental in showing that trial organisers have been overly optimistic in predicting the size of treatment differences that can be reasonably expected and that many of the trials that have been carried out have been grossly underpowered.

Whilst meta-analyses play a very important role in the decision-making process, they can be criticised just as with most scientific methods [68–72]. Criticisms generally concern the selection of studies, the choice of endpoint, the interpretation of heterogeneity and the generalisation and application of the results.

To a large extent many of these criticisms can be overcome by posing a well formulated question, excluding improperly randomised trials, collecting the individual patient data and using a hard endpoint such as survival. For these reasons, it is important that prior to its start a meta-analysis protocol be written and go through the proper review process just as one would with a clinical trial protocol [21,72,73].

It must be recognised that meta-analyses are not a panacea or cure all and are subject to bias just like individual clinical trials. They most certainly should not be a replacement for large scale randomised trials and should not be used as an excuse for conducting small, underpowered trials. They have replaced the traditional literature review, been instrumental in stimulating international cooperation and research, and have gained

considerable credibility, largely due to the efforts of the Early Breast Cancer Trialists Collaborative Group [18].

What is the future of meta-analyses? In the absence of large-scale trials, meta-analyses, when properly carried out, provide the best overall evidence of treatment effect. What is the alternative? Large-scale multicentre trials and intergroup trials (various cooperative groups prospectively enter patients in a common protocol with just one set of case report forms) which are designed with a high power to detect medically plausible treatment differences. In fact randomised clinical trials and meta-analyses are complementary. Meta-analyses of large randomised clinical trials provide the best overall estimate of treatment effect and may allow the exploration of interactions among subgroups, whether based on treatment modalities or patient characteristics, thus providing hypotheses for future research.

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