Article:
Efficace, F, Jacobs, M, Pusic, A et al. (6 more authors) (2014) Patient-reported outcomes in randomised controlled trials of gynaecological cancers: Investigating methodological quality and impact on clinical decision-making. European journal of cancer, 50 (11). 1925 - 1941. ISSN 0959-8049

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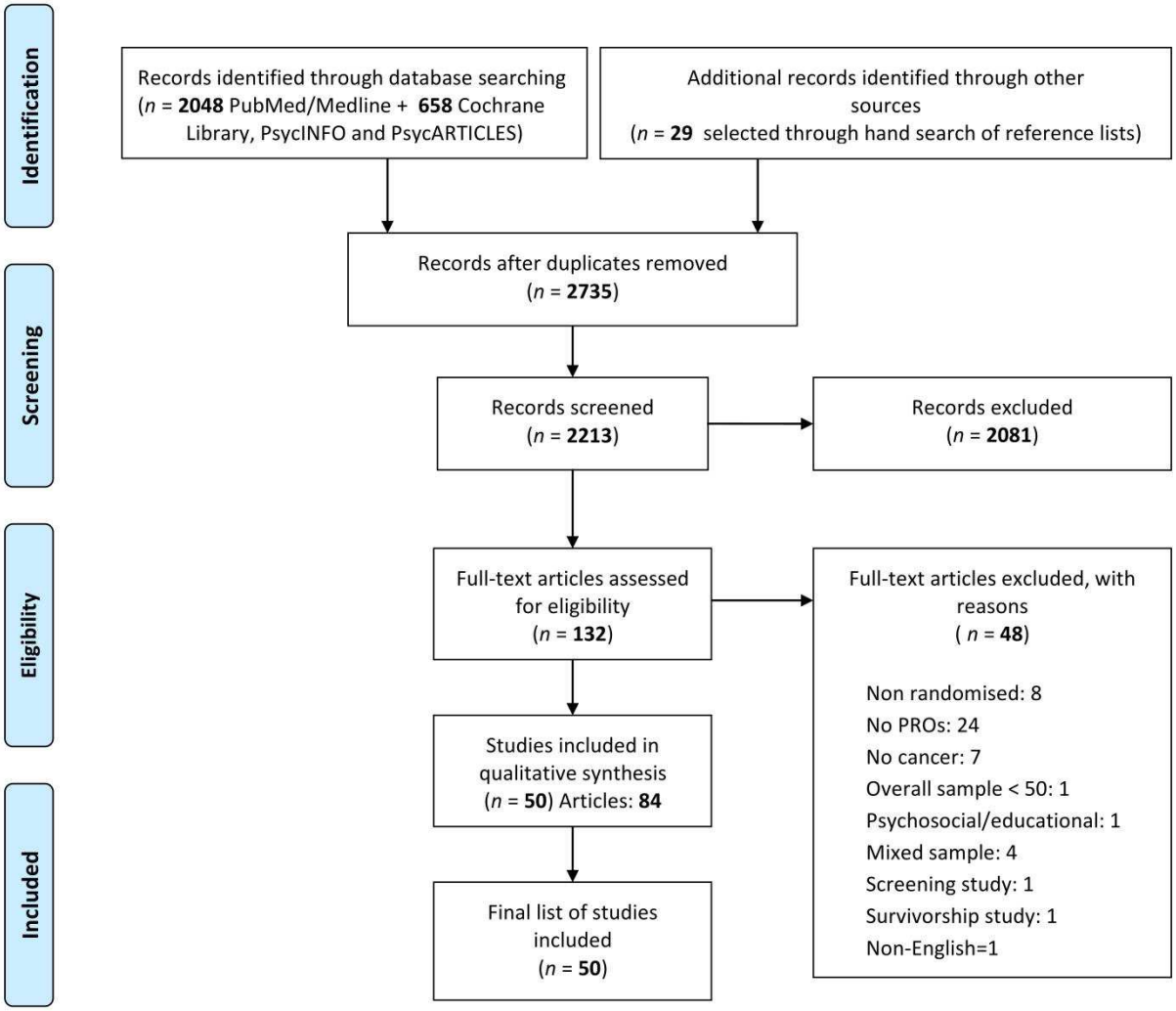
TABLES AND FIGURES

Fig.1 - Schematic breakdown of literature search results of Gynecological Randomised Controlled Trials (Preferred Reporting Items for Systematic Reviews and Meta-analysis).



PRO= patient-reported outcomes.

Table 1. RCT demographic characteristics.

Variable		PRO endpoint n (%)		Total n (%)
		Primary 8 (16%)	Secondary 42 (84%)	
Basic RCT demographics				
Anatomic site of cancer	Cervical	2 (25)	7 (16.675)	9 (18)
	Endometrial	2 (25)	6 (14.29)	8 (16)
	Ovarian	1 (12.50)	15 (35.72)	16 (32)
	Multiple disease sites	3 (37.50)	14 (33.33)	17 (34)
International	No	6 (75)	23 (54.76)	29 (58)
	Yes	2 (25)	19 (45.24)	21 (42)
Industry supported (fully or in part)*	No	7 (87.5)	17 (40.48)	24 (48)
	Yes	1 (12.5)	25 (59.52)	26 (52)
Overall study sample size (regardless of patients included in the PRO analysis)	≤ 200 patients	6 (75)	13 (30.95)	19 (38)
	> 200 patients	2 (25)	29 (69.05)	31 (62)
Disease stage	Advanced/metastatic	2 (25)	14 (33.33)	16 (32)
	Locoregional/no distant metastasis	5 (62.5)	5 (11.9)	10 (20)
	Mixed disease stages	1 (12.5)	22 (52.38)	23 (46)
	Unclear	0 (0)	1 (2.38)	1 (2)
Broad treatment type	Radiotherapy	2 (25)	7 (16.67)	9 (18)
	Surgery	4 (50)	6 (14.29)	10 (20)
	Chemotherapy	3 (37.50)	36 (85.71)	39 (78)
	Target therapy	2 (25)	1 (2.38)	3 (6)
Difference between treatment arms in the primary endpoint	No	0 (0)	20 (47.62)	20 (40)
	Yes	8 (100)	22 (52.38)	30 (60)
Overall Survival (OS) difference favoring experimental treatment	No	1 (12.5)	28 (66.67)	29 (58)
	Yes	0 (0)	7 (16.67)	7 (14)
	N/A (in case OS was not assessed)	7 (87.5)	7 (16.67)	14 (28)
PRO-related basic characteristics				
PRO instrument used	EORTC Instruments	3 (37.50)	21 (50)	24 (48)
	FACT Instruments	2 (25)	14 (33.33)	16 (32)
	VAS	2 (25)	1 (2.38)	3 (6)
	Others	1 (12.5)	6 (14.29)	7 (14)
PRO difference between treatment arms	No differences at all	1 (12.5)	18 (42.86)	19 (38)
	Yes broadly favoring experimental treatment †	7 (87.5)	12 (28.57)	19 (38)
	Yes broadly favoring standard treatment †	0 (0)	11 (26.19)	11 (22)
	N/A	0 (0)	1 (2.38)	1 (2)
If statistically significant PRO difference exists, in which domain?	Symptoms only	3 (42.86)	6 (26.09)	9 (30)
	PRO domains other than symptoms only (e.g. functional scales or global QoL)	0 (0)	4 (17.39)	4 (13.33)
	Both domains (symptoms + domains other than symptoms)	4 (57.14)	13 (56.52)	17 (56.67)
Length of PRO assessment during RCT	Up to 6 months	8 (100)	15 (35.71)	23 (46)
	Up to 1 year	0 (0)	13 (30.95)	13 (26)
	More than 1 year	0 (0)	14 (33.33)	14 (28)
Secondary paper on PRO‡	No	7 (87.5)	30 (71.43)	37 (74)
	Yes	1 (12.5)	12 (28.57)	13 (26)

Legend: * Assessed if explicitly stated or if one or more authors were affiliated to a pharmaceutical company. This evaluation is based solely on information extracted from the paper. † Often, multiple PRO domains (e.g. from multidimensional HRQOL questionnaires) are analyzed at the same time in longitudinal PRO-RCTs; to illustrate, difference in such domains might favor the experimental treatment arm at a given time-point and then favoring the control treatment arm at a different time point over the course of the study. So, the term "broadly" was inserted to account for this possible discrepancy; ‡ Assessed as "yes" if at least one paper was published in addition to the original RCT report.

Table 2 Level of Patient-Reported Outcomes (PRO) reporting by type of endpoint (PRO primary versus secondary endpoint of the trial).

		PRO endpoint n (%)		
		Primary 8 (16%)	Secondary 42 (84%)	Total n (%)
TITLE AND ABSTRACT				
The PRO should be identified as an outcome in the abstract	No	2 (25)	10 (23.81)	12 (24)
	Yes	6 (75)	32 (76.19)	38 (76)
The title of the paper should be explicit as to the RCT including a PRO	No	4 (50)	-	4 (50)
	Yes	4 (50)	-	4 (50)
INTRODUCTION, BACKGROUND AND OBJECTIVES				
The PRO hypothesis should be stated and should specify the relevant PRO domain if applicable	No	7 (87.5)	36 (85.71)	43 (86)
	Yes	1 (12.5)	4 (9.52)	5 (10)
	N/A (if explorative)	0 (0)	2 (4.76)	2 (4)
The introduction should contain a summary of PRO research that is relevant to the RCT	No	3 (37.5)	-	3 (37.5)
	Yes	5 (62.5)	-	5 (62.5)
Additional details regarding the hypothesis should be provided, including the rationale for the selected domain(s), the expected direction(s) of change, and the time points for assessment	No	8 (100)	-	8 (100)
METHODS				
Outcomes				
The mode of administration of the PRO tool and the methods of collecting data should be described	No	7 (87.5)	35 (83.33)	42 (84)
	Yes	1 (12.5)	7 (16.67)	8 (16)
Electronic mode of PRO administration*	No	1 (12.5)	7 (16.67)	8 (16)
	N/A	7 (87.5)	35 (83.33)	42 (84)
The rationale for choice of the PRO instrument used should be provided	No	8 (100)	34 (80.95)	42 (84)
	Yes	0 (0)	8 (19.05)	8 (16)
Evidence of PRO instrument validity and reliability should be provided or cited	No†	4 (50)	8 (19.05)	12 (24)
	Yes	4 (50)	34 (80.95)	38 (76)
The intended PRO data collection schedule should be provided	No	2 (25)	6 (14.29)	8 (16)
	Yes	6 (75)	36 (85.71)	42 (84)
PROs should be identified in the trial protocol post-hoc analyses should be identified	No	6 (75)	28 (66.67)	34 (68)
	Yes	2 (25)	14 (33.33)	16 (32)
The status of PRO as either a primary or secondary outcome should be stated	No	1 (12.5)	0 (0)	1 (2)
	Yes	5 (62.5)	39 (92.86)	44 (88)
	Unclear	2 (25)	3 (7.14)	5 (10)
A citation for the original development of the PRO instrument should be provided	No†	5 (62.5)	-	5 (62.5)
	Yes	3 (37.5)	-	3 (37.5)
Windows for valid PRO responses should be specified and justified as being appropriate for the clinical context	No	7 (87.5)	-	7 (87.5)
	Yes	1 (12.5)	-	1 (12.5)
Sample size				
There should be a power sample size calculation relevant to the PRO based on a clinical rationale	No	5 (62.5)	-	5 (62.5)
	Yes	3 (37.5)	-	3 (37.5)
Statistical methods				
There should be evidence of appropriate statistical analysis and tests of statistical significance for each PRO hypothesis tested	Yes	1 (12.5)	4 (9.52)	5 (10)
	N/A (If PRO hypotheses were not stated)	7 (87.5)	38 (90.48)	45 (90)
The extent of missing data should be stated ‡	No	3 (37.5)	17 (40.48)	20 (40)
	Yes	5 (62.5)	25 (59.52)	30 (60)
Statistical approaches for dealing with missing data should be explicitly stated ‡	No	7 (87.5)	34 (80.95)	41 (82)
	Yes	1 (12.5)	8 (19.05)	9 (18)
The manner in which multiple comparisons have been addressed should be provided	No	5 (62.5)	-	5 (62.5)
	Yes	3 (37.5)	-	3 (37.5)

Table 2 (continued). Level of Patient-Reported Outcomes (PRO) reporting by type of endpoint (PRO primary versus secondary endpoint of the trial).

		PRO endpoint n (%)		
		Primary 8 (16%)	Secondary 42 (84%)	Total n (%)
RESULTS (continued Table 2)				
Participant flow				
A flow diagram or a description of the allocation of participants and those lost to follow-up should be provided for PROs specifically	No	6 (75)	28 (66.67)	34 (68)
	Yes	2 (25)	14 (33.33)	16 (32)
The reasons for missing data should be explained	No	3 (37.5)	32 (76.19)	35 (70)
	Yes	5 (62.5)	10 (23.81)	15 (30)
Baseline data				
The study patients characteristics should be described including baseline PRO scores	No	3 (37.5)	16 (38.1)	19 (38)
	Yes	5 (62.5)	26 (61.9)	31 (62)
Outcomes and Estimation				
Are PRO outcomes also reported in a graphical format?*	No	4 (50)	22 (52.38)	26 (52)
	Yes	4 (50)	20 (47.62)	24 (48)
The analysis of PRO data should account for survival differences between treatment groups if relevant	No	1 (12.5)	-	1 (12.5)
	N/A (if not relevant)	7 (87.5)	-	7 (87.5)
Results should be reported for all PRO domains(if multi-dimensional)and items identified by the reference instrument	No	2 (25)	-	2 (25)
	Yes	6 (75)	-	6 (75)
The proportion of patients achieving pre-defined responder definitions should be provided where relevant	No	4 (50)	-	4 (50)
	Yes	1 (12.5)	-	1 (12.5)
	N/A (if not relevant)	3 (37.5)	-	3 (37.5)
DISCUSSION				
Limitations				
The limitations of the PRO components of the trial should be explicitly discussed	No	6 (75)	21 (50)	27 (54)
	Yes	2 (25)	21 (50)	23 (46)
Generalizability				
Generalizability issues uniquely related to the PRO results should be discussed	No	2 (25)	34 (80.95)	36 (72)
	Yes	6 (75)	8 (19.05)	14 (28)
Interpretation				
Are PRO interpreted? (Not only re-stated)*	No	3 (37.5)	19 (45.24)	22 (44)
	Yes	5 (62.5)	23 (54.76)	28 (56)
The clinical significance of the PRO findings should be discussed	No	7 (87.5)	28 (66.67)	35 (70)
	Yes	1 (12.5)	14 (33.33)	15 (30)
Methodology used to assess clinical significance (in case this was addressed)*	Anchor based	0 (0)	3 (21.43)	3 (20)
	Distribution based	1 (100)	9 (64.29)	10 (66.67)
	Other	0 (0)	2 (14.29)	2 (13.33)
The PRO results should be discussed in the context of the other clinical trial outcomes	No	2 (25)	20 (47.62)	22 (44)
	Yes	6 (75)	22 (52.38)	28 (56)
OTHER INFORMATION				
Protocol				
A copy of the instrument should be included if it has not been published previously (It could be found in the article appendix or in the online version	No	8 (100)	-	8 (100)

Legend:

For descriptive purposes, subheadings of this table reflect that of reported in the ISOQOL recommended standards, however, rating of items was independent of location of the information within the manuscript; N/A: Not Applicable.

- Indicates items that are not applicable as these are recommended to be reported only when PRO is a primary endpoint; * the following items have not been included in the ISOQOL recommended standards[16] but have been added in this table to have a wider outlook on the level of reporting. † We evaluated as "no" if all PRO measures used in the study were not validated; ‡ These items were originally combined in the ISOQOL recommended standards[16] but have been split in this report to better investigate possible discrepancies between documentation of PRO missing data (i.e., reporting how many patients did not complete a given questionnaire at any given time point) *versus* actual reporting of statistical methods to address this issue. Also, we wanted to be consistent with items reported in the CONSORT PRO Extension (i.e., *statistical approaches for dealing with missing data* is reported as a standalone issue).

Table 3. Randomized Controlled Trials with robust PRO design: basic study characteristics.

Study*	International	Age of patients (years) †	Overall study sample size	Baseline PRO sample size	PRO instruments used	Primary endpoint	Treatment outline	Summary of main clinical results	Summary of PRO results/PRO treatment recommendations	Anatomic site of cancer
Metastatic/Advanced disease stage										
Kurtz JE et al. Ann Oncol 2011;22(11):2417-23; Alexandre J et al. Br J Cancer 2012;106(4):633-7; Brundage M et al. Ann Oncol 2012; 23(8):2020-7; Gladieff L et al. Ann Oncol 2012; 23(5):1185-9; Joly et al; Gynecol Oncol 2011;122(2):226-32; Pujade-Lauraine et al. J Clin Oncol 2010; 28(20):3323-9.	Yes	Median (range) carboplatin–pegylated liposomal doxorubicin (CD): 60.5 (24-82) carboplatin–paclitaxel (CP): 61 (27-82)	976	879	EORTC QLQ-C30; EORTC QLQ-OV28.	progression free-survival.	CD arm: combination of pegylated liposomal doxorubicin (PLD) (30mg/m2 intravenously on day 1) and carboplatin (AUC 5 based on the Calvert formula using glomerular filtration rate calculated from serum creatinine values according to the method of Cockroft and Gault, administered intravenously on day 1 at 4-week intervals. CP arm: combination of paclitaxel (175 mg/m2 intravenously on day 1) and carboplatin (AUC 5 intravenously on day 1) at 3-week intervals. Random assignment was performed in permuted blocks of 6 cycles.	With median follow-up of 22 months, Progression Free-Survival for the pegylated liposomal doxorubicin with carboplatin arm was statistically superior to the carboplatin and paclitaxel arm (hazard ratio, 0.821; 95% CI, 0.72 to 0.94; P =0 .005); median Progression Free Survival (PFS) was 11.3 versus 9.4 months, respectively. Overall severe non-hematologic toxicity (36.8% v 28.4%; P < 0.01) leading to early discontinuation (15% v 6%; P<0.001) occurred more frequently in the CP arm.	Global Quality of Life (QoL) and abdominal symptom scores improved over time in both arms; at 6 months, 36% of patients met criteria for improved symptoms. Treatment with CD resulted in less peripheral neuropathy (9.8 versus 24.2), fewer other chemotherapy side-effects (9.5 versus 16.2), and less impact on body image (3.8 versus 10.4) versus CP (all P < 0.02) at 6 months.	Multiple disease sites.

Cella D et al. Gynecol Oncol. 2010;119(3):531-7; Monk BJ et al. J Clin Oncol 2009;27(28): 4649-55.	No	Median (range) Vinorelbine (VC) = 49; (24-76) gemcitabine (GC) =45; (20-89) topotecan (TC) = 48; (25-75) paclitaxel (PC) = 50; (29-81)	513	410	FACT-Cx TOI; FACT/GOG-NTX; BPI	Overall survival.	Patients were randomly assigned to paclitaxel 135 mg/m2 over 24 hours plus Cis 50 mg/m2 day 2 every 3 weeks (PC, reference arm); vinorelbine 30 mg/m2 days 1 and 8 plus Cis 50 mg/m2 day 1 every 3 weeks (VC); gemcitabine 1,000 mg/m2 day 1 and 8 plus Cis 50 mg/m2 day 1 every 3 weeks (GC); or topotecan 0.75 mg/m2 days 1, 2, and 3 plus Cis 50 mg/m2 day 1 every 3 weeks (TC). Duration: up to 6 months	No statistically significant difference.	No statistically signficant differences in Health-related Quality of Life (HRQL), neuropathy, or pain.	Cervical
Long HJ et al. J Clin Oncol 2005;23(21): 4626-33; Monk BJ et al. J Clin Oncol 2005;23(21): 4617-25; Long HJ et al. Gynecol Oncol 2006;100(3): 537-43.Long HJ.	No	Cisplatin-topotecan (CT): 46(22-84) Cisplatin (CPT): 48 (27-76)	364	284	FACT-G, FACT-Cx, FACT/GOG-NTX, BPI, UNI.	overall survival.	cisplatin 50 mg/m2 every 3 weeks (CPT); cisplatin 50 mg/m2 IV day 1 plus topotecan 0.75 mg/m2 days 1 to 3 every 21 days (CT) (methotrexate 30 mg/m2 days 1, 15, and 22, vinblastine 3 mg/m2 days 2, 15, and 22, doxorubicin 30 mg/m2 day 2, and cisplatin 70 mg/m2 day 2 every 28 days. methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Max 6 cycles	Patients receiving cisplatin and topotecan CT had statistically superior outcomes to those receiving cisplatin CPT, with median overall survival of 9.4 and 6.5 months (P =0 .017), median PFS of 4.6 and 2.9 months (P = 0.014), and response rates of 27% and 13%, respectively.	There was no statistical evidence suggesting that reported QoL and adverse effects scores changed over time differently across regimens. Baseline FACT-G (P = 0.0016) and BPI (P = 0.0001) scores were significantly associated with patient age; older patients had better QOL and less pain. Baseline UNI was positively correlated with FACT-G (r = 0.66; P <0.001) and Cx subscale (r= 0.29; P < 0.001), and negatively related to BPI (r=-0.41; P <0.0001). Baseline FACT-Cx (FACT-G + Cx subscale) was associated with survival.	Cervical

Moore DH et al. J Clin Oncol 2004; 22(15):3113-9; McQuellon RP et al. Gynecol Oncol 2006; 101(2):296-304;	No	Median (range) Cisplatin (C): 46.0 (22-84) Cisplatin plus paclitaxel (CP): 48.5 (21-77)	280	252	FACT-G; FACT-Cx; A Trial Outcome Index representing Physical Well Being (PWB) + Functional Well-Being (FWB) + the Cervix subscale; BPI-SF; neurotoxicity subscale	overall survival; progression free-survival; Objective Response Rate.	Cisplatin (C): IV dose of 50 mg/m2 at the rate of 1 mg/min. Cisplatin plus paclitaxel (CP): paclitaxel IV dose of 135 mg/m2 as a 24-hour infusion followed immediately by cisplatin at a dose of 50 mg/m2 Duration every 3 weeks for 6 cycles	Objective responses occurred in 19% (6% complete plus 13% partial) of patients receiving cisplatin versus 36% (15% complete plus 21% partial) receiving cisplatin plus paclitaxel (P=0.002). The median (PFS) was 2.8 and 4.8 months, respectively, for cisplatin versus cisplatin plus paclitaxel (P < 0.001).	There was no significant difference in QOL scores. The BPI-SF revealed a decline in pain scores in both arms from the first to fourth assessments. The rate of QOL drop-out for any reason was higher for C (53%) compared to CP (38%) (P < 0.05). At the fourth time point, 60% of living patients in both arms completed a QOL assessment.	Cervical
Fleming GF et al. J Clin Oncol 2004; 22(11):2159-66.	No	<= 50, N=22 51-60 , N=72 61-70, N=110 71-80, N=54 >=81, N=5	273	216	FACT/GOG-NTX	Overall survival.	Doxorubicin cisplatin (AP) doxorubicin 60 mg/m2 and cisplatin 50 mg/m2. Doxorubicin cisplatin paclitaxel (TAP) doxorubicin 45 mg/m2 and cisplatin 50 mg/m2 (day 1), followed by paclitaxel 160 mg/m2 (day 2) with filgrastim support every 3 weeks to a maximum of seven cycles.	Objective response (57% v 34%; P< 0.01), PFS (median, 8.3 v 5.3 months; P=<0 .01), and OS (median, 15.3 v 12.3 months; P = 0.037) were improved with TAP.	Following two cycles of chemotherapy, patients on the TAP arm reported a significantly higher neurotoxicity score than did patients on the AP arm. Significant differences in the mean score were observed, and sustained following the second cycle of chemotherapy. Furthermore, patients reported neurotoxicity increased significantly during the treatment period in the TAP arm, but not in the AP arm.	Endometrial
Non-metastatic disease stage										
Armstrong DK et al. N Engl J Med 2006; 354(1):34-43; Wenzel LB et al. J Clin Oncol 2007; 25(4):437-43; von Gruenigen VE et al. Gynecol Oncol 2012;124(3):	No	Intravenous-Therapy (IV) (N = 210) and Intraperitoneal- Therapy (IP) (N = 205) 21–30 0; 4(2) 31–40 15 (7); 8 (4) 41–50 43	429	399	FACT-O; FACT-TOI; FACT-G subscales (PWB, Physical Well Being; FWB, Functional Well-Being, SWB, Social well-being and EWB, Emotional Well-being); FACT / GOG NTX	progression free-survival and overall survival.	Intravenous-therapy (IV): 135 mg of intravenous paclitaxel per square meter of body-surface area over a 24-hour period on day 1 followed by 75 mg of intravenous cisplatin per square meter on day 2. intraperitoneal-	The median duration of progression-free survival in the intravenous-therapy and intraperitoneal-therapy groups was 18.3 and 23.8 months, respectively (P = 0.05). The median duration of overall survival in the intravenous-therapy and intraperitonealtherapy groups was 49.7 and 65.6 months, respectively (P = 0.03).	Quality of Life was significantly worse in the intraperitoneal-therapy group before cycle 4 and three to six weeks after treatment but not one year after treatment Physical and functional well-being and ovarian cancer symptoms were significantly worse in the IP arm before cycle 4 (P = 0.001) and 3 to 6 weeks after treatment (P =0.001	Multiple disease sites.

379-82; Krivak TC et al. Gynecol Oncol 2009; 115(1):81-5.		(20); 52 (25) 51–60 74 (35); 62 (30) 61–70 56 (27); 53 (26) 71–80 19 (9); 24 (12) >80 3 (1); 2 (1)					therapy (IP): 135 mg of intravenous paclitaxel per square meter over a 24-hour period on day 1 followed by 100 mg of intraperitoneal cisplatin per square meter on day 2 and 60 mg of intraperitoneal paclitaxel per square meter on day 8 duration: every 3 weeks for 6 cycles.		for FACT-TOI). Patients in the IP arm also reported significantly worse abdominal discomfort (AD) before cycle 4 (P = 0.001) and significantly worse Ntx 3 to 6 weeks (P =0.001) and 12 months (P = 0.003) after completing IP treatment. In general, however, the quality of life of both groups improved over time.	
Janda M et al. Contemp Clin Trials 2006; 27(4):353-63; Janda M et al. Lancet Oncol 2010; 11(8):772-80.	Yes	Total laparoscopic hysterectomy (TLH): mean (SD) 62.8 (10.0) Total abdominal hysterectomy (TAH): Mean (SD) 62.7 (9.7)	361	332	FACT-G; EnWB (FACT subscale Endometrial) (FACT-G+ EnWB= FACT-Endometrial) Body image scale; EQ-5D (EuroQoL-VAS).	Patient Reported Outcomes (PRO) (including QOL or symptoms relief). QoL at 6 months.	Total laparoscopic hysterectomy (TLH). Total abdominal hysterectomy (TAH).	Operating time was significantly longer in the TLH group (138 min [SD 43]) than in the TAH group (109 min [SD 34]; p=0.001). Postoperatively, twice as many patients in the TAH group experienced adverse events of grade 3 or higher (33 of 142 [23.2%] vs 22 of 190 [11.6%] in the TLH group; p=0.004). Postoperative serious adverse events occurred more in the TAH group (27 of 142 [19.0%]) than in the TLH group (16 of 190 [7.9%]; p=0.002).	Patients who had TLH reported significantly greater improvement in QoL from baseline compared wit those that had TAH, in all subscales apart from emotional and social well-being. Improvements in QoL up to 6 months after surgery continued to favor TLH, except in the emotional and social well-being measures of the FACT and the visual analogue scaled of the EuroQol-VAS. The greatest differences were noted in FWB (13% greater improvement for patients with TLH), PWB (11%), EnWB (6%), and the overallFACT-G summary score (7%; p=0.001 for all comparisons). Patients in the TLH group also reported a 5% (p=0.001) greater improvement in body image and 7.5% (p=0.001) greater improvement in overall QoL (EuroQoL-VAS) than patients in the TAH group. During the late post-op	Endometrial

									recovery phase (3–6 mths after surg),TLH patients recovered significantly more in their physical, (p=0.008), functional (p=0.009), endometrial cancer-specific (p=0.003), and overall wellbeing (FACT-G; p=0.03), and also had better QoL recovery with regard to body image (p=0.001)	
Mourits MJ et al. Lancet Oncol 2010; 11(8):763-71; Bijen CB et al. Gynecol Oncol 2011; 121(1):76-82.	No	Total abdominal hysterectomy (TLH): n=185 median: 62 range 40-89; Total abdominal hysterectomy (TAH): n=94 median 63 range 39-86	283	0	SF-36, SAQ, BIS, VAS for general health perception. EQ-5D.	Major complication rate.	Total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy vs Total laparoscopic hysterectomy (TLH) and bilateral salpingo-oophorectomy.	The proportion of major complications was 14·6% (27 of 185) in the TLH group versus 14·9% (14 of 94) in the TAH group, with a diff erence of –0.3% (95% CI –9.1 to 8.5; p=0.95).TLH was associated with signifi cantly less blood loss (p<0.0001), less use of pain medication (p<0.0001), a shorter hospital stay (p<0.0001), and a faster recovery (p=0.002), but the procedure took longer than TAH (p<0.0001).	A higher percentage of patients in TLH group (76.3%) resumed daily activities after 6 weeks than in TAH group (62.2%). Patients who had TLH scored significantly higher on the physical functioning subscale of the SF-36 at 6 weeks, and on the role-physical subscale at 3 months after the procedure. Patients who had TAH scored signifi cantly higher on the vitality subscale of the mental dimension 3 months after surgery.	Endometrial
Mixed disease stage (loco-regional disease and metastatic disease)										
Walker JL et al. J Clin Oncol 2009; 27(32):5331-6; Kornblith AB et al. J Clin Oncol 2009; 27(32):5337-42; Walker JL et al. J Clin Oncol 2012; 30(7):695-700.	Yes	Median (Range) Laparoscopy 62.8 (55.4-71.6) Laparotomy 62.7 (54.9-70.6)	2616	727	FACT-G; AP MOS-SF36; PF BPI; BI.	Recurrence free servival.	Patients with clinical stage I to IIA uterine cancer were randomly assigned to laparoscopy (n 1,696) or open laparotomy (n 920), including hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and para-aortic lymphadenectomy.	Laparoscopy had fewer moderate to severe postoperative adverse events than laparotomy (14% v 21%, respectively; P < 0.0001); significantly longer operative time (median, 204 v 130 minutes, respectively; P < 0.001). Hospitalization of more than 2 days was significantly lower in laparoscopy versus laparotomy patients (52% v 94%, respectively; P < 0.0001). Pelvic and para-aortic nodes were not removed in 8% of laparoscopy patients and 4%	In an intent-to-treat analysis, laparoscopy patients reported significantly higher Functional Assessment of Cancer therapy–General (FACT-G) scores (P = 0.001), better physical functioning (P = 0.006), better body image (BI; P < 0.001), less pain (P < 0.001) and its interference with QoL (P <0.001), and an earlier resumption of normal activities (P = 0.003) and return to work (P = 0.04) over the 6-week postsurgery period, as compared with laparotomy	Endometrial

								of laparotomy patients (P <0.0001).	patients. By 6 months, the only difference between arms was the better BI in laparoscopy.	
Greimel ER et al. J Clin Oncol 2006; 24(4):579-86; du Bois AJ et al. J Natl Cancer Inst. 2003;95(17):1320-9. Hilpert F et al. Ann Oncol 2007; 18(2):282-7.	Yes	mean 56.7, Standard deviation (SD) 10.93; range 20.8-77.4 and 57.7 SD 10.11; range 25.4-83.6 in the paclitaxel plus carboplatin (TC) and paclitaxel plus cisplatin (PT)	798	TC: 397 eligible, 366 forms returned PT : 386 eligible, 357 forms returned	EORTC QLQ-C30	progression free-survival.	Paclitaxel (185 mg/m2) + carboplatin (AUC=6) (TC arm) vs. paclitaxel (185 mg/m2) + cisplatin 75 mg/m2 (PT arm) - all six courses per 3 weeks	The proportion of patients without progression at 2 years was not statistically significantly different between the two treatment arms (40.0% for PT versus 37.5% for TC, difference = 2.5%, one-sided 95% confidence interval [CI] = $-\infty$ to 8.2%). Median progression-free survival time in the TC arm (17.2 months, 95% CI = 15.2 to 19.3 months) and the PT arm (19.1 months, 95% CI = 16.7 to 21.5 months) were also not statistically significantly different; the same was true of median overall survival time (43.3 months, 95% CI = 37.2 to 47.8 months versus 44.1 months, 95% CI = 40.2 to 49.4 months, for the TC and PT arms, respectively).	Patients in the TC arm showed better means scores after treatment on overall QoL overall QoL (P=0.012), physical functioning (P= 0.012), role functioning (P = 0.005), and cognitive functioning (P = 0.024), compared with the PT arm. Concerning symptom experience, patients undergoing TC showed less nausea and vomiting (P <0.001), less appetite loss (P< 0.001), and less fatigue (P=0.033) after completion of treatment compared with patients undergoing PT.	Ovarian
Carey MS et al. Gynecol Oncol 2008; 108(1):100-5; Butler L et al. J Clin Oncol 2004; 22(12):2461-8; Piccart MJ J Natl Cancer Inst 2000; 92(9):699-708; Bezjak A et al. J Clin Oncol 2004;22(22):4595-603.	Yes	Median (Range) Cyclophosphamide (CP): 58 (22-85) paclitaxel (TP): 58 (23-79)	680	152	EORTC QLQ-C30	progression free-survival.	TP arm= paclitaxel at a dose of 175 mg/m2 as a 3-hour infusion followed by cisplatin at a dose of 75 mg/m2 CP arm= cyclophosphamide at 750 mg/m2 followed by cisplatin at 75 mg/m2. Duration every 3 weeks between 3 and 9 cycles.	At a median follow-up of 38.5 months and despite a high rate of crossover (48%) from the cyclophosphamide arm to the paclitaxel arm at first detection of progression of disease, a longer progression-free survival (log-rank P = 0.0005; median of 15.5 months versus 11.5 months) and a longer overall survival (log-rank P = 0.0016; median of 35.6 months versus 25.8 months) were seen in the paclitaxel regimen compared with the cyclophosphamide regimen.	Clinically meaningful improvements compared with baseline (change scores > 10) were found in both arms during the treatment period in a number of domains and items, including global QOL, emotional function, social function, fatigue, pain, sleep, constipation, appetite, abdominal swelling, and abdominal cramps. Improvements in global QOL persisted for the duration of follow-up. More neurosensory effects and myalgia were found in the paclitaxel arm.	Ovarian
Wenzel L et al. J Clin Oncol 2005; 23(24):5605-	No	Median (range) Secondary	550	376	FACT-G; FACT-O; GOG (supplemental	overall survival.	Name drugs: paclitaxel + cisplatin	No statistically significant differences.	For all patients, QOL decreased approximately 1 unit from the first to second assessment.	Ovarian.

12; Rose PG et al. N Engl J Med 2004;351(24):2489-97.		surgery plus chemotherapy group: 58.1 (25.4-81.6) Chemotherapy-alone group: 57.0 (27.0-81.6)			questions)		Doses: Chemo only: paclitaxel 135 mg/m2 over 24 hours followed by immediately by cisplating Cis 75 mg/m2; Duration: maximum of 6 cycles of 3 weeks Surgery + chemo: paclitaxel 135 mg/m2 over 24 hours followed by immediately by cisplating Cis 75 mg/m2 every 3 weeks for max 6 cycles. Secondary cytoreduction performed as soon as possible after hematologic recovery of the 3rd cycle, but within six weeks after the completion of the third cycle.		Significant improvement observed at 6 months (P < 0.001) was sustained at 12 months, with no appreciable between-group difference (P=0.048). The baseline FACT-O score was associated with overall survival (P =0.048) but not progression-free survival. Less neurotoxicity was reported among patients who did (38.4%) versus did not (54.0%) undergo interval secondary cytoreduction at the third assessment (P= 0.005), and older patients experienced more long-term effects.	
Nout RA et al. Lancet 2010; 375(9717):816-23; Nout RA et al. Eur J Cancer 2012;48(11):1638-48; Nout RA et al. J Clin Oncol 2009; 27(21):3547-56.	No	pelvic external beam radiotherapy (EBRT)= Median 69 (SD:7); vaginal brachytherapy (VBT)= Median:70 (SD:7),	427	0	EORTC QLQ-C30 version 3.0; subscales for bowel and bladder symptoms from from the prostate cancer module (PR25) and subscale for sexual functioning and symptoms from Ovarian Cancer Module (OV28).	vaginal recurrence.	vaginal brachytherapy (VBT) = 1. High–dose-rate (HDR). schedules aimed at 45-50 Gy by schedules of 21 Gy in three fractions of 7 Gy, 1 week apart for the high-dose rate; 2. Low-dose rate (LDR) schedules: 30 Gy at 50–70 cGy/h 3. Medium-dose-rate. (MDR) schedules: 28 Gy at 100 cGy/h in one session. pelvic external beam radiotherapy	No significant differences between arms regarding vaginal recurrence. Rates of acute grade 1–2 gastrointestinal toxicity were signifi cantly lower in the vaginal brachytherapy VBT group than in the pelvic external beam radiotherapy EBRT group at completion of radiotherapy (12.6% [27/215] vs 53.8% [112/208].	Patients in the VBT group reported better social functioning (P<0.002) and lower symptom scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms (P<0.001). At baseline, 15% of patients were sexually active; this increased significantly to 39% during the first year (P<0.001). Sexual functioning and symptoms did not differ between the treatment groups.	Endometrial

							(EBRT) = A dose of 46 Gy 2 Gy fractions, five times per week, duration unclear.			
Randall ME et al. J Clin Oncol 2006; 24(1):36-44; Bruner DW et al. Qual Life Res 2007;16(1):89-100.	No	Median =63	422	317	FS; APN; FACE; FACT-G.	progression free-survival.	Whole-abdominal irradiation (WAI): irradiation dose was 30Gyin 20 daily fractions. After WAI, patients received a boost to the true pelvis or to an extended field encompassing pelvic lymph nodes (PLNs) and positive para-aortic lymph nodes (PALNs). The boost dose was 15 Gy in 8 fractions. All fields were treated once daily, 5 days per week. AP: chemotherapy; doxorubicin 60 mg/m2 plus cisplatin 50 mg/m2 every 3 weeks for seven cycles, followed by 1 cycle of cisplatin.	The stage-adjusted hazard ratio for progression was 0.71 favoring doxorubicin-cisplatin AP (95% CI, 0.55 to 0.91; P =0.01). At 60 months, 50% of patients receiving AP were predicted to be alive and disease free adjusting for stage compared with 38% of patients receiving whole-abdominal irradiation WAI. The stage-adjusted death hazard ratio was 0.68 (95% CI, 0.52 to 0.89; P =0.01) favoring AP. At 60 months and adjusting for stage, 55% of AP patients were predicted to be alive compared with 42% of WAI patients (HR: 0.68; 95% CI: 0.52–0.89, p<0.01).	WAI patients reported worse FS (p<0.001) and FACE (p<0.001) scores at end of treatment and poorer FACE scores 3 months post-treatment (p = 0.004) compared to AP patients. APN scores were significantly worse among AP patients at end of treatment, and 3 and 6 months post-treatment (p<0.001 for all). FACT-G scores did not differ between the two arms at any assessment point.	Endometrial
Wilkinson PM et al. Br J Cancer 2006; 94(7):947-54.	Yes	mean: Epoetin alfa =59.1 (+-10.6) (range 35-87) Best standard treatment = 60.3 (+-11.2) (range (30-79)	182	102	FACT-G, FACT-An, CLAS; LASA	Changes in haemoglobin (Hb) level from baseline to study end.	Epoetin alfa 10 000–20 000 IU three times weekly plus best standard treatment (BST= transfusion of red blood cells, as needed) / BST only. The planned duration of study treatment was a maximum of 28 weeks, which included 18– 24 weeks of chemotherapy (maximum, six cycles) plus up to 4 weeks after the last chemotherapy dose.	For the epoetin alfa group, mean Hb increased by 1.8 g dl(raise to the -1power) by weeks 4–6 and was significantly increased from baseline through study end (P<0.001). The mean change in Hb from baseline was significantly (P<0.001) greater for epoetin alfa than BST patients at all postbaseline evaluations. Significantly fewer epoetin alfa than BST patients required transfusion(s) after the first 4 weeks of treatment (7.9 vs 30.5%; P<0.001).	Significant differences from baseline favouring epoetin alfa over BST for all three CLAS change scores (Energy Level, Ability to Do Daily Activities, Overall QOL) and the average median CLAS change score during chemotherapy.	Ovarian

Unclear disease stage										
Alvarez Secord A et al. Cancer 2012;118(13):3283-93; Pokrzywinski R et al. Gynecol Oncol 2011;123(3):505-10; Havrilesky LJ et al. Cancer 2012; 118(2):386-91.	No	Mean / median (SD) (range) Docetaxel and Carboplatin (cDC) : 63.8 / 64 (10.2) (43-84) Sequential Docetaxel and Carboplatin (sDC): 63.0 / 64.5 (10.0) (39-82)	150	148	FACT-O	Progression free-survival	Name drugs: docetaxel & carboplatin Doses: cDC: docetaxel (30 mg/m2 iv on days 1 and 8) combined with carboplatin (AUC=6 mg/mL/minute iv on day 1) every 3 weeks. sDC: docetaxel (30 mg/m2 iv on days 1 and 8) every 3 weeks followed by carboplatin at an AUC of 6 intravenously every 3 weeks at first progression or after 6 cycles of docetaxel for stable disease or a partial response. Duration: 6 cycles of 3 weeks.	The median progression-free survival (PFS) was 13.7 months (95% confidence interval [CI], 9.9-16.8) for combination docetaxel & carboplatin cDC and 8.4 months (95% CI, 7.1-11.0) for sequential docetaxel & carboplatin sDC.	Sequential docetaxel followed by carboplatin (sDC) was associated with significant improvements in the FACT-O TOI (p=0.013), FACT-O total score (p=0.033), and ovarian cancer-specific (OCS) module (p=0.029) compared to the combination docetaxel and carboplatin group (cDC).	Multiple disease sites

***Legend**:*

* No ranking was made based on level or reporting in this table. Studies are ordered by overall number of patients recruited in the study. † Data are reported so as available in the paper.

Abbreviations:

EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EORTC QLQ-OV28: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Ovarian Module-28; AUC: area under the curve; FACT-G: Functional Assessment of Cancer Therapy - General; FACT-Cx: Functional Assessment of Cancer Therapy-Cervix; TOI: Trial Outcome Index; FACT/GOG-NTX: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group -Neurotoxicity four-item scale; UNI=UNISCALE ; BPI-SF: Brief Pain Inventory- short form; FACT-O: Functional Assessment of Cancer Therapy – Ovarian ; EQ-5D: European Quality of Life-5 Dimensions; VAS: visual analogue scale; SF-36: The Medical Outcomes Study Short Form 36-Item Health Survey; SAQ: the Sexual Activity Questionnaire; BIS: Body Image Scale; MOS-SF36 PF: The Physical Functioning Subscale of the Medical Outcome Study–Short Form; AP: Additional Treatment Related Symptoms; BI: Body Image; APN: Assessment for Peripheral Neuropathy Scale; FS: Fatigue Scale; FACE: Functional Alterations due to Changes in Elimination; FACT-An: the Fact-Anaemia; CLAS: Cancer Linear Analog Scale; LASA: Linear Analog Scale Assessment.

Figure 2.
Risk bar chart showing risk of bias across RCTs by quality of PRO studies.