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Table 1: Demographics Key Characteristics and Main Results of the RCTs between 2001 and 2014
When appropriate, percentage were calculated excluding the Not Applicable (NA) results.

Review Criteria	No.	No.of patients	%
Demographics and Key Characteristics of the RCTs			
Total number of reviewed RCTs	49		100%
No. of RCTs with HRQOL as primary endpoint	5		10%
No. of RCTs with additional HRQOL publications	14		29%
No. of RCTs discussing HRQOL in the main publication	30		61%
Studies location			
International§	31		63%
Single country:	18		37%
European	11		23%
USA	5		10%
Canada	1		2%
South Korea	1		2%
Industry funded	38		78%
Treatment focus			
Chemotherapy alone	28	9,557 (48%)	57%
Chemotherapy plus targeted agent	13	6,035 (30%)	27%
Chemotherapy plus hormonal therapy	1	579 (3%)	2%
Hormonal therapy	5	2,346 (12%)	10%
Hormonal therapy plus targeted agent	1	1,286 (6%)	2%
Targeted agent alone	1	114 pts(1%)	2%
Disease Stage			
MBC	27	9,558(48%)	55%
MBC and LABC	20	9,822(49%)	41%
LABC	2	537(3%)	4%
Clinical and Main HRQOL Results			
OS/PFS/TTP: Difference demonstrated in the RCTs**	24 of 47		51%
Reported Main HRQOL difference when OS/PFS/TTP difference was reported	8 of 24		33%
Reported Main HRQOL difference when no difference in OS/PFS/TTP was reported**	5 of 23		24%
Trial Design Aspects Relevant to HRQOL Endpoints			
Method of randomization reported	28		57%
Reporting of informed consent reported	48		98%
Reporting of inclusion and exclusion criteria	49		100%
Total number of patients		19,917 pts.	

Range of patients in each study		66 to 1,286	
Distribution of patients			
66-300	18	3,299 pts.	
301-500	19	7,556 pts.	
501-1000	11	7,776 pts.	
1000-1300	1	1,286 pts.	
HRQOL as a primary endpoint	5		10%
Baseline HRQOL assessment mandatory	5/47		11%
Validity data presented/ referenced	37/48		77%
Reliability data presented/ referenced	37/48		77%
Cultural validity referenced	10/39		26%
A priori HRQOL hypothesis stated	10/48		21%
Abbreviations: HRQOL - Health Related Quality of Life; OS - Overall Survival; RCT - Randomized Controlled Trial; §More than one country, * Excluding trials with NA evaluation			

Table 2: Statistically Significant Clinical and HRQOL benefits by treatment type

Authors	Year	Treatment Type	OS/PFS benef	QOL benef (+), no difference (=), deterioration (-)	Instrument
9. Nuzzo F. ³¹	2011	Chemo	NO	+	QLQ-C30, DDC
16. Liu J ²⁵ (Reyno)	2006	Chemo	OS	-	QLQC30, QLQ-BR23
17. Jones S.E. ³²	2005	Chemo	TTP/OS	=	FACT-B
18. Bottomley A. ³³ (Therasse)	2005	Chemo	NO	=	QLQ-C30
19. Fountzilas G. ³⁴	2004	Chemo	NO	=	QLQ-C30
26. Conte P.F. ³⁵	2004	Chemo	NO	=	QLQC30
28. Keller A.M. ³⁶	2004	Chemo	NO	=	QLQ-C30
30. O'Shaughnessy J. ³⁷	2002	Chemo	PFS/OS	=	QLQ-C30, QLQ-BR23
32. Lück H.J. ³⁸	2013	Chemo	NO	=	QLQ-C30, QLQ-BR23
36. Bachelot T. ³⁹	2011	Chemo	PFS	=	QLQ-C30
37. Walker L.G. ⁴⁰	2011	Chemo	NO	=	FACT-B (TOI), RSCL, MRS, HADS, GDS, TSEQ
41. Svensson H. ⁴¹ (Hatschek)	2010	Chemo	NO	+	QLQ-C30, QLQ-BR23
45. Meier C.R. ⁴²	2008	Chemo	NO	NA (Qol was worse in patients crossing treatment arms, in either direction)	QLQ-C30
48. Crump M. ²⁴	2008	Chemo	PFS	-	QLQ-C30, FACT-BMT, five-question trial-specific checklist
49. Karamouzis M.W. ⁴³	2007	Chemo (vs supportive care)	NA	+	QLQ-C30, QLQ-BR23
50. Cassier P.A. ⁴⁴	2008	Chemo	NO	=	QLQC30
51. Von Minckwitz G. ⁴⁵	2005	Chemo	TTP	=	QLQ-C30
53. Bottomley A. ⁴⁶ (Biganzoli)	2004	Chemo	NO	=	QLQ-C30, QLQ-BR23
54. Winer E.P. ⁴⁷	2004	Chemo	NO	=	FLIC, SDS
57. Nabholz J.M. ⁴⁸	2003	Chemo	TTP	=	QLQ-C30, QLQ-BR23
58. Sledge G.W. ⁴⁹	2003	Chemo	NO	=	FACT-B
59. Heidemann E. ⁵⁰	2002	Chemo	NO	+	Modified Brunner's Score
64. Chan S. ²³	2009	Chemo	NO	=	Rotterdam Symptom Checklist
65. Del Mastro L. ⁵¹	2013	Chemo	NO	Not Reported	Rotterdam Symptom Checklist

66. Park Y.H. ²²	2013	Chemo	PFS/OS	=	NA
8. Corey-Lisle P.K. ⁵² (Thomas)	2012	Chemo	PFS	+	FBSI
14. Hopwood P. ⁵³ (Albain)	2008	Chemo	OS	+	RSCL and brief pain inventory
39. Schroder C.P. ⁵⁴	2011	Chemo	OS	=	QLQ-C30, QLQ-BR23
61. Osoba D. ⁵⁵ (Slamon)	2002	Chemo + targeted agent	PFS/OS	+	QLQ-C30
1. Burris J. ⁵⁶ (Baselga)	2013	Chemo + targeted agent	PFS	+	QLQ-C30, QLQ-BR23
2. Welslau M. ⁵⁷ (Verma)	2013	Chemo + targeted agent	PFS/OS	+	FACT-B (TOI-PFB), DAS
5. Hurvitz S.A. ⁵⁸	2013	Chemo + targeted agent	PFS	+	FACT-B (TOI-PFB)
7. Brufsky A. ⁵⁹	2011	Chemo + targeted agent	NO	-	FACT-B (TOI-PFB)
13. Zhou X. ⁶⁰ (Geyer)	2009	Chemo + targeted agent	TTP	=	FACT-B, EQ-5D (VAS)
31. Cortes J. ⁶¹ (Baselga)	2013	Chemo + targeted agent	PFS/OS	=	FACT-B (TOI-PFB)
33. Gianni L. ⁶²	2013	Chemo + targeted agent	NO	=	FACT-B
43. Wu Y. ⁶³ (Blackwell)	2011	Chemo + targeted agent	PFS/OS	=	FACT- B (TOI)
46. Fountzilas G. ⁶⁴	2009	Chemo + targeted agent	OS	=	EQ-5D
47. Miller K. ⁶⁵	2007	Chemo + targeted agent	PFS	=	FACT-B (TOI)
52. Miller K.D. ⁶⁶	2005	Chemo + targeted agent	NO	=	FACT-B
63. Eiermann W. ⁶⁷	2001	Chemo + targeted agent	TTP/OS	=	QLQ-C30
11. Di leo A. ⁶⁸	2010	Hormonal therapy	PFS	=	FACT-B (TOI)
12. Ellis M.J. ⁶⁹	2009	Hormonal therapy	NO	=	FACT-B, + 6 item estrogen adverse side-effect questionnaire
15. Chia S. ⁷⁰	2008	Hormonal therapy	NO	=	FACT-ES (TOI)
24. Howell A. ⁷¹	2002	Hormonal therapy	NO	=	FACT-B
25. Osborne C.K. ⁷²	2002	Hormonal Therapy	NO	=	FACT-B (TOI)
44. Sherill B. ⁷³ (Di Leo)	2010	Chemo + hormonal therapy	TTP	=	FACT-B
40. Sherill B. ⁷⁴ (Johnson)	2010	Hormonal therapy + targeted agent	PFS	=	FACT-B
62. Vogel C.L. ⁷⁵	2002	Targeted agent alone: one arm	NA	NA	QLQ-C30, QLQ-BR23

Table 3: Comparison of Clinical and HRQOL Statistically Significant Results

	HRQOL benefit	HRQOL no difference	HRQOL deterioration	Total
OS/PFS/TTP benefit	6	16	2	24
No OS/PFS/TTP benefit (or not applicable)	4	17	1	22
Total	10	33	3	46

Table 4: Quality of the HRQOL Measurements of the RCTs between 2001 and 2014

When appropriate, percentage were calculated excluding the Not Applicable (NA) results.

Review criteria		
Rationale for instruments	10/47	21%
Instrument administration reported	8/47	17%
Timing of assessments reported	46/48	96%
Main HRQOL assessment tools		
EORTC QLQ-C30 alone	10/48	21%
EORTC QLQ-C30 plus QLQ-BR23	10/48	21%
EORTC QLQ-C30 plus Daily Diary Card (DDC)	1/48	2%
FACT-B alone	15/48	31%
FACT-B plus additional measures	4/48	8%
EORTC QLQ-C30 plus FACT BMT plus additional checklist	1/48	2%
Rotterdam Symptom Checklist	4/48	8%
Others	3/48	6%
No of RCTs using two or more HRQOL assessment tools	18/48	37%
HRQOL domains covered adequately	33/48	69%
Statistical Analysis and Presentation of HRQOL Results		
Test of significance between arms applied	42/47	89%
Difference between treatment arms reported (if statistical test was reported)	26/47	55%
Clinical significance assessed	23/47	49%
Presentation of results		
Yes	22	45%
Limited	24	49%

No	3	6%
Missing data reported		
Yes	18/47	38%
Limited	13/47	28%
No	16/47	34%
Abbreviations: HRQOL - Health Related Quality of Life; OS - Overall Survival; RCT - Randomized Controlled Trial; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core Module; EORTC QLQ-BR23 - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Breast Cancer Module §More than one country, * Excluding trials with NA evaluation		

