CAT (Critically Appraised Topic): Applying the 5 steps of EBCP (Evidence-Based Clinical Practice)

Intervention Studies

Developed by
EPIQ: Effective Practice, Informatics and Quality Improvement
www.epiq.co.nz

THE UNIVERSITY OF AUCKLAND
FACULTY OF MEDICAL AND HEALTH SCIENCES
School of Population Health

CAT Maker

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Clinical Scenario

This study by Romond et al presents combined results from the National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) with results of NCCTG trial N9831.

NSABP (accrual from Feb 2000) compares 2 arms:
Control=Group 1: 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel
Concurrent exposure= Group 2 with same chemo as above plus 52 weeks of trastuzumab beginning day 1 paclitaxel

NCCTG trial N9831(accrual from May 2000) had 3 arms;
1) 4 cycles of doxorubicin and cyclophosphamide followed by weekly paclitaxel for 12 weeks (control=Group A);
2) same chemo plus 52 weeks of trastuzumab beginning day 1 paclitaxel (concurrent exp=Group C)
3) same chemo plus 52weeks of trastuzumab after completion of paclitaxel (sequential exposure=Group B).
The control groups of these 2 trials as well as the concurrent trastuzumab-paclitaxel exposure groups differed in terms of scheduling of paclitaxel treatment and some aspects of hormonal therapy and radiotherapy but were otherwise identical and NCI and FDA approved a joint analysis plan.
Group B (trastuzumab post paclitaxel) was excluded.

Step 1: Ask a clinical question using PECOT framework

Population or patient	For women with metastatic breast cancer who have an overexpression of HER2
Exposure (intervention)	Does 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel plus 52 weeks of trastuzumab beginning day 1 of paclitaxel (as well as other established surgical and radiotherapy regimens)
Comparison (control)	compared to 4 cycles of doxorubicin and cyclophosphamide followed by paclitaxel (and established surgical, radiotherapy regimens) alone
Outcomes	influence disease-free survival and overall survival and what are the adverse outcomes associated with the use of trastuzumab?
Time	1 year, 2+ years

Step 2: Access (search) for the best evidence using PECO(T) framework

Key search terms

PECO(T) component	Primary search term		Synonym 1		Synonym 2	
Population or patient	N/A	OR		OR		AND
Exposure (experimental)	N/A	OR		OR		AND
Comparison (control)	N/A	OR		OR		AND
Outcomes	N/A	OR		OR		AND
(Time)	N/A	OR		OR		AND
Filters & limits	N/A	AND		AND		

Databases searched

Database:	Cochrane	Other secondary sources	PubMed / OvidMedline	Other:
Number of hits:				

Evidence selected

Romond et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 2005;353:1673-84.

Justification for selection (if evidence already independently appraised by reliable source, go to Page 4)

Randomised controlled trials identified by Pharmac via Belgian Health Care Knowledge Centre.

Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz

Intervention Studies

Step 3: Appraise the study using the PECOT framework

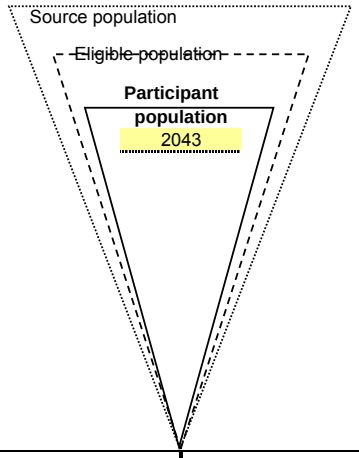
a. "hang" the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

Assessed by: | Publication details:

NSABP B-31 description

Populations

Notes for use show to right of screen



Source **P**opulation	Women from at least 18 institutions and several states in USA
Eligible **P**opulation	Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease.As of May 2003, also included high risk node negative disease (tumour>2cm, positive for estrogen or progesterone receptors or tumour >1cm, negative for hormone receptors). Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl:Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)
Participant **P**opulation	Women enrolled as above between May 2000-Feb 2005

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1019	1024
Follow-up:		
dropped pre-intervention:	3	10
completed follow-up:	864	872
drop-outs / lost during/post-intervention:	152	142
Percentage lost to follow up:	15%	15%

Method of allocation to groups	Stratified Randomisation Treatment assignment stratified by nodal status, planned hormonal Rx, type of surgery (lumpectomy vs mastectomy), the intended DXT & institution.[biased coin minimization algorithm]
Exposure(s)	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by 4 cycles of paclitaxel 175mg/sqm every 3 weeks plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekly infusions 2mg/kg for 51 weeks. From May 16, 2003 paclitaxel could also be given weekly for 12 weeks @ 80mg/sqm dose.
Comparison	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by 4 cycles of paclitaxel 175mg/sqm every 3 weeks. From May 16, 2003 paclitaxel could also be given weekly for 12 weeks @ 80mg/sqm dose.

Outcomes

If categorical....

what e.g. death?

participants with outcome:	a: b:
without outcome:	c: d:

If continuous....

what measure?

mean:	
standard deviation:	
or , standard error:	

Outcomes: ...primary	Primary end-point: Disease-free survival determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.
...secondary	Seconday end-points: overall survival, time to distant recurrence, death from breast cancer (if occurred after recurrence and attributed to breast cancer), contralateral breast cancer and other secondary primary cancers and adverse cardiac events
...adverse	

Time

Unit of time (e.g. year) if rate wanted:	
If **rate** wanted, enter average length of follow-up. If a **proportion**, enter 1.0:	1.00 | 1.00
Report results per (e.g. per 100):	persons

Time	Median follow-up 2.4 years

Results (unadjusted) with 95 % confidence intervals

Calculated in GATE frame

	Occurrence per 1 persons in exposure group (EGO)	Occurrence per 1 persons in comparison group (CGO)	Intervention effects per 1 persons Relative effect (EGO/CGO)	Intervention effects per 1 persons Absolute effect (EGO-CGO)	Number needed to treat (NNT) in 1 person-
Categorical outcome: Intention to treat analyses	0.00	0.00	0.00	0.00	0
95% CIs	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0 to 0
Categorical outcome: On-treatment analyses	0.00	0.00	0.00	0.00	0
95% CIs	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0 to 0
Continuous outcome: Analysis of means	0.00	0.00	0.00	0.00	
95% CIs					

Reported

Key outcome & analysis method, as published:	
Key results	
Reported CIs	

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Intervention Studies

Step 3: Appraise the study using the PECOT framework

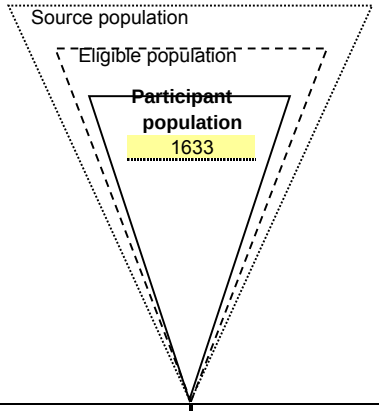
a. "hang" the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

Assessed by: | Publication details:

N9831 description

Populations

Notes for use show to right of screen



Source **P**opulation	Women from at least 17 institutions and several states in USA
Eligible **P**opulation	Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease.Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl:Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)
Participant **P**opulation	Women enrolled as above between Feb 2000-Feb 2005

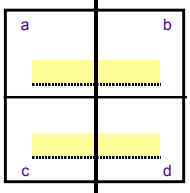
Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	814	819
Follow-up:		
dropped pre-intervention:	5	9
completed follow-up:	808	807
drop-outs / lost during/post-intervention:	1	3
Percentage lost to follow up:	1%	1%

Method of allocation to groups	Stratified Randomisation Dynamic allocation procedure that balanced the marginal distributions of nodal status and hormone receptor status between groups
Exposure(s)	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekly infusions 2mg/kg for 51 weeks
Comparison	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks

Outcomes

If categorical....
what e.g. death?
participants with outcome:
without outcome:



If continuous....
what measure?
mean:
standard deviation:
or, standard error:

Outcomes: ...primary	Primary end-point: Disease-free survival determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.
...secondary	Seconday end-points: overall survival, time to distant recurrence, death from breast cancer (if occurred after recurrence and attributed to breast cancer), contralateral breast cancer and other secondary primary cancers and adverse cardiac events
...adverse	

Time

Unit of time (e.g. year) if rate wanted:

If **rate** wanted, enter average length of follow-up. If a **proportion**, enter 1.0:

Report results per (e.g. per 100):

1.00	1.00
	persons

Time: Median follow-up 1.5 years

Results (unadjusted) with 95 % confidence intervals

Calculated in GATE frame

	Occurrence per 1 persons in exposure group (EGO)	Occurrence per 1 persons in comparison group (CGO)	Intervention effects per 1 persons Relative effect (EGO/CGO)	Intervention effects per 1 persons Absolute effect (EGO-CGO)	Number needed to treat (NNT) in 1 person-
Categorical outcome: Intention to treat analyses	0.00	0.00	0.00	0.00	0
95% CIs	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0 to 0
Categorical outcome: On-treatment analyses	0.00	0.00	0.00	0.00	0
95% CIs	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0.00 to 0.00	0 to 0
Continuous outcome: Analysis of means	0.00	0.00	0.00	0.00	
95% CIs					

Reported

Key outcome & analysis method, as published:	
Key results	
Reported CIs	

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Intervention Studies

Step 3: Appraise the study using the PECOT framework

a. "hang" the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

Assessed by:				Publication details:	**Combined results from the National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) and NCCTG trial N9831.**

Populations

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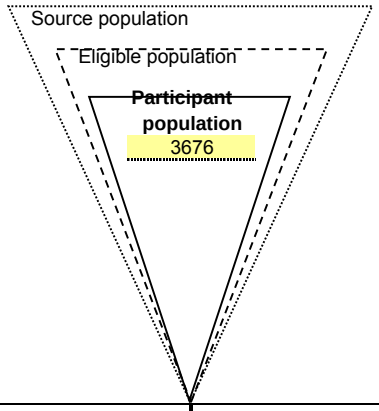

Source **P**opulation	Women attending at least 35 institutions from several states in America
Eligible **P**opulation	Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease plus high risk node negative disease.Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Excl:Clinical or radiologic evidence of metastatic disease and cardiac disease (see bottom of page)
Participant **P**opulation	Women enrolled as above between Feb 2000-Feb 2005

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1833	1843
Follow-up:		
dropped pre-intervention:	8	19
completed follow-up:	1672	1679
drop-outs / lost during/post-intervention:	153	145
Percentage lost to follow up:	9%	9%

Method of allocation to groups	Stratified Randomisation Two types of stratified allocation
Exposure(s)	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks) plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekly infusions 2mg/kg for 51 weeks
Comparison	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks)

Outcomes

If categorical....

what e.g. death? disease free survival

	a	b
participants with outcome:	133	261
without outcome:		
	c	d

If continuous....

what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary end-point: **Disease-free survival** determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.
...secondary	Seconday end-points: overall survival, time to distant recurrence, death from breast cancer (if occurred after recurrence and attributed to breast cancer), contralateral breast cancer and other secondary primary cancers and adverse cardiac events
...adverse	

Time

Unit of time (e.g. year) if rate wanted:		
If **rate** wanted, enter average length of follow-up. If a **proportion**, enter 1.0:	1.00	1.00
Report results per (e.g. per 100):	persons	

Time	Median follow-up 2 years (2.4yrs B-31 trial; 1.5 yrs in N9831 trial)

Results (unadjusted) with 95 % confidence intervals

Calculated in GATE frame

	Occurrence per 1 persons in exposure group (EGO)	Occurrence per 1 persons in comparison group (CGO)	Intervention effects per 1 persons Relative effect (EGO/CGO)	Intervention effects per 1 persons Absolute effect (EGO-CGO)	Number needed to treat (NNT) in 1 person-
Categorical outcome: Intention to treat analyses	0.07	0.14	0.51	-0.07	-14
95% CIs	0.06 to 0.09	0.13 to 0.16	0.42 to 0.62	-0.09 to -0.05	-11 to -21
Categorical outcome: On-treatment analyses	0.08	0.16	0.51	-0.08	-13
95% CIs	0.07 to 0.09	0.14 to 0.17	0.42 to 0.62	-0.10 to -0.05	-10 to -19
Continuous outcome: Analysis of means	0.00	0.00	0.00	0.00	
95% CIs					

Reported

Key outcome & analysis method, as published:	Disease free survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals.
Key results	0.48
Reported CIs	0.39 to 0.59

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Intervention Studies

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Populations

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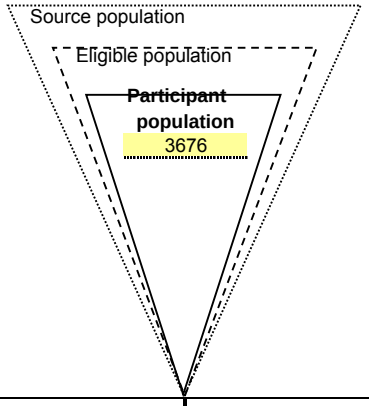
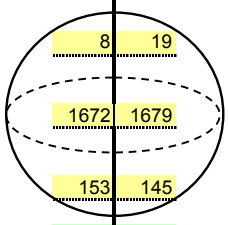


Source **P**opulation	Women attending at least 35 institutions from several states in America
Eligible **P**opulation	Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease plus high risk node negative disease.Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Ex
Participant **P**opulation	Women enrolled as above between Feb 2000-Feb 2005

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1833	1843
Follow-up:		
dropped pre-intervention:	8	19
completed follow-up:	1672	1679
drop-outs / lost during/post-intervention:	153	145
Percentage lost to follow up:	9%	9%



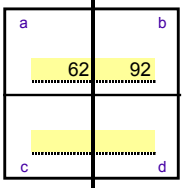
Method of allocation to groups	Stratified Randomisation Two types of stratified allocation
Exposure(s)	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks) plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekl
Comparison	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks)

Outcomes

If categorical....

what e.g. death? overall survival

participants with outcome:	62	92
without outcome:		



If continuous....

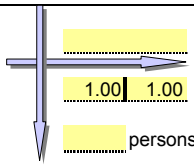
what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary end-point: Disease-free survival determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.
...secondary	Seconday end-points: **overall survival**, time to distant recurrence, death from breast cancer (if occurred after recurrence and attributed to breast cancer), contralateral breast cancer and other secondary primary cancers and adverse cardiac events
...adverse	

Time

Unit of time (e.g. year) if rate wanted:		
If **rate** wanted, enter average length of follow-up. If a **proportion**, enter 1.0:	1.00	1.00
Report results per (e.g. per 100):		persons



Time	Median follow-up 2 years (2.4yrs B-31 trial; 1.5 yrs in N9831 trial)

Results (unadjusted) with 95 % confidence intervals

Calculated in GATE frame

	Occurrence per 1 persons in exposure group (EGO)	Occurrence per 1 persons in comparison group (CGO)	Intervention effects per 1 persons Relative effect (EGO/CGO)	Intervention effects per 1 persons Absolute effect (EGO-CGO)	Number needed to treat (NNT) in 1 person-
Categorical outcome: Intention to treat analyses	0.03	0.05	0.68	-0.02	-62
95% CIs	0.03 to 0.04	0.04 to 0.06	0.49 to 0.93	-0.03 to 0.00	-34 to -317
Categorical outcome: On-treatment analyses	0.04	0.05	0.68	-0.02	-56
95% CIs	0.03 to 0.05	0.04 to 0.07	0.49 to 0.93	-0.03 to 0.00	-31 to -282
Continuous outcome: Analysis of means	0.00	0.00	0.00	0.00	
95% CIs					

Reported

Key outcome & analysis method, as published:	Overall survival -Kaplan-Meir curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals.
Key results	0.67
Reported CIs	0.43 to 0.93

Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz

Intervention Studies

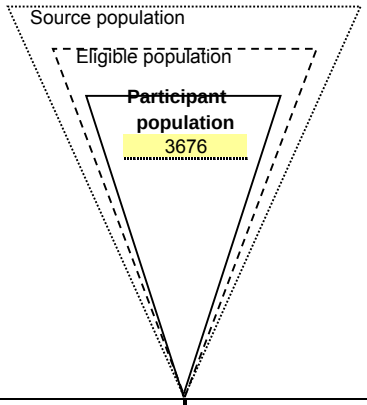
Step 3: Appraise the study using the PECOT framework

a. "hang" the study on the GATE (Graphic Appraisal Tool for Epidemiology) Frame

Assessed by:				Publication details:	**Combined results from the National Surgical Adjuvant Breast and Bowel Project trial B-31 (NASBP trial B-31) and NCCTG trial N9831.**

Populations

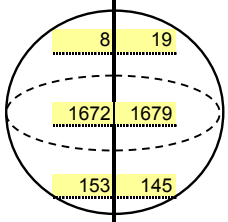
Notes for use show to right of screen



Source **P**opulation	Women attending at least 35 institutions from several states in America
Eligible **P**opulation	Women with adenocarcinoma breast with HER2 3+/amplification and node positive disease plus high risk node negative disease.Needed adequate haemopoietic, hepatic and renal function (not described) and LVEF greater than or equal to lower limit of normal. Ex
Participant **P**opulation	Women enrolled as above between Feb 2000-Feb 2005

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1833	1843
Follow-up:		
dropped pre-intervention:	8	19
completed follow-up:	1672	1679
drop-outs / lost during/post-intervention:	153	145
Percentage lost to follow up:	9%	9%



Method of allocation to groups	Stratified Randomisation Two types of stratified allocation
Exposure(s)	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks) plus trastuzumab 4mg/kg with 1st dose of paclitaxel followed by weekl
Comparison	4 cycles of Doxorubicin 60mg/sqm BSA and cyclophosphamide 600mg/sqm every 21 days followed by paclitaxel 80mg/sqm weekly for 12 weeks (or 4 cycles of paclitaxel 175mg/sqm every 3 weeks)

Outcomes

If categorical....

what e.g. death? adverse cardiac events

	a	b
participants with outcome:	52	5
without outcome:		

	c	d

If continuous....

what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary end-point: Disease-free survival determined by local/regional and distant recurrence; contralateral breast cancer including DCIS; other secondary primary cancers; and death if before above.
...secondary	Seconday end-points: **adverse cardiac events** (B-31 trial-31 in trastuzumab gp had CHF, in control gp 4 had CHF and 1 death from cardiac causes) (N9831 trial 20 had CHF, died of cardiomyopathy in trastuzumab group, none in control group)
...adverse	

Time

Unit of time (e.g. year) if rate wanted:		
If **rate** wanted, enter average length of follow-up. If a **proportion**, enter 1.0:	1.00	1.00
Report results per (e.g. per 100):		persons

Time	Median follow-up 2 years (2.4yrs B-31 trial; 1.5 yrs in N9831 trial)

Results (unadjusted) with 95 % confidence intervals

Calculated in GATE frame

	Occurrence per 1 persons in exposure group (EGO)	Occurrence per 1 persons in comparison group (CGO)	Intervention effects per 1 persons Relative effect (EGO/CGO)	Intervention effects per 1 persons Absolute effect (EGO-CGO)	Number needed to treat (NNT) in 1 person-
Categorical outcome: Intention to treat analyses	0.03	0.00	10.46	0.03	39
95% CIs	0.02 to 0.04	0.00 to 0.01	4.19 to 26.12	0.02 to 0.03	56 to 30
Categorical outcome: On-treatment analyses	0.03	0.00	10.44	0.03	36
95% CIs	0.02 to 0.04	0.00 to 0.01	4.18 to 26.08	0.02 to 0.04	51 to 28
Continuous outcome: Analysis of means	0.00	0.00	0.00	0.00	
95% CIs					

Reported

Key outcome & analysis method, as published:	
Key results	
Reported CIs	

Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz

Intervention Studies

Step 3: Appraise the study using the PECOT framework

b. assess study quality (RAAMbo) + = good, ~ = mixed, x = poor, nr = not reported, na = not applicable

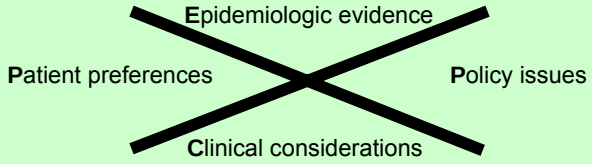
	Evaluation criteria (RAAMbo)	Quality + ~ x nr na	
Populations	**R**epresentative?		
	Source population well described?	x	No other than acknowledgements to people/institutions that contributed 25 or more women to the trials from USA
	Eligible population well described?	+	Yes, the inclusion and exclusion criteria were explicit and clear for both trials allowing replication within the various states and institutions and appropriate for the study objectives.
	Participants representative of eligibles?	nr	This is unknown- we are given no reports on how participants were selected from the eligible population, nor what % of eligible women actually consented to take part.
	Were relevant personal (prognostic) characteristics of participants reported?	~	There is data on age, tumour size, grade, nodal and hormone receptor status, planned hormonal therapy but there is no data on other potential confounders such as menopausal status, smoking and socioeconomic status.
Exposure & Comparison	**A**llocated appropriately (or Adjusted) and **A**ccounted for?		
	Exposure & comparison interventions well described & valid?	+	The exposure and comparison interventions were described in sufficient detail and appears valid, assuming that trastuzumab and other chemotherapy are able to be delivered in the doses/cycles described.
	Allocation to exposure and comparison groups randomised?	nr	Yes we assume so but who, what centre etc is not explicitly stated
	Allocation concealed?	nr	Allocation concealment is not reported but stratifying by multiple factors is very difficult to do without computer generated algorithms/sequences
	Exposure and comparison groups similar at baseline? If not, were these adjusted?	+	With the exception of the 191 patients with node-negative breast cancer enrolled in N9831, the groups from each study were similar and exposure and comparison groups were also similar. Adjustments were made in the analyses for nodal status, tumour size , receptor status, age, tumour grade, histological findings and trial (B-31 or N9831)
	Participants and/or staff blind to exposure and comparison?	x	No - this is an open-label trial- neither participants or staff were blind to their treatment assignment
	Compliance with exposure and comparison adequate?	+	Compliance was well reported. Most had all doxo/cyclo/paclitaxel but about 1/3 stopped trastuzumab before 52 weeks. 31/1843 (1.6%) in the control gp declined Rx and 9/1833 (0,4% in trastuzumab gp declined Rx. 97.9% received 4 cycles of doxorubicin and cyclophosphamide; 2.7% did not begin paclitaxel but of those who did 94.7% completed all cycles.Of the 1159 women with adequate LVEF post doxorubicin and cyclophosphamide Rx- 364 (31.4%) discontinued Rx before 52weeks due to recurrence (1.9%), decline in LVEF(14.2%), CHF or other sdverse cardiac effect (4.7%), other adverse event (2.3%), patient initiated (6%) and other reasons (2.3%)
	Contamination acceptably low?	nr	Not reported if any of the control group received any trastuzumab
	Other interventions similar in both groups?	~	This is not reported per se - in both trials allowable concomitant Rx (surgery, radiotherapy, tamoxifen and aromatase inhibitors) was indicated in the protocols and the numbers for planned hormonal therapy at baseline were similar.
	All participants accounted for at study conclusion?	+	Whether women declined therapy or not they were included in follow-up with 9% from each arm with "follow-up" pending
	Could interventions be applied in real life?	+	Yes, if the drug was available with appropriate oncology services and follow-up for adverse side effects.
Outcomes	**M**easured well (blinded or objective?)		
	Outcome measures well described & valid?	+	Yes primary endpoint well described and would be fairly objective. Disease free survival- death or detection o local, regional or distant recurrence, contralateral breast cancer including DCIS and other secondary primary cancers. It is not described how these were confirmed. Secondary outcomes; Time to distant recurrence and overall survival measured from time of randomisation are objective and valid measures.The cardiac secondary endpoints included multiple asessment via MUGA (B-31) or either echocardiography or MUGA scanning (N9831) It is not reported who did the scans and no measures of reliability (inter-rater) were given.
	Blinded outcome measurement?	x	No, it appears that outcomes were not assessed by people blind to allocation. I don't think that this would lead to major assessment bias given objective outcomes eg total mortality and fairly objective outcomes eg, time from randomisation to detection of distant metastases
	Outcome measurement complete?	~	Yes it appears that they followed up all patients except for the 9% in each arm
	Were all important outcomes assessed?	+	Important objective outcomes were assessed - although I would like to know longer term effects on cardiac status and survival and if there were any differences in quality of life, return to usual activities of daily living.
Time	Similar follow-up time in exposure & comparison groups?	+	Yes, follow-up time similar in both groups.
	Was follow-up time meaningful?	+	Yes although it would be important to continue following these women to see if the survival curves continue to diverge.
Results	Intention to treat analysis?	~	No, not true ITT analysis as per supplementary appendix. Women who declined initial Rx and were subsequently lost to follow-up were not included in the analyses. The methods discuss secondary on-treatment analyses where they excluded ineligible women or women who did not continue therapy after doxorubicin and cyclophosphamide, or those who became ineligible for trastuzumab due to cardiac symps/decline in LVEF. However the results via GATE crude analyses do not vary significantly with either OTT or ITT.
	Estimates of Intervention effects given or calculable?	+	Both given and calculable
	Precision of intervention effects given or calculable?	+	Both given and calculable
	Analytical methods appropriate?	+	Yes appropriate analytic methods using Cox proportional hazards regression analysis. Hazard ratios were compared according to length of follow-up (<1yr, 1-2 yrs, 2-3yrs and >3yrs) and stratified according to study, intended paclitaxel schedule, nodal and hormone receptor stsatus
Summary	Are the study results internally valid (i.e unbiased)?	~	Study quality mixed and missing some reporting on key areas of validity. Key factors to minimise bias are randomisation, allocation concealment, blinding to allocation and blind and objective outcome assessment. The study was randomised and outcomes were fairly objective.However allocation concealment was not reported and both exposure assignment and outcome assessment were unblinded. It is difficult to ascertain how much this would affect the effect estimates. True ITT was not conducted but unlikely to have much effect on results.
	Are results precise enough to be meaningful? If not, was power sufficient?	+	Yes the results were precise and power calculations were reported for the primary outcome.Power was sufficient to detect effects on overall survival and combined cardiac adverse events.
	Can the applicability of the results (i.e external validity) be determined?	~	This was poorly reported. These results apply to women with HER2 positive early stage invasive breast cancer who had, surgical, radiotherapeutic and concomitant hormonal(if appropriate) therapy and had normal LVEF and no major cardiac disease. The women were American, 2/3 between 40 and 60yrs, with the other 1/3 equally divided between those less than 40 and over 60yrs. They were of unknown ethnicity, smoking and socioeconomic status and presumed treated in secondary care/specialist cancer settings with surgical, radiation, cardiac imaging, pathology and other services available.
	Overall study quality	~	The 2 studies are reported to be of similar design/protocol and the joint results will improve power to to demonstrate an effect whereas on their own they may not. Ideally however, both trials need to be reported separately to assess quality of each study as several areas relating to validity were not reported or poorly reported.

Please contribute your comments and suggestions on this form to: rt.jackson@auckland.ac.nz

Intervention Studies

Step 4: Apply the evidence

The X-factor



Summarise epidemiologic evidence

This study	Note rare cases of interstitial pneumoinitis or pulmonary infiltrates appearing to be related to trastuzumab therapy.
Consistency with other studies	
Debate & Discussion	

Identify other issues

Patient preferences	
Policy issues	
Clinical considerations	

The bottom line: weigh everything up

Step 5: Audit personal EBP skills (for professional development) and audit usual clinical practice (for quality improvement)

Assess personal skills	
Plan to implement decision in your practice setting. How can you (or your team) improve practice with respect to the topic covered in this CAT?	

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