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

Name & date	Dr S Wells	email address	s.wells@auckland.ac.nz

Clinical Scenario

Salmon D et al.on behalf of BCIRG 006 investigators. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: Second interim efficacy analysis (available as slide presentation only ASCO annual meeting 2006)

Study question as below:

Population or patient	For women with HER2 positive breast cancer (node positive or high risk node negative disease)
Exposure (intervention)	Does 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm and concurrent trastuzumab ?dose for one year (AC-TH arm) OR 6 cycles of doxecetal 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (TCH arm)
Comparison (control)	Compared to 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (AC-T arm)
Outcomes	influence disease-free survival and overall survival and what are the adverse outcomes associated with these regimens?
Time	median follow-up 36 months

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

Salmon D et al.on behalf of BCIRG 006 investigators. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer patients: Second interim efficacy analysis

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.

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Intervention Studies

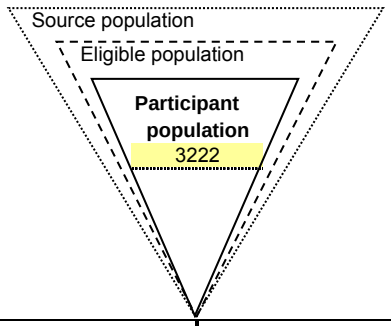
Step 3: Appraise the study using the PECOT framework

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

Assessed by:				Publication details:	**Salmon et al. Slide show BCIRG 006 DESCRIPTION WHOLE TRIAL**

Populations

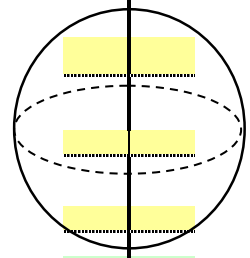
Notes for use show to right of screen



Source **P**opulation	Women from 24 countries including NZ
Eligible **P**opulation	**Incl:**Women with HER2 positive breast cancer, node positive or high risk node negative disease. No other description or exclusion criteria available
Participant **P**opulation	3,222 women enrolled between April 2001 and March 2004 meeting the above criteria and consenting to participate in trial with 3 arms -

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:		
Follow-up:		
dropped pre-intervention:		
completed follow-up:		
drop-outs / lost during/post-intervention:		
Percentage lost to follow up:	0%	0%



Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
Exposure(s)	1) **AC-T** 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073) 2) **AC-TH** 4 cycles AC (60/ 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm and concurrent trastuzumab ?dose for one year (n=1074)
Comparison	3) **TCH:** 6 cycles of doxecetal 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (n=1075)

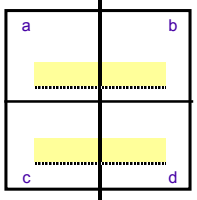
Outcomes

If categorical....

what e.g. death? Disease-free survival

participants with outcome:

without outcome:



If continuous....

what measure?

mean:

standard deviation:

or, standard error:

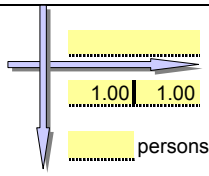
Outcomes: ...primary	**Primary outcome: Disease free survival** (no definition available)
...secondary	Secondary outcomes: overall survival, toxicity and pathologic and molecular markers
...adverse	

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): persons



Time	**second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)**

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 0.00	0.00 0.00	0 0
Categorical outcome: On-treatment analyses	0.00	0.00	0.00	0.00	0
95% CIs			0.00 0.00	0.00 to #DIV/0!	0 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:	**Salmon et al. Slide show BCIRG 006 DESCRIPTION AC-T VS AC-TH**

Populations

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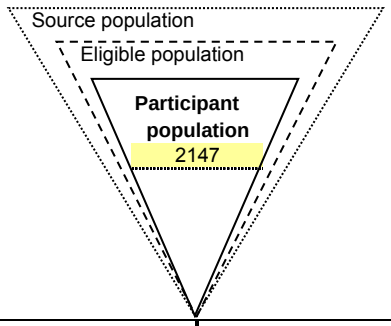

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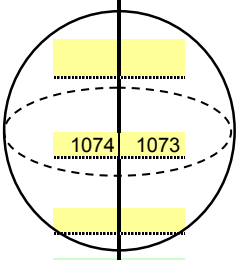
Participant **P**opulation	3,222 women enrolled between April 2001 and March 2004 meeting the above criteria and consenting to participate in trial with 3 arms -

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1074	1073
Follow-up:		
dropped pre-intervention:		
completed follow-up:	1074	1073
drop-outs / lost during/post-intervention:		
Percentage lost to follow up:	0%	0%



Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
Exposure(s)	**AC-TH 4 cycles AC (60/ 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm and concurrent trastuzumab ?dose for one year (n=1074)**
Comparison	**AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)**

Outcomes

If categorical....

what e.g. death? Disease-free survival

participants with outcome:	a: 128	b: 192
without outcome:	c:	d:

If continuous....

what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	**Primary outcome: Disease free survival** (no definition available)
...secondary	Secondary outcomes: overall survival, toxicity and pathologic and molecular markers
...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	second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)

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	0.12	0.18	0.67	-0.06	-16
95% CIs	0.10 to 0.14	0.16 to 0.20	0.54 to 0.82	-0.09 to -0.03	-11 to -34
Categorical outcome: On-treatment analyses	0.12	0.18	0.67	-0.06	-16
95% CIs	0.10 to 0.14	0.16 to 0.20	0.54 to 0.82	-0.09 to -0.03	-11 to -34
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	0.67
Reported CIs	0.54 to 0.83

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Populations

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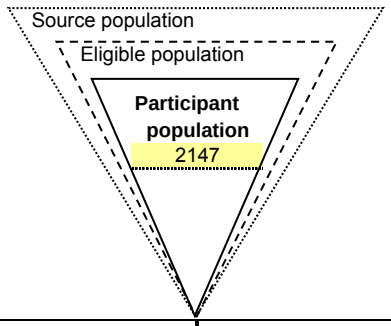

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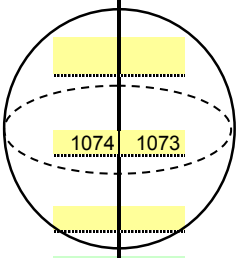
Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1074	1073
Follow-up:		
dropped pre-intervention:		
completed follow-up:	1074	1073
drop-outs / lost during/post-intervention:		
Percentage lost to follow up:	0%	0%



Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
Exposure(s)	**AC-TH 4 cycles AC (60/ 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm and concurrent trastuzumab ?dose for one year (n=1074) 1)**
Comparison	**AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)**

Outcomes

If categorical....

what e.g. death? Disease-free survival

	a	b
participants with outcome:	49	80
without outcome:		
	c	d

If continuous....

what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary outcome: Disease free survival (no definition available)
...secondary	**Secondary outcomes: overall survival,** toxicity and pathologic and molecular markers
...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	second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)

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Categorical outcome: Intention to treat analyses	0.05	0.07	0.61	-0.03	-34
95% CIs	0.03 to 0.06	0.06 to 0.09	0.43 to 0.86	-0.05 to -0.01	-20 to -113
Categorical outcome: On-treatment analyses	0.05	0.07	0.61	-0.03	-34
95% CIs	0.03 to 0.06	0.06 to 0.09	0.43 to 0.86	-0.05 to -0.01	-20 to -113
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	0.59
Reported CIs	0.42 to 0.85

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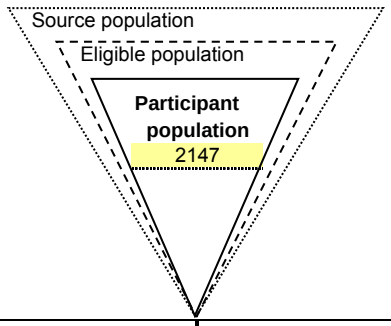

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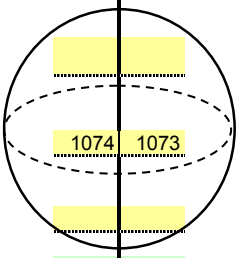
dropped pre-intervention:		
completed follow-up:	1074	1073
drop-outs / lost during/post-intervention:		
Percentage lost to follow up:	0%	0%



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Comparison	**AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)**

Outcomes

If categorical....

what e.g. death? Disease-free survival

	a	b
participants with outcome:	20	4
without outcome:		
	c	d

If continuous....

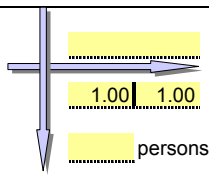
what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary outcome: Disease free survival (no definition available)
...secondary	**Secondary outcomes:** overall survival, toxicity, **CONGESTIVE HEART FAILURE,** and pathologic and molecular markers
...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



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Results (unadjusted) with 95 % confidence intervals

Calculated in GATE frame

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Categorical outcome: Intention to treat analyses	0.02	0.00	5.00	0.01	68
95% CIs	0.01 to 0.03	0.00 to 0.01	1.71 to 14.57	0.01 to 0.02	166 to 43
Categorical outcome: On-treatment analyses	0.02	0.00	5.00	0.01	68
95% CIs	0.01 to 0.03	0.00 to 0.01	1.71 to 14.57	0.01 to 0.02	166 to 43
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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Populations

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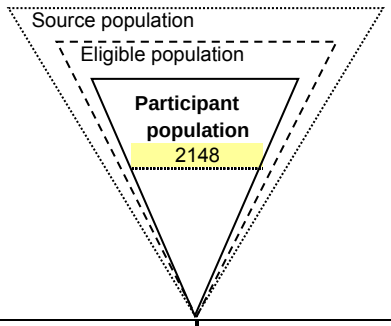

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Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1075	1073
Follow-up:		
dropped pre-intervention:		
completed follow-up:	1075	1073
drop-outs / lost during/post-intervention:		
Percentage lost to follow up:	0%	0%

Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
Exposure(s)	**TCH:** 6 cycles of docetaxel 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (n=1075)1)
Comparison	**AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)**

Outcomes

If categorical….		
what e.g. death?	Disease-free survival	
participants with outcome:	a: 142	b: 192
without outcome:	c:	d:
If continuous….		
what measure?		
mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	**Primary outcome: Disease free survival** (no definition available)
...secondary	Secondary outcomes: overall survival, toxicity and pathologic and molecular markers
...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
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Categorical outcome: Intention to treat analyses	0.13	0.18	0.74	-0.05	-21
95% CIs	0.11 to 0.15	0.16 to 0.20	0.60 to 0.90	-0.08 to -0.02	-12 to -62
Categorical outcome: On-treatment analyses	0.13	0.18	0.74	-0.05	-21
95% CIs	0.11 to 0.15	0.16 to 0.20	0.60 to 0.90	-0.08 to -0.02	-12 to -62
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	0.67
Reported CIs	0.54 to 0.83

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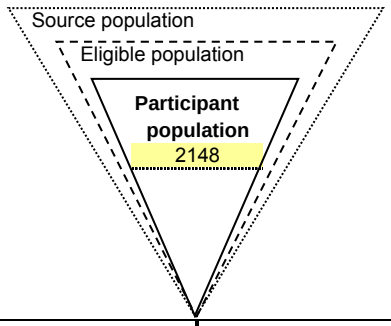

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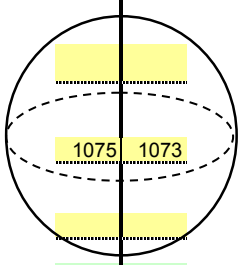


Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
Exposure(s)	**TCH:** 6 cycles of docetaxel 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (n=1075)1)
Comparison	**AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)**

Outcomes

If categorical....

what e.g. death? Disease-free survival

	a	b
participants with outcome:	56	80
without outcome:		
	c	d

If continuous....

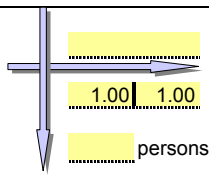
what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary outcome: Disease free survival (no definition available)
...secondary	**Secondary outcomes: overall survival**, toxicity and pathologic and molecular markers
...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	second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)

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	0.05	0.07	0.70	-0.02	-44
95% CIs	0.04 to 0.07	0.06 to 0.09	0.50 to 0.97	-0.04 to 0.00	-23 to -534
Categorical outcome: On-treatment analyses	0.05	0.07	0.70	-0.02	-44
95% CIs	0.04 to 0.07	0.06 to 0.09	0.50 to 0.97	-0.04 to 0.00	-23 to -534
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	0.66
Reported CIs	0.47 to 0.93

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Intervention Studies

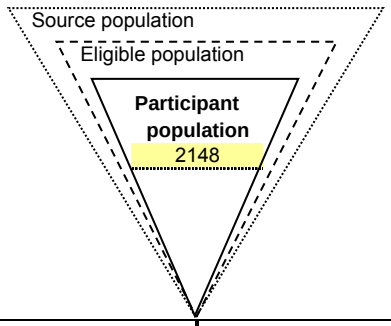
Step 3: Appraise the study using the PECOT framework

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

Assessed by:				Publication details:	**Salmon et al. Slide show BCIRG 006 DESCRIPTION AC-T vs TCH**

Populations

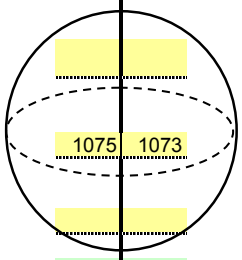
Notes for use show to right of screen



Source **P**opulation	Women from 24 countries including NZ
Eligible **P**opulation	**Incl:**Women with HER2 positive breast cancer, node positive or high risk node negative disease. No other description or exclusion criteria available
Participant **P**opulation	3,222 women enrolled between April 2001 and March 2004 meeting the above criteria and consenting to participate in trial with 3 arms -

Exposure & Comparison

	Exposure Group (EG)	Comparison Group (CG)
Participants in each group:	1075	1073
Follow-up:		
dropped pre-intervention:		
completed follow-up:	1075	1073
drop-outs / lost during/post-intervention:		
Percentage lost to follow up:	0%	0%



Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
Exposure(s)	**TCH:** 6 cycles of docetaxel 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (n=1075)1)
Comparison	**AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)**

Outcomes

If categorical....

what e.g. death? Disease-free survival

	a	b
participants with outcome:	4	4
without outcome:		
	c	d

If continuous....

what measure?

mean:		
standard deviation:		
or, standard error:		

Outcomes: ...primary	Primary outcome: Disease free survival (no definition available)
...secondary	**Secondary outcomes:** overall survival, toxicity, **Congestive Heart Failure** and pathologic and molecular markers
...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	second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)

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	1.00	0.00	-144184
95% CIs	0.00 to 0.01	0.00 to 0.01	0.25 to 3.98	-0.01 to 0.01	-193 to ∞ to 195
Categorical outcome: On-treatment analyses	0.00	0.00	1.00	0.00	-144184
95% CIs	0.00 to 0.01	0.00 to 0.01	0.25 to 3.98	-0.01 to 0.01	-193 to ∞ to 195
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

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?		Women from 24 countries including NZ
	Eligible population well described?		Only presentation slide with brief inclusion criteria, no exclusion criteria given
	Participants representative of eligibles?		This is unknown. Enrolment between April 2001 and March 2004
	Were relevant personal (prognostic) characteristics of participants reported?		Data given on women participants: median age 49 yrs (Range 23-74yrs) KPS??, mastectomy, radiotherapy or hormonal therapy, number of nodes, tumour size, hormonal receptor status and cardiovascular risk factors .
Exposure & Comparison	**A**llocated appropriately (or Adjusted) and **A**ccounted for?		
	Exposure & comparison interventions well described & valid?		Brief description of treatments only- unsure dosage of trastuzumab and frequency
	Allocation to exposure and comparison groups randomised?		Yes random assignment into groups -unknown if stratified by key prognostic factors
	Allocation concealed?		Unknown
	Exposure and comparison groups similar at baseline? If not, were these adjusted?		Baseline characteristics are reported in 3 slides. The treatment groups are well-balanced according the prognostic breast cancer characteristics recorded but differ according to CVD risk factors.
	Participants and/or staff blind to exposure and comparison?		Unknown
	Compliance with exposure and comparison adequate?		Unknown
	Contamination acceptably low?		17 patients of 1073 randomised to control arm (AC-T) crossed over to receive trastuzumab.
	Other interventions similar in both groups?		Unknown
	All participants accounted for at study conclusion?		Not reported
	Could interventions be applied in real life?	+	Yes, if the drugs were available with appropriate oncology services and follow-up for adverse side effects.
Outcomes	**M**easured well (blinded or objective?)		
	Outcome measures well described & valid?	+	No
	Blinded outcome measurement?	~	Unknown
	Outcome measurement complete?	+	Unknown
	Were all important outcomes assessed?	+	Important objective outcomes were assessed - although I would like to know 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?	+	Unknown
	Was follow-up time meaningful?	+	From our crude analyses...important effects were shown in this second interim analyses. AC-TH vs AC-T showed a 33% reduction in disease free survival which was a 6% absolute difference from years 2 to 4 and TCH vs AC-T indicate a 26% reduction in DFS (or a 5% absolute difference from years 2-4).However AC-TCH had approx 5x the risk of grade 3/4 CHF than either AC-T or TCH with authors reporting overall global safety better in TCH compared to AC-TH.
Results	Intention to treat analysis?	~	unknown
	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 appears to be appropriate analytic methods using Cox proportional hazards regression analysis
Summary	Are the study results internally valid (i.e unbiased)?		Study validity unable to be assessed from this powerpoint presentation
	Are results precise enough to be meaningful? If not, was power sufficient?		Yes, the results given were precise
	Can the applicability of the results (i.e external validity) be determined?		No, not until internal validity assessed
	Overall study quality	~	Unknown

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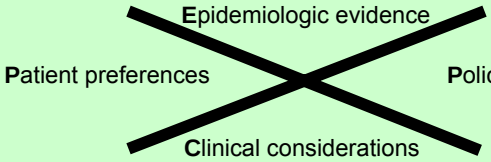
Intervention Studies

Step 4: Apply the evidence

The X-factor



Summarise epidemiologic evidence

This study	The authors write that the 006 update for HER2 positive malignancies show a difference of DFS and breast cancer deaths in favour of AC-TH but this difference is now exceeded by the number of critical adverse events (including grade III/IV CHF and AC related leukemia as well as a small AND sustained loss of LVEF for 18% of patients) Appears TCH safer alternative (docetaxel, cisplatin and concomitant trastuzumab continuing for 1yr) than AC-TH (doxorubicin, cyclophosphamide followed by docetaxel and concomitant trastuzumab continuing for 1yr)
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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