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 Quality Improvement**  
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**THE UNIVERSITY OF AUCKLAND**  
 FACULTY OF MEDICAL AND  
 HEALTH SCIENCES

School of Population Health

**CAT Maker**

Name & date	Dr S Wells	email address	<a href="mailto:s.wells@auckland.ac.nz">s.wells@auckland.ac.nz</a>
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**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:**

<b>Population or patient</b>	For women with HER2 positive breast cancer (node positive or high risk node negative disease)
<b>Exposure (intervention)</b>	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 doxectal 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (TCH arm)
<b>Comparison (control)</b>	Compared to 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (AC-T arm)
<b>Outcomes</b>	influence disease-free survival and overall survival and what are the adverse outcomes associated with these regimens?
<b>Time</b>	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	
<b>Population or patient</b>	N/A	OR		OR		AND
<b>Exposure (experimental)</b>	N/A	OR		OR		AND
<b>Comparison (control)</b>	N/A	OR		OR		AND
<b>Outcomes (Time)</b>	N/A	OR		OR		AND
<b>Filters &amp; limits</b>	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.

# 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:	<b>Salmon et al. Slide show BCIRG 006</b> <b>DESCRIPTION WHOLE TRIAL</b>				
Populations				Source Population	Women from 24 countries including NZ				
	<b>Notes for use show to right of screen</b>			Eligible Population	<b>Incl:</b> Women with HER2 positive breast cancer, node positive or high risk node negative disease. No other description or exclusion criteria available				
			Participant Population	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				Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status				
	<b>Participants in each group:</b>			Exposure(s)	1) <b>AC-T</b> 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073) 2) <b>AC-TH</b> 4 cycles AC ( 60/ 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm and concurrent trastuzumab ?dose for one year (n=1074)				
<b>Follow-up:</b>			Comparison	3) <b>TCH:</b> 6 cycles of doxecetal 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (n=1075)					
<b>drop-outs / lost during/post-intervention:</b>									
<b>Percentage lost to follow up:</b>									
Outcomes	<p><b>If categorical....</b> what e.g. death? <span style="border: 1px solid black; padding: 2px;">Disease-free survival</span> participants with outcome:</p> <table border="1" style="margin-left: auto; margin-right: auto; border-collapse: collapse;"> <tr> <td style="padding: 2px;">a</td> <td style="padding: 2px;">b</td> </tr> <tr> <td style="padding: 2px;">c</td> <td style="padding: 2px;">d</td> </tr> </table> <p>without outcome:</p>			a	b	c	d	Outcomes: ...primary	<b>Primary outcome: Disease free survival</b> ( no definition available)
	a	b							
c	d								
<p><b>If continuous....</b> what measure? mean: standard deviation: or, standard error:</p>			...secondary	Secondary outcomes: overall survival, toxicity and pathologic and molecular markers					
<b>Unit of time</b> (e.g. year) if rate wanted:			Time	<b>second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)</b>					
If <b>rate</b> wanted, enter average length of follow-up. If a <b>proportion</b> , enter 1.0: Report results per (e.g. per 100):									
<b>Results (unadjusted) with 95 % confidence intervals</b>									
Calculated in GATE frame			Occurrence per 1 persons		Intervention effects per 1 persons		Number needed to treat (NNT) in 1 person-		
			in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)		Absolute effect (EGO-CGO)		
	Categorical outcome: Intention to treat analyses 95% CIs		0.00	0.00	0.00	0.00	0.00	0.00	0
	Categorical outcome: On-treatment analyses 95% CIs		0.00	0.00	0.00	0.00	0.00	to #DIV/0!	0
Continuous outcome: Analysis of means 95% CIs		0.00	0.00	0.00	0.00				
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](mailto: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:	<b>Salmon et al. Slide show BCIRG 006</b> <b>DESCRIPTION AC-T VS AC-TH</b>												
Populations	Notes for use show to right of screen				Source Population	Women from 24 countries including NZ											
					Eligible Population	<b>Incl:</b> Women with HER2 positive breast cancer, node positive or high risk node negative disease. No other description or exclusion criteria available											
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Exposure & Comparison	Participants in each group:	<table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;"><b>Exposure Group (EG)</b></td> <td style="width: 50%; text-align: center;"><b>Comparison Group (CG)</b></td> </tr> <tr> <td style="text-align: center;">1074</td> <td style="text-align: center;">1073</td> </tr> </table>	<b>Exposure Group (EG)</b>	<b>Comparison Group (CG)</b>	1074	1073	Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status									
	<b>Exposure Group (EG)</b>	<b>Comparison Group (CG)</b>															
1074	1073																
	Follow-up:		Exposure(s)	<b>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)</b>													
	drop-outs / lost during/post-intervention:	<table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;">0%</td> <td style="width: 50%; text-align: center;">0%</td> </tr> </table>	0%	0%	Comparison	<b>AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)</b>											
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	Percentage lost to follow up:	<table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;">0%</td> <td style="width: 50%; text-align: center;">0%</td> </tr> </table>	0%	0%													
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Outcomes	If categorical.... what e.g. death?	<table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;">Disease-free survival</td> <td style="width: 50%;"></td> </tr> <tr> <td style="text-align: center;">participants with outcome:</td> <td style="text-align: center;"> <table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;">a</td> <td style="width: 50%; text-align: center;">b</td> </tr> <tr> <td style="text-align: center;">128</td> <td style="text-align: center;">192</td> </tr> <tr> <td style="width: 50%; text-align: center;">without outcome:</td> <td style="width: 50%;"></td> </tr> <tr> <td style="text-align: center;">c</td> <td style="text-align: center;">d</td> </tr> </table> </td> </tr> </table>	Disease-free survival		participants with outcome:	<table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;">a</td> <td style="width: 50%; text-align: center;">b</td> </tr> <tr> <td style="text-align: center;">128</td> <td style="text-align: center;">192</td> </tr> <tr> <td style="width: 50%; text-align: center;">without outcome:</td> <td style="width: 50%;"></td> </tr> <tr> <td style="text-align: center;">c</td> <td style="text-align: center;">d</td> </tr> </table>	a	b	128	192	without outcome:		c	d	Outcomes: ...primary	<b>Primary outcome: Disease free survival ( no definition available)</b>	
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	If continuous.... what measure?	<table border="1" style="margin: auto;"> <tr> <td style="width: 50%; text-align: center;">mean:</td> <td style="width: 50%;"></td> </tr> <tr> <td style="width: 50%; text-align: center;">standard deviation:</td> <td style="width: 50%;"></td> </tr> <tr> <td style="width: 50%; text-align: center;">or, standard error:</td> <td style="width: 50%;"></td> </tr> </table>	mean:		standard deviation:		or, standard error:		...secondary	Secondary outcomes: overall survival, toxicity and pathologic and molecular markers							
mean:																	
standard deviation:																	
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			...adverse														
Time	Unit of time (e.g. year) if rate wanted:		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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		in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)												
	Categorical outcome: Intention to treat analyses 95% CIs	0.12 0.10 to 0.14	0.18 0.16 to 0.20	0.67 0.54 to 0.82	-0.06 -0.09 to -0.03	-16 -11 to -34											
	Categorical outcome: On-treatment analyses 95% CIs	0.12 0.10 to 0.14	0.18 0.16 to 0.20	0.67 0.54 to 0.82	-0.06 -0.09 to -0.03	-16 -11 to -34											
Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00													
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 Reported CIs			0.67 0.54 to 0.83													

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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:	<b>Salmon et al. Slide show BCIRG 006</b> <b>DESCRIPTION AC-T VS AC-TH</b>													
Populations	Notes for use show to right of screen				Source Population	Women from 24 countries including NZ												
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	<b>Exposure Group (EG)</b>	<b>Comparison Group (CG)</b>																
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Follow-up:					Exposure(s)	<b>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)</b>												
	Percentage lost to follow up:	0%	0%		Comparison	<b>AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)</b>												
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mean:																		
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Time	Unit of time (e.g. year) if rate wanted:				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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		in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)													
	Categorical outcome:																	
	Intention to treat analyses 95% CIs	0.05 0.03 to 0.06	0.07 0.06 to 0.09	0.61 0.43 to 0.86	-0.03 -0.05 to -0.01	-34 -20 to -113												
Categorical outcome:																		
On-treatment analyses 95% CIs	0.05 0.03 to 0.06	0.07 0.06 to 0.09	0.61 0.43 to 0.86	-0.03 -0.05 to -0.01	-34 -20 to -113													
Continuous outcome:																		
Analysis of means 95% CIs	0.00	0.00	0.00	0.00														
Reported	Key outcome & analysis method, as published:	Disease free survival -Kaplan-Meier curves presented with Cox proportional hazards regression analysis to estimate hazard ratios and 95% confidence intervals.																
	Key results Reported CIs			0.59 0.42 to 0.85														

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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



<b>Assessed by:</b>				<b>Publication details:</b>	<b>Salmon et al. Slide show BCIRG 006 DESCRIPTION AC-T VS AC-TH</b>
<b>Populations</b>				<b>Source Population</b>	Women from 24 countries including NZ
	<p><b>Notes for use show to right of screen</b></p>			<b>Eligible Population</b>	<b>Incl:</b> Women with HER2 positive breast cancer, node positive or high risk node negative disease. No other description or exclusion criteria available
<b>Exposure &amp; Comparison</b>	<p><b>Exposure Group (EG)      Comparison Group (CG)</b></p>			<b>Participant Population</b>	3,222 women enrolled between April 2001 and March 2004 meeting the above criteria and consenting to participate in trial with 3 arms -
	<p><b>Participants in each group:</b></p>			<b>Method of allocation to groups</b>	Stratified randomisation by nodes and hormonal receptor status
	<p><b>Follow-up:</b></p>			<b>Exposure(s)</b>	<b>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)</b>
	<p>dropped pre-intervention: [ ] [ ]</p> <p>completed follow-up: [1074] [1073]</p> <p>drop-outs / lost during/post-intervention: [ ] [ ]</p> <p><b>Percentage lost to follow up:</b> 0% 0%</p>			<b>Comparison</b>	<b>AC-T: 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)</b>
<b>Outcomes</b>	<p><b>If categorical....</b></p> <p>what e.g. death? <b>Disease-free survival</b></p> <p>participants with outcome: [20] [4]</p> <p>without outcome: [ ] [ ]</p> <p><b>If continuous....</b></p> <p>what measure? [ ]</p> <p>mean: [ ]</p> <p>standard deviation: [ ]</p> <p>or, standard error: [ ]</p>			<b>Outcomes: ...primary</b>	Primary outcome: Disease free survival ( no definition available)
				<b>...secondary</b>	<b>Secondary outcomes:</b> overall survival, toxicity, CONGESTIVE HEART FAILURE, and pathologic and molecular markers
<b>Time</b>	<p><b>Unit of time</b> (e.g. year) if rate wanted: [ ]</p> <p>If <b>rate</b> wanted, enter average length of follow-up. If a <b>proportion</b>, enter 1.0: [1.00] [1.00]</p> <p>Report results per (e.g. per 100): [ ] persons</p>			<b>...adverse</b>	
				<b>Time</b>	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		Intervention effects per 1 persons		Number needed to treat (NNT) in 1 person-
	in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)	
Categorical outcome: Intention to treat analyses 95% CIs	0.02 0.01 to 0.03	0.00 0.00 to 0.01	5.00 1.71 to 14.57	0.01 0.01 to 0.02	68 166 to 43
Categorical outcome: On-treatment analyses 95% CIs	0.02 0.01 to 0.03	0.00 0.00 to 0.01	5.00 1.71 to 14.57	0.01 0.01 to 0.02	68 166 to 43
Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00	
Reported	Key outcome & analysis method, as published:				
	Key results Reported CIs				

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					Participant Population	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	<b>Exposure Group (EG)</b> <b>Comparison Group (CG)</b>				Method of allocation to groups	Stratified randomisation by nodes and hormonal receptor status
	Participants in each group:	1075	1073		Exposure(s)	<b>TCH:</b> 6 cycles of docetaxel 75mg/sqm and caboplatin AUC6 with concurrent trastuzumab ?dose for one year (n=1075)1
	Follow-up:				Comparison	<b>AC-T:</b> 4 cycles AC (doxorubicin 60mg/sqm and cyclophosphamide 600mg/sqm) followed by 4 cycles of docetaxel 100mg/sqm (n=1073)
	dropped pre-intervention:					
	completed follow-up:	1075	1073			
	drop-outs / lost during/post-intervention:					
	Percentage lost to follow up:	0%	0%			
Outcomes	If categorical... what e.g. death?				Outcomes: ...primary	Primary outcome: Disease free survival ( no definition available)
	If continuous... what measure?				...secondary	<b>Secondary outcomes:</b> overall survival, toxicity, <b>Congestive Heart Failure</b> and pathologic and molecular markers
	mean:				...adverse	
	standard deviation:					
	or, standard error:					
Time	Unit of time (e.g. year) if rate wanted:				Time	second interim analysis cutoff date Nov 01, 2006. Median follow-up time 36 months (462 disease free survival events, 185 Deaths)
	If rate wanted, enter average length of follow-up. If a proportion, enter 1.0: Report results per (e.g. per 100):					

### Results (unadjusted) with 95 % confidence intervals

Calculated In GATE frame		Occurrence per 1 persons		Intervention effects per 1 persons		Number needed to treat (NNT) in 1 person-
		in exposure group (EGO)	in comparison group (CGO)	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)	
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					

Please contribute your comments and suggestions on this form to: [rt.jackson@auckland.ac.nz](mailto:rt.jackson@auckland.ac.nz)

## Intervention Studies



### Step 3: Appraise the study using the PECOT framework

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

Evaluation criteria (RAAMbo)		Quality	
		+ ~ x	
		nr na	
Populations	<b>Representative?</b>		
	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	<b>Allocated appropriately (or Adjusted) and Accounted for?</b>		
	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	<b>Measured well (blinded or objective?)</b>		
	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
	<b>Overall study quality</b>	~	Unknown

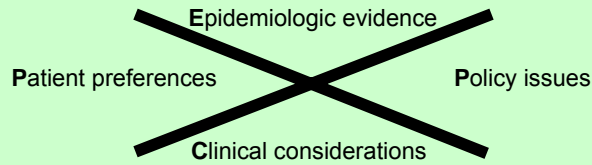
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## Intervention Studies



### Step 4: Apply the evidence

#### The X-factor



### Summarise epidemiologic evidence

<b>This study</b>	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)
<b>Consistency with other studies</b>	
<b>Debate &amp; Discussion</b>	

### Identify other issues

<b>Patient preferences</b>	
<b>Policy issues</b>	
<b>Clinical considerations</b>	

### The bottom line: weigh everything up

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

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

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