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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	s.wells@auckland.ac.nz
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Clinical Scenario

Trastuzumab is a monoclonal antibody against human epidermal growth receptor 2 protein (HER2). Overexpression of the HER2 protein, amplification of the HER2 gene, or both, occur in approximately 15-25% of breast cancers and are associated with aggressive behaviour in the tumour (Slamon et al.1987, Slamon et al.1989). Hence the hypothesis that for women with metastatic breast cancer who have an overexpression of HER2, trastuzumab might be useful as adjuvant therapy (before/after/in combination) with established other chemotherapeutic agents (eg anthracyclines and taxanes), surgery and radiation treatment.

This GATE appraisal is for HERA trial 2-year follow-up Smith I. et al (2007).

This study asked the following research question:

Step 1: Ask a clinical question using PECOT framework

P opulation or patient	For women with HER2 positive invasive breast cancer (node positive or node negative) who have completed surgery +/- radiotherapy and a minimum of 4 cycles of approved chemotherapy regimens (anthracyclines +/- taxanes) given pre-operatively, post-operatively or both
E xposure (intervention)	Does trastuzumab given at 8mg/kg infusion followed by 6mg/kg every 3 weeks for one year (OR for 2 years)
C omparison (control)	Compared to established surgical, radiotherapy and chemotherapeutic regimens alone
O utcomes	influence disease-free survival and overall survival and what are the adverse outcomes associated with the use of this drug?
T ime	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	
P opulation or patient	N/A	OR		OR		AND
E xposure (experimental)	N/A	OR		OR		AND
C omparison (control)	N/A	OR		OR		AND
O utcomes	N/A	OR		OR		AND
(T ime)	N/A	OR		OR		AND
F ilters & limits	N/A	AND		AND		

Databases searched

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

Evidence selected

Smith I. Et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.

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:	Smith I. Et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.	
Populations	Notes for use show to right of screen				Source Population	Women with breast cancer enrolled from 478 participating institutions in 39 countries.
					Eligible Population	Incl: Women with HER2 positive completely excised invasive breast cancer, node positive or node negative disease who had completed surgery +/- DXT and a minimum of 4 cycles of approved chemotherapy regimens (post-op, pre-op or both) AND normal LVEF post chemo. Excl: Distant metastases, prev invasive breast ca or other neoplasm, T4 tumours, suspicious internal mammary nodes not irradiated, prior mediastinal irradiation, cumulative doses >360mg/m2 for doxorubicin, >720mg/m2 for epirubicin, stem cell support, CHF, CHD, uncontrolled hypertension, sig valvular disease, unstable arrhythmias.
Exposure & Comparison	Participants in each group:	Exposure Group (EG)	Comparison Group (CG)		Method of allocation to groups	Stratified randomisation within 7 weeks of day1 last chemo cycle, 6wks from end DXT or definitive surgery (whichever was last).
	Follow-up:				Exposure(s)	Surgery and adjuvant or neoadjuvant chemotherapy or both, with or without radiation therapy then randomised to 3 groups: 1) trastuzumab given at dose of 8mg/kg i.v. 90minute infusion loading dose followed by 6mg/kg every 3 weeks for one year (GATE n=1703); 2) trastuzumab given at above dose for 2 years (n=1701)
Outcomes	If categorical... what e.g. death?	overall survival			Outcomes: ...primary	Primary outcome: Disease free survival defined as time from randomisation to the first occurrence of any of the following events: recurrence of breast ca at any site; development of ipse- or contralateral breast cancer (including DCIS but not LCIS); second nonbreast malignancy excl basal cell or squamous cell carcinoma or CIS cervix.
	If continuous... what measure?	mean:			...secondary	Secondary outcomes: cardiac safety, overall survival, site of 1st disease-free survival event, time to distant recurrence
Time	Unit of time (e.g. year) if rate wanted:				Time	2 years (median follow-up 23.5 months with range 0-48 months)
	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 95% CIs	0.03 0.03 to 0.04	0.05 0.04 to 0.06	0.65 0.47 to 0.90	-0.02 -0.03 to 0.00	-54 -31 to -218
	Categorical outcome: On-treatment analyses 95% CIs	0.04 0.03 to 0.05	0.06 0.05 to 0.07	0.64 0.46 to 0.88	-0.02 -0.03 to -0.01	-49 -28 to -169
	Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00	
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 Reported CIs			0.66 0.47 to 0.91		

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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:	Smith I. Et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.								
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Exposure & Comparison	Exposure Group (EG) Comparison Group (CG)				Method of allocation to groups	Stratified randomisation within 7 weeks of day 1 last chemo cycle, 6wks from end DXT or definitive surgery (whichever was last).							
	Participants in each group: Follow-up: dropped pre-intervention: completed follow-up: drop-outs / lost during/post-intervention: Percentage lost to follow up:	<table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 2px;">1703</td> <td style="padding: 2px;">1698</td> </tr> <tr> <td style="padding: 2px;">1645</td> <td style="padding: 2px;">1601</td> </tr> <tr> <td style="padding: 2px;">58</td> <td style="padding: 2px;">97</td> </tr> <tr> <td style="padding: 2px;">3%</td> <td style="padding: 2px;">6%</td> </tr> </table>	1703	1698	1645	1601	58	97	3%	6%			Exposure(s)
1703	1698												
1645	1601												
58	97												
3%	6%												
Outcomes	If categorical... what e.g. death? serious adverse event participants with outcome: without outcome:	<table border="1" style="margin-left: auto; margin-right: auto;"> <tr> <td style="padding: 2px;">a</td> <td style="padding: 2px;">b</td> </tr> <tr> <td style="padding: 2px;">156</td> <td style="padding: 2px;">97</td> </tr> <tr> <td style="padding: 2px;">c</td> <td style="padding: 2px;">d</td> </tr> </table>			a	b	156	97	c	d	Outcomes: ...primary	Primary outcome: Disease free survival defined as time from randomisation to the first occurrence of any of the following events: recurrence of breast ca at any site; development of ipse- or contralateral breast cancer (including DCIS but not LCIS); second nonbreast malignancy excl basal cell or squamous cell carcinoma or CIS cervix.	
	a	b											
156	97												
c	d												
	If continuous... what measure? _____ mean: _____ standard deviation: _____ or, standard error: _____			...secondary	Secondary outcomes: cardiac safety, overall survival analysed acc to total mortality, site of 1st disease-free survival event, time to distant recurrence, serious adverse events (mainly infection, cardiac adverse events)								
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):				Time	2 years (median follow-up 23.5 months with range 0-48 months)							
	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	0.09 0.08 to 0.11	0.06 0.05 to 0.07	1.60 1.26 to 2.05	0.03 0.02 to 0.05		30 59 to 20						
Categorical outcome: On-treatment analyses 95% CIs	0.09 0.08 to 0.11	0.06 0.05 to 0.07	1.57 1.23 to 2.00	0.03 0.02 to 0.05	30 62 to 20								
Continuous outcome: Analysis of means 95% CIs	0.00	0.00	0.00	0.00									
Reported	Key outcome & analysis method, as published:	Data reported is on Rx analyses (1442 in control group, 1688 on trastuzumab) and does not include 271/851 patients with at least one adverse event after moving to tratuzumab group											
	Key results Reported CIs	p=0.0103											

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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:	Smith I. Et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.						
Populations				Source Population	Women with breast cancer enrolled from 478 participating institutions in 39 countries.						
	<p>Notes for use show to right of screen</p>			Eligible Population	Incl: Women with HER2 positive completely excised invasive breast cancer, node positive or node negative disease who had completed surgery +/- DXT and a minimum of 4 cycles of approved chemotherapy regimens (post-op, pre-op or both) AND normal LVEF post chemo. Excl: Distant metastases, prev invasive breast ca or other neoplasm, T4 tumours, suspicious internal mammary nodes not irradiated, prior mediastinal irradiation, cumulative doses >360mg/m2 for doxorubicin, >720mg/m2 for epirubicin, stem cell support, CHF, CHD, uncontrolled hypertension, sig valvular disease, unstable arrhythmias.						
				Participant Population	5102 women between Dec 2001 and June 2005 meeting the above criteria and consenting to participate- 3401 randomised to 1 year of trastuzumab or observation						
Exposure & Comparison	<p>Exposure Group (EG) Comparison Group (CG)</p> <p>Participants in each group: 1703 1698</p> <p>Follow-up:</p> <p style="padding-left: 20px;">dropped pre-intervention: _____</p> <div style="text-align: center;"> </div> <p style="padding-left: 20px;">completed follow-up: 1645 1601</p> <p style="padding-left: 20px;">drop-outs / lost during/post-intervention: 58 97</p> <p>Percentage lost to follow up: 3% 6%</p>			Method of allocation to groups	Stratified randomisation within 7 weeks of day1 last chemo cycle, 6wks from end DXT or definitive surgery (whichever was last).						
				Exposure(s)	Surgery and adjuvant or neoadjuvant chemotherapy or both, with or without radiation therapy then randomised to 3 groups: 1) trastuzumab given at dose of 8mg/kg i.v. 90minute infusion loading dose followed by 6mg/kg every 3 weeks for one year (GATE n=1703); 2) trastuzumab given at above dose for 2 years(n=1701)						
				Comparison	observation (n= 1698)						
Outcomes	<p>If categorical.... what e.g. death? symptomatic CHF</p> <p style="padding-left: 20px;">participants with outcome: <table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="padding: 2px;">a</td><td style="padding: 2px;">b</td></tr><tr><td style="text-align: center; padding: 2px;">36</td><td style="text-align: center; padding: 2px;">2</td></tr><tr><td style="padding: 2px;">c</td><td style="padding: 2px;">d</td></tr></table></p> <p style="padding-left: 20px;">without outcome: _____</p> <p>If continuous.... what measure? _____</p> <p style="padding-left: 20px;">mean: _____</p> <p style="padding-left: 20px;">standard deviation: _____</p> <p style="padding-left: 20px;">or, standard error: _____</p>			a	b	36	2	c	d	Outcomes: ...primary	Primary outcome: Disease free survival defined as time from randomisation to the first occurrence of any of the following events: recurrence of breast ca at any site; development of ipse- or contralateral breast cancer (including DCIS but not LCIS); second nonbreast malignancy excl basal cell or squamous cell carcinoma or CIS cervix.
	a	b									
36	2										
c	d										
			...secondary	Secondary outcomes: Symptomatic CHF as diagnosed by a cardiologist & a decrease in LVEF by 10% or more from baseline to an LVEF of less than 50% at any time.							
Time	<p>Unit of time (e.g. year) if rate wanted: _____</p> <p>If rate wanted, enter average length of follow-up. If a proportion, enter 1.0: Report results per (e.g. per 100): <table style="display: inline-table;"><tr><td style="text-align: center;">1.00</td><td style="text-align: center;">1.00</td></tr></table> persons</p>			1.00	1.00	Time	2 years (median follow-up 23.5 months with range 0-48 months)				
	1.00	1.00									
Results (unadjusted) with 95 % confidence intervals											
Calculated in GATE frame			Occurrence per 1 persons		Number needed to treat (NNT) in 1 person-						
			in exposure group (EGO)	in comparison group (CGO)							
	Categorical outcome:		Intervention effects per 1 persons								
	Intention to treat analyses	0.02	0.00	Relative effect (EGO/CGO)	Absolute effect (EGO-CGO)	51					
95% CIs	0.02 to 0.03	0.00 to 0.00	4.33 to 74.42	0.01 to 0.03	77 to 38						
Categorical outcome:		Intervention effects per 1 persons									
On-treatment analyses	0.02	0.00	17.52	0.02	49						
95% CIs	0.02 to 0.03	0.00 to 0.00	4.23 to 72.64	0.01 to 0.03	74 to 36						
Continuous outcome:		Intervention effects per 1 persons									
Analysis of means	0.00	0.00	0.00	0.00							
95% CIs											
Reported	Key outcome & analysis method, as published:										
	Key results Reported CIs										
		Data reported is on Rx analyses (1708 in control group, 1678 on trastuzumab)									
		p<0.0001									

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Intervention Studies		
Step 3: Appraise the study using the PECOT framework		
b. assess study quality (RAAMt: + = good, ~ = mixed, x = poor, nr = not reported, na = not applicable)		
Evaluation criteria (RAAMbo)	Quality + ~ x nr na	
Populations	Representative? Source population well described?	~ No other than these were women (83% Caucasian, 12% Asian) with breast cancer enrolled from 478 participating institutions in 39 countries. Participants were mainly (71%) from Western and northern Europe, Canada, South Africa, Australia and New Zealand. In terms of generalisability- relates to women in mainly developed countries who were diagnosed with local invasive breast cancer with facilities available for surgery, radiotherapy and pathology.
	Eligible population well described?	+ Yes, the inclusion and exclusion criteria were reasonably explicit allowing replication within the 39 countries 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?	~ While there is much data on tumour size, histology, nodal and hormone receptor status, adjuvant chemotherapy, 40% of women were unable to be categorised according to their menopausal status at the time of randomisation and there is no data on other potential confounders such as smoking and socioeconomic status.
Exposure & Comparison	Allocated appropriately (or Adjusted) and Accounted for?	
	Exposure & comparison interventions well described & valid?	+ The exposure and comparison interventions were described in sufficient detail and appears valid, assuming that trastuzumab is a stable compound that was able to be delivered in the doses described.
	Allocation to exposure and comparison groups randomised?	+ Yes random assignment into groups with stratification according to key confounding factors; region of the world, age, nodal status, type of chemotherapy and hormone receptor status and use of endocrine therapy.
	Allocation concealed?	nr This is an important validity criteria that is not reported and would need follow-up to primary authors- It is likely that there was 3rd party computerised randomisation with stratification so that those involved in the trial were shielded from knowledge of upcoming assignment. Knowledge of the group to which a participant is assigned can affect the decision about whether to enter him/her into the trial. Inadequate or unclear allocation concealment have been associated with 30-40% larger estimates of treatment effects.
	Exposure and comparison groups similar at baseline? If not, were these adjusted?	+ Baseline characteristics are reported in Table 1. The exp and comparison groups are to be well- balanced according the characteristics recorded. No adjustments were made in the analyses.
	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?	~ From the HERA 2005 study, 20/1694 (1%) patients originally assigned to trastuzumab did not receive treatment. This is not updated in this paper nor is it reported what % women continued to have trastuzumab cycles every 3 weeks for a year ie% compliance with full therapy. Table 2 states that 11% had at least one grade 3 or 4 event. This is reported in HERA 2005 as an event requiring discontinuation (temporarily or permanently) and it is reported that 172/1703 (10.1%) were withdrawn from trastuzumab 115(6.8%) because of safety issues, 43 (2.5%) because of refusal, and 14 (0.8%) because of other reasons.
	Contamination acceptably low?	x Only 2/1693 (0.1%) received trastuzumab in HERA 2005. But following these results women in observation group were allowed to switch to trastuzumab irrespective of the time since randomisation and data was censored from the time of switching. 861 women switched from observation to trastuzumab and this is likely to cause important bias. In ITT analysis, this contamination may reduce the difference in the effect of the drug/control. Furthermore, for on-treatment analyses, if early treatment is important to the efficacy of this drug- this delay in Rx may also reduce its effect.
	Other interventions similar in both groups?	nr This is not reported- especially if trastuzumab was considered to be an effective drug, clinicians looking after women on observation alone may be inclined to use other therapies more eg, endocrine therapies.
	All participants accounted for at study conclusion?	+ It appears so- the authors of HERA 2005 report that "all patients adhered to the same schedule of follow-up visits (every three months for first 2 years)" with deaths reported separately. This paper states that 155/3401 (4.6%) were lost to follow-up; 97 (5.7%) from observation group and 58 (3.4%) from trastuzumab group.
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	Measured well (blinded or objective?)	
	Outcome measures well described & valid?	+ Yes primary endpoint well described with recurrence/development of new cancer needing histological confirmation. The cardiac secondary endpoints included multiple modes of assessment- questionnaire, physical exam, ECG, echocardiography or MUGA scanning every 3 months. The Echoc and MUGA scan results were reviewed by "core" staff, however no measures of reliability (inter-rater) were given.
	Blinded outcome measurement?	~ 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 disease survival outcomes eg, histology confirmation of recurrent distal cancer
	Outcome measurement complete?	+ It appears so other than the small % lost to follow-up.
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 and the short time frame of the study precludes any answer to longterm cardiac toxicity with trastuzumab	
Time	Similar follow-up time in exposure & comparison groups?	+ Yes, follow-up time similar in both groups.
	Was follow-up time meaningful?	+ Yes. From our crude analyses...Two year median follow up showed 32% reduction in disease free survival (note less than 1-year results) which was a 6% absolute difference over 3years and these analyses now indicate a 35% reduction in overall mortality (or a 2% absolute difference over 3years).
Results	Intention to treat analysis?	~ Whilst ITT was conducted for primary endpoints including those who violated eligibility criteria, they did not conduct ITT for safety analyses- rather on treatment analyses -BUT in this paper they also did not include 271/861 patients who after moving to trastuzumab developed an adverse event.
	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
Summary	Are the study results internally valid (i.e unbiased)?	~ The key factors to minimise bias are randomisation, allocation concealment, blinding to allocation and blind and objective outcome assessment. Whilst the study was randomised, and outcomes were fairly objective, allocation concealment was not reported, it was unblinded (potential co-intervention), and since the last publication 861 women had switched to trastuzumab (contamination). Outcomes were also assessed unblinded. The authors conducted 2 analyses, ITT and with censored data from women at time of switching and found similar results. The key factor would be determining whether allocation concealment occurred.
	Are results precise enough to be meaningful? If not, was power sufficient?	+ Yes, for the primary endpoint the results were precise and power calculations were reported. The study was not powered for the secondary endpoints (overall survival) but these 2 year median results have indicated a significant mortality difference.
	Can the applicability of the results (i.e external validity) be determined?	+ Reasonably- these results apply only to women with HER2 positive early stage invasive breast cancer who completed locoregional therapy and chemotherapy and had normal LVEF and no major cardiac disease. The women were mainly white or Asian (less than 5% black or other), 75% between 35-59 years, unknown smoking and socioeconomic status and treated in secondary care settings with surgical, radiation, cardiac imaging, pathology and other services available.
	Overall study quality	~ A reasonably good study but some methodological issues. Significant contamination that may well influence future results.

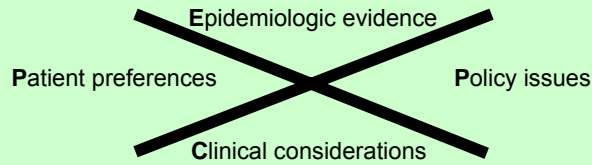
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Intervention Studies



Step 4: Apply the evidence

The X-factor



Summarise epidemiologic evidence

This study	
Consistency with other studies	
Debate & Discussion	

Identify other issues

Patient preferences	
Policy issues	
Clinical considerations	

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)

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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