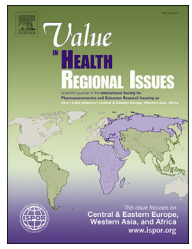
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Cost-Effectiveness of Docetaxel and Paclitaxel for Adjuvant Treatment of Early Breast Cancer: Adaptation of a Model-Based Economic Evaluation From the United Kingdom to South Africa

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ABSTRACT

Objectives: Transferability of economic evaluations to low- and middle-income countries through adaptation of models is important; however, several methodological and practical challenges remain. Given its significant costs and the quality-of-life burden to patients, adjuvant treatment of early breast cancer was identified as a priority intervention by the South African National Department of Health. This study assessed the cost-effectiveness of docetaxel and paclitaxel-containing chemotherapy regimens (taxanes) compared with standard (non-taxane) treatments. **Methods:** A cost-utility analysis was undertaken based on a UK 6-health-state Markov model adapted for South Africa using the Mullins checklist. The analysis assumed a 35-year time horizon. The model was populated with clinical effectiveness data (hazard ratios, recurrence rates, and adverse events) using direct comparisons from clinical trials. Resource use patterns and unit costs for estimating cost parameters (drugs, diagnostics, consumables, personnel) were obtained from South Africa. Uncertainty was assessed using probabilistic and deterministic sensitivity analyses. **Results:** The incremental cost per patient for the docetaxel regimen compared with standard treatment was R6774. The incremental quality-adjusted life years (QALYs) were 0.24, generating an incremental cost-effectiveness ratio of R28430 per QALY. The cost of the paclitaxel regimen compared with standard treatment was estimated as −R578 and −R1512, producing an additional 0.03 and 0.025 QALYs, based on 2 trials. Paclitaxel, therefore, appears to be a dominant intervention. The base case results were robust to all sensitivity analyses. **Conclusions:** Based on the adapted model, docetaxel and paclitaxel are predicted to be cost-effective as adjuvant treatment for early breast cancer in South Africa.
Keywords: transferability, model adaptation, low- and middle-income countries, early breast cancer

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Introduction

Evidence from economic evaluations and broader health technology assessments (HTAs) can be useful to inform difficult decisions in priority setting and health sector resource allocation.[1,2] Globally, there has been a growth in the systematic incorporation of economic evidence in healthcare decision making, particularly in high-income countries (HICs). More

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recently, this trend has also been observed in low- and middle-income countries (LMICs), where there has been a steady growth in the number of economic evaluation studies.[3-5] Nevertheless, formal structures and processes for the systematic utilization of economic evidence to inform decision making are less evident in these settings.[6-8] This has become an important agenda item because LMICs aim to develop equitable and sustainable healthcare systems for delivering universal health coverage.[1,2,9]

Despite an increased demand for economic evidence, LMICs are often constrained by limited technical capacity, insufficient resources, and poor data availability.[7,10-12] The development of de novo models for economic evaluations is both time-consuming and expensive. This has generated an interest in the transferability of economic evaluations through adapting cost-effectiveness models.[13]

An economic evaluation is considered to be transferable if it can be appropriately adapted for application in another setting, as distinct from a generalizable evaluation whose results can be applied without adjustment to other settings.[14,15] A range of approaches has been proposed for judging transferability.[13,14] Nevertheless, there is limited evidence on their implementability and several important methodological and practical challenges remain, such as poor methodological and reporting standards.[13-16] Practical case studies on transferability are therefore needed to provide pragmatic help for LMICS on methodology and the empirical challenges in adapting economic evaluation models from one setting to another.

Many LMICs, including South Africa, have taken practical steps toward institutionalizing HTA for prioritizing resource allocation in healthcare. Context-specific challenges for undertaking economic evaluation include the quality of data and lack of local technical capacities.[12] South Africa is an upper-middle income country moving toward universal health coverage through the implementation of national health insurance. Although the 2018 National Health Insurance Bill cites institutionalizing HTA as a mechanism for resource allocation decisions,[17,18] the widespread use of economic evaluation in decision making in the short term is limited by local resource and data constraints. Adapting economic evaluation models may, therefore, be one way of circumventing some of these challenges.

Adjuvant treatment of early breast cancer was identified as a priority area by the South African National Department of Health (NDoH), given the significant health and economic burden of breast cancer in South Africa.[19] Trastuzumab has recently been adopted by the South African public system for HER2 (human epidermal growth factor 2) amplified breast cancer[20] despite its cost-effectiveness being under debate in most LMICs.[21] Early breast cancer is defined as "breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA, stage IIB, and stage IIIA breast cancers."[22] Standard management of early breast cancer is surgery followed by adjuvant systemic treatment with chemotherapy or hormonal therapy, depending on the menopausal status of the patient.[20,23]

South African guidelines regarding adjuvant chemotherapy treatment recommend anthracycline-based chemotherapy regimens for low-risk patients and a combination of taxane and anthracycline-based chemotherapy regimens for high-risk patients.[20] Taxanes are defined as "any of various tricyclic compounds (such as docetaxel and paclitaxel) with anticancer activity that are obtained from yew trees (genus Taxus) or are made synthetically."

This article presents an economic evaluation of docetaxel and paclitaxel-containing chemotherapy regimens compared with standard treatments for adjuvant treatment of early breast cancer in South Africa. Docetaxel, paclitaxel, and trastuzumab are included in the Essential Medicines List in South Africa. The analysis was based on an economic model originally developed in an HIC (UK),[24] which we adapted for the upper-middle income country setting of South Africa. We also outline our findings regarding the appropriateness and practicality of existing model adaptation methods using this decision problem as a case study.

Methods

Overview

A cost-utility analysis was undertaken to assess the cost-effectiveness of docetaxel and paclitaxel-containing chemotherapy regimens (taxanes) compared with non-taxane standard regimens for adjuvant treatment of early breast cancer in South Africa. The analysis was based on a Markov model (originally developed in the UK) and further adapted in this study for use in South Africa. The analysis took a South African public health system perspective over a 35-year time horizon. A longer time horizon was considered unnecessary based on life tables for South Africa.[25] Outcomes were assessed in quality-adjusted life-years (QALYs) and resource use costs were assessed in South African rand at 2017 values. Both QALYs and costs were discounted at 5% per year as recommended by the NDoH in South Africa.[26]

Model Adaptation Methods

Eight model adaptation methods were identified from an existing systematic review[13] supplemented by a citation search of key papers[13,27,28] using Web of Science and Scopus databases. The methods thus identified[14,16,29-34] were then appraised against criteria developed by the authors. The criteria were: (1) relevance (needed to be specifically about model adaptation), (2) endorsement from a respected organization (eg, International Society for Pharmacoeconomics and Outcomes Research, International Health Economics Association), (3) compatibility with the International Decision Support Initiative's reference case for economic evaluation[35] (ie, do address the 11 methodological principles outlined in the International Decision Support Initiative reference case?), (4) transparency (ie, is there an explanation of how the method was developed?), (5) inclusiveness (ie, was the method used to develop the checklist comprehensive? automatically "no" if no explanation given), (6) practicality—length (shorter is better), (7) external validity—tested in case studies, and (8) external validity—tested in case studies in LMICs.[36] A traffic light system was used in relation to whether each method met the appraisal criteria, with 3 options: yes (green), partially (orange), and no (red) (see Appendix Tables 1 and 2 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003).[36] Based on this appraisal and after discussion with the wider team of the relative merits of each of the methods, the Mullins checklist was chosen as the most appropriate guide to the model adaptation process (see Appendix 2 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003).

Model Structure

The analysis was based on an existing six-health-state Markov model,[24] which was adapted using the Mullins checklist.[16] The model structure (Fig. 1) illustrates the 6 different health states used and how a patient moves from one to another. The health states modeled were (1) disease-free survival, (2) locoregional or contralateral relapse, (3) metastatic disease, (4) remission, (5) death from breast cancer, and (6) death from other causes. No structural changes were made to the model. All patients start in

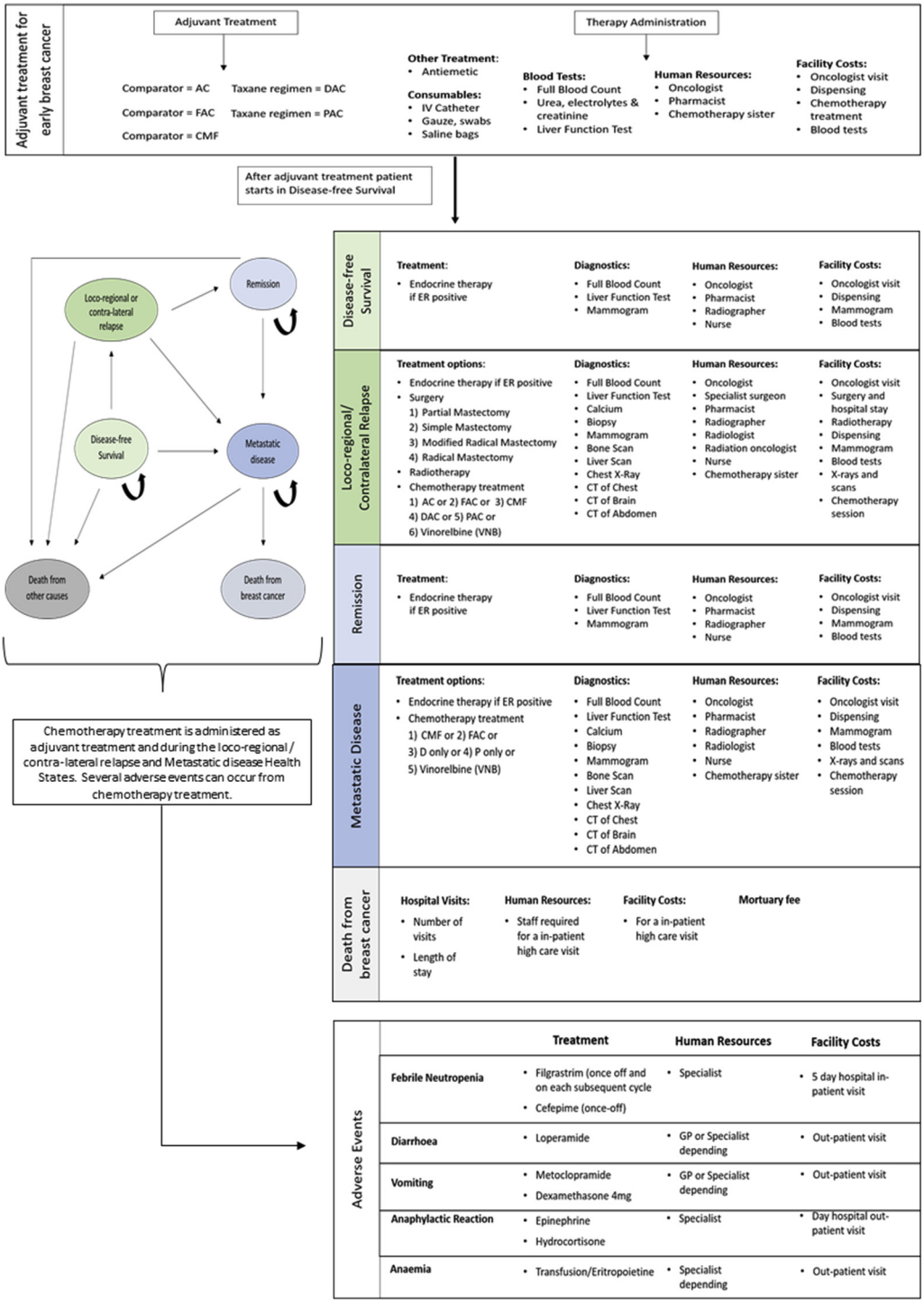


Figure 1 – Model structure and adjuvant treatment pathways for early breast cancer in South Africa.

the disease-free survival state after adjuvant treatment. A patient then transitions to one of 3 possible states: first, locoregional, contralateral relapse, or metastatic disease; second, death from other causes (not breast cancer related); or third, the patient remains in the disease-free survival health state. From locoregional or contralateral relapse, a patient transitions into remission, metastatic disease, or death from other causes. The metastatic disease state is an absorbing state: a patient remains in it, dies from breast cancer, or dies from other causes. A patient in the remission state will remain in that state, transition to metastatic disease, or die from other causes.

The cycle length in the model was 1 year, and half-cycle correction was applied to take into account the differences in timing of events within each cycle. The model derives the

Table 1 – Model parameters

Parameter	Value	Distribution	Updated/replaced with data from South Africa (N/Y)
General parameters			
Time horizon	35 years	NA	N
Cycle length	1 year	NA	N
Start age	50 years	NA	N
Discount rate (QALYs)	5%	NA	Y
Discount rate (costs)	5%	NA	Y
HRs			
DAC vs FAC (based on BCIRG 001)	0.71 (95% CI: 0.58-0.87)	Log-normal	N
ACP vs AC (based on NSABP B28)	0.82 (95% CI: 0.72-0.94)	Log-normal	N
ACP vs AC (based on CALGB 9344)	0.83 (95% CI: 0.73-0.94)	Log-normal	N
DAC vs FAC, 10-year follow-up based on BCIRG 001 (used in sensitivity analysis)	0.80 (95% CI: 0.68-0.93)	Log-normal	Y
Type of recurrence in taxane arm based on trials			
DAC (based on BCIRG 001)	Local, 19% Contralateral, 5% Distant, 76%	Dirichlet	N
ACP (based on NSABP B28)	Local, 29% Contralateral, 5% Distant, 66%	Dirichlet	N
ACP (based on CALGB 9344)	As for NSABP B28	Dirichlet	N
Type of recurrence in comparator arm			
FAC (based on BCIRG 001)	Local, 19% Contralateral, 4% Distant, 77%	Dirichlet	N
AC (based on NSABP B28)	Local, 32% Contralateral, 7% Distant, 61%	Dirichlet	N
AC (based on CALGB 9344)	As for NSABP B28	Dirichlet	
Annual probability of metastatic disease in patients with locoregional or contralateral recurrence			
Year 1	0.18 (95% CI: 0.12 to 0.25)	Beta	N
Year 2	0.19 (95% CI: 0.13 to 0.27)	Beta	N
Year 3	0.12 (95% CI: 0.06 to 0.19)	Beta	N
Year 4	0.09 (95% CI: 0.04 to 0.16)	Beta	N
Year 5 and beyond	0.12 (95% CI: 0.05 to 0.20)	Beta	N
Annual probability of death in patients with metastatic disease			
Each year	0.37 (95% CI: 0.32-0.43)	Beta	N
Quality of life multipliers for health states			
Disease free	0.940 (SE = 0.11)	Beta	N
Ipsilateral recurrence	0.740 (SE = 0.26)	Beta	N
Contralateral recurrence	0.740 (SE = 0.26)	Beta	N
Metastatic recurrence	0.500 (SE = 0.196)	Beta	N
Remission	0.850 (SE = 0.196)	Beta	N
Drug costs (including administration cost)			
Comparator regimen (FAC)	R9477	Fixed	Y
Comparator regimen (AC)	R5338	Fixed	Y
Docetaxel regimen (DAC)	R15 928	Fixed	Y
Paclitaxel regimen (ACP) based on NSABP B28 trial regimen	R8252	Fixed	Y
Paclitaxel regimen (ACP) based on CALGB 9344 trial regimen	R7633	Fixed	Y
AE cost in taxane arm			
Febrile neutropenia (DAC)	R16 092 (LUB: 12 069-20 115)	Gamma	Y
Febrile neutropenia (ACP)	R15 163 (LUB: 11 373-18 954)	Gamma	Y
Diarrhea	R176.25 (LUB: 132-220)	Gamma	Y
Vomiting	R176.91 (LUB: 132-221)	Gamma	Y

continued on next page

Table 1 – *continued*

Parameter	Value	Distribution	Updated/replaced with data from South Africa (N/Y)
Stomatitis	R176.91 (LUB: 132-221)	Gamma	Y
Blood transfusion	R1605.60 (LUB: 1204-2007)	Gamma	Y
Allergy	R1401.87 (LUB: 1051-1752)	Gamma	Y
AE cost in comparator arm if different			
Febrile neutropenia: FAC	R16 092 (LUB: 12 069-20 115)	Gamma	Y
Febrile neutropenia: AC	R15 163 (LUB: 11 373-18 954)	Gamma	Y
Chemotherapy for locoregional/contralateral recurrence (additional following local recurrence)			
Comparator arm (FAC)	R28 430 (LUB: 21 322-35 537)	Gamma	Y
Comparator arm (AC)	R17 650 (LUB: 13 237-22 062)	Gamma	Y
Taxane arm (DAC)	R4778 (LUB: 3584-5973)	Gamma	Y
Taxane arm (ACP): based on NSABP B28 trial regimen	R2476 (LUB: 1857-3095)	Gamma	Y
Taxane arm (ACP): based on CALGB 9344 trial regimen	R2290 (LUB: 1717-2862)	Gamma	Y
Health state costs			
Disease free	R2663 (LUB: 1997-3329)	Gamma	Y
Ipsilateral recurrence	R37 134 (LUB: 27 851-46 418)	Gamma	Y
Contralateral recurrence	R37 134 (LUB: 27 851-46 418)	Gamma	Y
Metastatic recurrence	R15 726 (LUB: 11 794-19 657)	Gamma	Y
Remission (no costs after 5 years)	R2538 (LUB: 1904-3173)	Gamma	Y
Death due to breast cancer	R41 173 (LUB: 30 880-51 466)	Gamma	Y
Disease-free survival >5 years	R1430 (LUB: 1072-1787)	Gamma	Y
Cost from 5 years after remission	R1413 (LUB: 1060-1766)	Gamma	Y

AC indicates doxorubicin (Adriamycin), cyclophosphamide; ACP, doxorubicin, cyclophosphamide, paclitaxel; DAC, docetaxel, doxorubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide; HR, hazard ratio; LUB, lower and upper bound; NSABP, National Surgical Adjuvant Breast and Bowel Project; QALYs, quality-adjusted life-years; N, no; Y, yes.

probabilities of patients moving between health states from clinical trials.[16,37-39] Some probabilities, such as those for disease-free survival and locoregional or contralateral relapse, depend on the initial and follow-up treatments (comparator or taxane treatment) received. Other probabilities relating to death or transition to metastatic disease are assumed to be the same in both the comparator and taxane treatment regimens

Evidence Used to Inform the Model Parameters

Model parameters, including mean estimates, 95% confidence intervals (CIs), distributions assigned, and sources of evidence are presented in Table 1. Based on estimates from clinical trials,[38,39] women were assumed to enter the model aged 50 years. Evidence for estimating clinical effectiveness, health-related quality of life, mortality rates, and costs is presented in the following subsections.

Clinical Effectiveness

The interventions and comparators assessed are (1) docetaxel regimen: doxorubicin (Adriamycin) 50 mg/m^2 intravenous (IV) infusion for 15 minutes followed by cyclophosphamide 500 mg/m^2 IV for 1 to 5 minutes, after a 1-hour interval docetaxel 75 mg/m^2 IV infusion for 1 hour, 6 21-day cycles (DAC), compared with 50 mg/m^2 of doxorubicin, followed by 500 mg/m^2 of fluorouracil as IV infusion for 15 minutes, then 500 mg/m^2 IV infusion of cyclophosphamide for 1 to 5 minutes, 6 21-day cycles (FAC); and (2) paclitaxel regimen: 60 mg/m^2 of doxorubicin, 600 mg/m^2 of cyclophosphamide, 4 3-week cycles, followed by paclitaxel 225 mg/m^2 3-hour infusion, 4 3-week cycles (ACP) compared with 60 mg/m^2 of doxorubicin, 600 mg/m^2 of cyclophosphamide, 4 3-week cycles (AC).[40]

Clinical effectiveness estimates (including hazard ratios (HRs), transition probabilities, and adverse events) came from 3 clinical trials that compared these interventions in head-to-head experimental designs. The BCIRG (Breast Cancer International Research Group) 001 trial[39] compared DAC and FAC regimens; National Surgical Adjuvant Breast and Bowel Project (NSABP) B-28[38] and Intrinsic Breast Cancer Subtypes and Benefit of Paclitaxel (CALGB)-9344[37] both compared ACP with AC regimens. The BCIRG 001 study was a multinational study with participants from 20 countries including South Africa. The distribution of breast cancer stages in these trials is published elsewhere.[24] The cyclophosphamide, methotrexate, fluorouracil regimen was in current use in South Africa but was excluded from the analysis for 2 main reasons: first, its current use is, we understand, limited to small regions, and second, a direct comparison for this regimen was not found in the literature review.

To update the clinical effectiveness evidence used to populate the original model, the MEDLINE database was searched for clinical trials published between 2005 and 2017. Trials were included if they reported any of the interventions assessed (DAC, ACP) with similar dosing regimens as reported in Ward et al.[24] Studies were also included if they reported any of the comparators assessed in this study (AC, FAC). The outcome measures of interest include disease-free survival and type of recurrence (contralateral breast cancer, distant recurrence, or

local/regional recurrence). Evidence from 10 years' follow-up for docetaxel[41] was identified and used in the analysis (see Appendix 3 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003).

Health-Related Quality of Life

Health state utilities used in the original model mainly came from a systematic review of publicly available source documents.[42] To account for the decrease in health-related quality of life with age, general population values were applied using a regression analysis of utility versus age.[24] Patients enter the model at age 50 years with an age-related utility of 0.85, and their utility is estimated to decline by 0.04 per 10-year increase in age. The utilities for all health states were multiplied by the age-related utility value for each year cycle in the model. To update the utility data, a search was made of the School of Health and Related Research health utility database, the Tufts Cost-Effectiveness Analysis database, and recent National Institute of Clinical Excellence Appraisals.[43] These searches found, however, no relevant updates to UK or South Africa specific utility values for the modeled health states (see Appendix 4 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003 for full results of the review).

Mortality Rates

Mortality rates for women by age group in South Africa came from the World Health Organization's Global Health Observatory Data repository.[25] All mortality rates used in the original model were replaced by South African-specific mortality rates as part of the model adaptation process (see Appendix 4 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003).

Costs

Cost estimates were based on specific South African data from document reviews, expert opinion, and national reference unit costs (see Appendix 5 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003). Documents reviewed included the NDoH's basic breast cancer package, its Master Procurement Catalogue, and a draft version of the NDoH's breast cancer guidelines. Three clinicians from the Expert Review Group were consulted. The Expert Review Group provides recommendations on revisions of the Essential Medicines List and the Standard Treatment Guidelines. The clinical experts provided information on current clinical practice for treatments and management of early breast cancer in South Africa.

Resource use estimates such as treatments, diagnostics, consumables, personnel, and time required were identified for each activity performed for adjuvant treatment and for each health state in the model. Information from experts was incorporated into data sourced from the 3 core documents listed above and applied to estimate specific South African cost parameters. An overview of the clinical pathways with all resource use identified and included in estimating cost parameters is given in Figure 1. Unit costs for docetaxel and paclitaxel were based on the Master Procurement Catalogue. Both products were generics.[44] The detailed cost data including drug costs, therapy administration costs, resource associated with each health state, and adverse event costs are provided as supplementary material (see Appendix 5 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003).

Cost-Effectiveness Threshold

This study uses a South Africa-specific cost-effectiveness threshold, which attempts to capture the true opportunity costs of resource allocation decisions. Cost-effectiveness thresholds based on opportunity costs are derived indirectly from estimates of the marginal effects of health expenditures on mortality.[45-47] Woods et al 2016[47] indirectly estimated a cost per QALY threshold for several countries (including South Africa) using a previously estimated opportunity cost-based threshold for the UK[39] weighted by each country's income (gross domestic product per capita) and income elasticity for the value of a statistical life. Using this approach, Woods et al estimated a cost per QALY threshold of $1175 to $4714 for South Africa. This is equal to R15 630 to R62 700 (16%-63% of South Africa's gross domestic product per capita), which was calculated using an exchange rate of 13.3 South African rand per $1.00 in base year 2017. This threshold was used as the benchmark for assessing the cost-effectiveness of docetaxel and paclitaxel in South Africa.

Cost-Effectiveness Analysis

Our cost-utility analysis was based on the adapted model using pairwise comparisons of taxanes versus usual care comparators. The results were expressed as incremental costs per QALY gained. Robustness was assessed using both probabilistic sensitivity analysis (PSA) and 1-way deterministic sensitivity analysis (DSA). The PSA was run on 10 000 Monte Carlo simulations, and the results were generally stable at 10 000 iterations. The DSA explored parameters where more uncertainty was anticipated. This included 10-year disease-free survival HR and recurrence rates based on a long-term follow-up from the BCIRG 001 trial, using the Department of Public Service and Administration unit costs for drugs and health states, applying a 1.5% discount rate for QALYs, and assuming no cost for granulocyte colony-stimulating factor following febrile neutropenia.

Results

Base-Case Estimates of Cost-Effectiveness

The base-case estimates of cost-effectiveness using average estimates from the 10 000 runs of the PSA are presented in Table 2. This shows the incremental mean costs per patient, incremental mean QALYs, incremental cost-effectiveness ratio or dominance, and the probability of cost-effectiveness at the lower and upper bound of the cost-effectiveness threshold for South Africa.

Docetaxel

The probabilistic ICER for the docetaxel regimen (DAC) compared with the non-taxane regimen (FAC) was estimated at R28 483 per QALY gained. It was generated from an incremental mean cost of R6774 per patient and incremental mean QALYs per patient of 0.24 (see Table 2). This result suggests that a docetaxel-containing chemotherapy regimen is cost-effective at the upper bound of the cost-effectiveness threshold (R62 700 per QALY) with 0.93 probability of cost-effectiveness. Nevertheless, docetaxel is unlikely to be cost-effective at the lower bound of the threshold (R15 630 per QALY)—the probability of cost-effectiveness is only 0.04.

The cost-effectiveness acceptability curve in Figure 2 shows the probability that docetaxel is cost-effective for a range of cost-effectiveness thresholds. Figure 3 shows the net monetary benefit (NMB) for 1000 women over the analysis time horizon using both the lower and upper bound of the cost-effectiveness threshold. As shown in the Figure, the NMB starts off with a negative value up to a point around year 7 and then gradually becomes positive up to R8.3 million over 35 years using the upper bound of the threshold. Nevertheless, at the lower bound of the threshold, the NMB remained negative over the analysis time horizon.

Table 2 – Base-case estimates of cost-effectiveness

Analysis	Incremental Cost	Incremental QALYs	ICER (rand per QALY gained)	Probability of cost-effectiveness at R15 630 (R62 700) threshold
Docetaxel based on BCIRG 001 trial (DAC vs FAC)	R6774	0.238	28 483	0.04 (0.93)
Paclitaxel based on NSABP B-28 trial (ACP vs AC)	−R578	0.030	Dominant	0.86 (0.96)
Paclitaxel based on CALGB 9344 trial (ACP vs AC)	−R1512	0.025	Dominant	0.74 (0.90)

AC indicates doxorubicin (Adriamycin), cyclophosphamide; ACP, doxorubicin, cyclophosphamide, paclitaxel; FAC, fluorouracil, doxorubicin, cyclophosphamide; DAC, docetaxel, doxorubicin, cyclophosphamide; ICER, incremental cost-effectiveness ratio; NSABP, National Surgical Adjuvant Breast and Bowel Project; QALYs, quality-adjusted life-years.

Paclitaxel

The results show that paclitaxel regimen (ACP) is dominant versus non-taxane (AC) because it is both less costly and more effective. The estimated difference in mean cost per patient was −R578 and −R1512, generating 0.03 and 0.025 QALYs based on NSABP and CALGB trials, respectively. The probability of cost-effectiveness is 0.86 and 0.74 at the R15 630 threshold. At the upper bound of the threshold, the probability of cost-effectiveness increases to 0.96 and 0.9. Figure 4 shows the NMB results based on the NSABP B-28 trial. As shown in the Figure, the paclitaxel regimen has a positive NMB beyond the 7-year time horizon, when both upper and lower bounds of the cost-effectiveness threshold are considered, although the magnitude of benefit is higher when the upper bound is considered. Paclitaxel results based on the CALGB-9344 trial produced approximately similar NMB results (Table 2).

Sensitivity Analysis Results

The results from the DSAs on the base-case ICER estimates show the high robustness of our primary cost-effectiveness estimates in all the sensitivity analyses performed. Using updated clinical effectiveness evidence for docetaxel (HR and recurrence rates over a 10-year follow-up) did not change the base-case results. Ignoring the cost for granulocyte colony-stimulating factor following febrile neutropenia reduced the ICER for the DAC regimen compared with FAC to R11 899 per QALY gained. All results from the sensitivity analysis performed are provided as supplementary material (see Appendix 6 in Supplemental Materials found at https://doi.org/0.1016/j.vhri.2019.03.003).

Discussion

Using resource cost data from South Africa, combined with effectiveness evidence from clinical trials, the analysis suggests that docetaxel and paclitaxel regimens are both cost-effective interventions given the postulated South African threshold. A docetaxel regimen (DAC) has an incremental cost per QALY of R28 483 compared with a non-taxane chemotherapy regimen (FAC). A paclitaxel regimen (ACP) is dominant (lower cost and

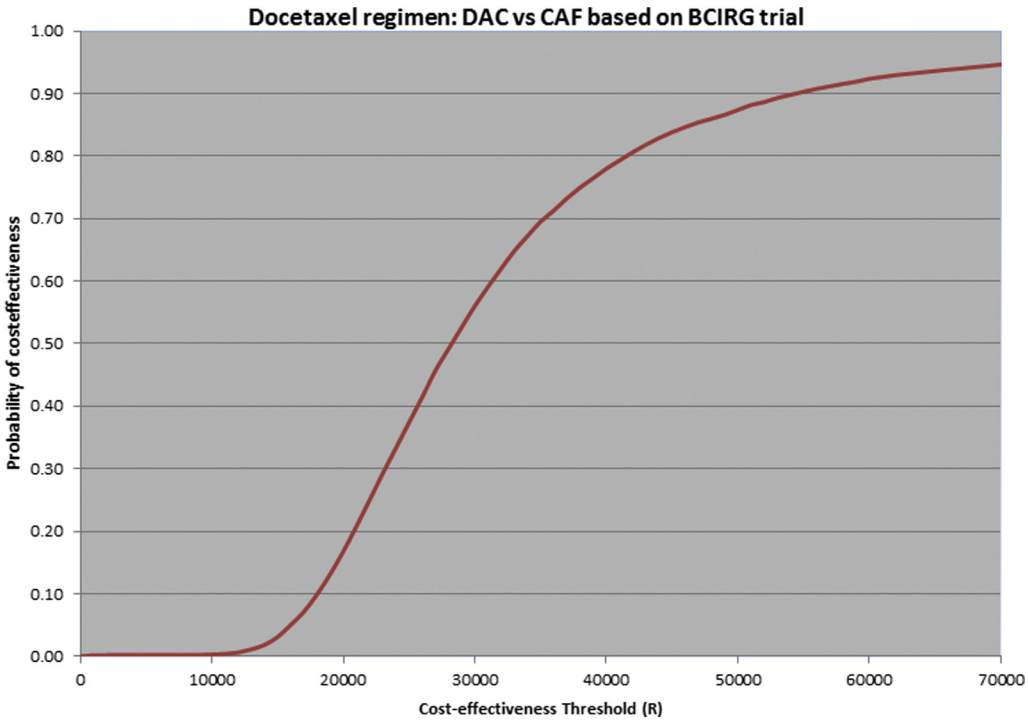


Figure 2 – Cost-effectiveness acceptability curve of docetaxel regimen (DAC vs FAC) based on BCIRG 001 trial. BCIRG indicates Breast Cancer International Research Group; DAC, docetaxel, doxorubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide.

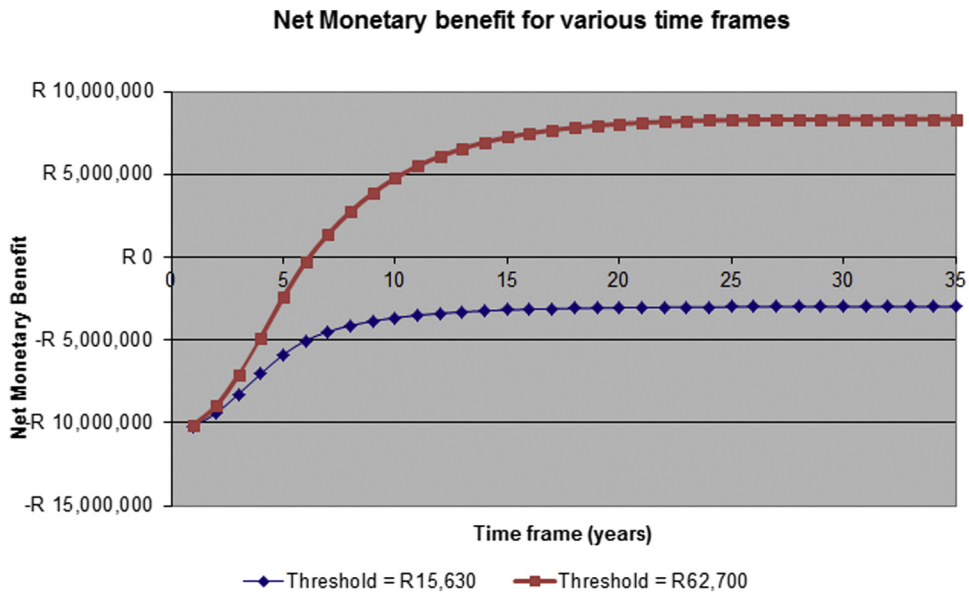


Figure 3 – Net monetary benefit of docetaxel regimen (DAC vs FAC) in 1000 women based on BCIRG trial. BCIRG indicates Breast Cancer International Research Group; DAC, docetaxel, doxorubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide.

greater benefit) compared with an AC regimen. Docetaxel has a 0.93 probability of cost-effectiveness at the upper bound of the cost-effectiveness threshold (R62 700 per QALY). Nevertheless, docetaxel was not cost-effective at the lower bound of cost-effectiveness threshold (R15 630), where the probability of cost-effectiveness was estimated as 0.04. The primary cost-effectiveness results were robust in all sensitivity analyses.

Although the HR for recurrence was lower for docetaxel based on BCIRG 001 trial compared with paclitaxel (based on the 2 trials, NSABP B-28 and CALGB 9344), paclitaxel showed better cost-effectiveness results. This is largely due to the lower price of (generic) paclitaxel in South Africa (R7633-R8252) compared with a generic docetaxel cost of R15 928 for all cycles specified by the regimens used in these trials. This is contrary to results from the

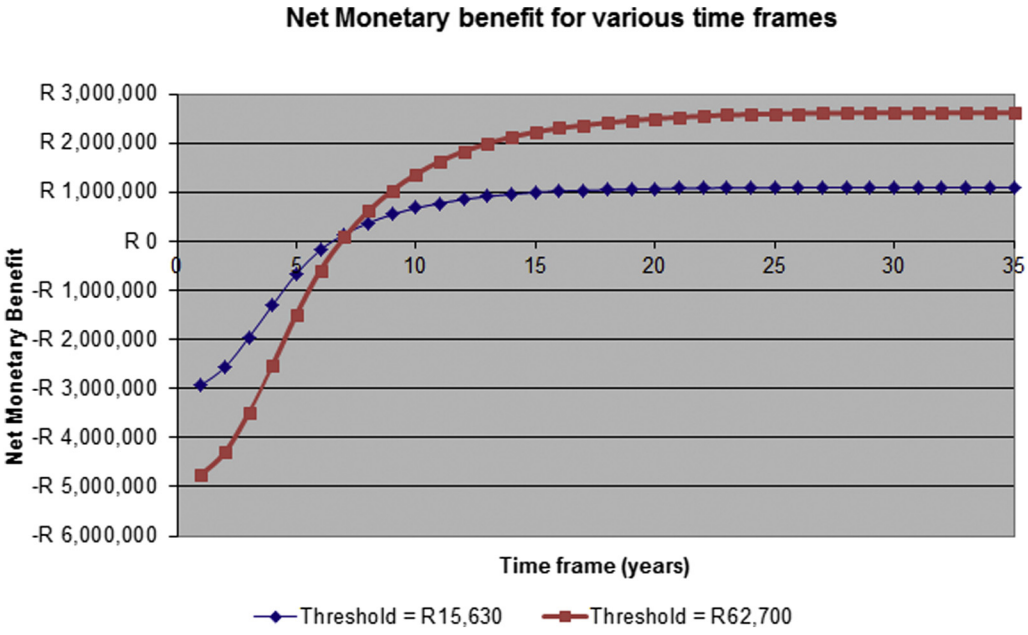


Figure 4 – Net monetary benefit of paclitaxel regimen (ACP vs AC) in 1000 women based on NSABP B28 trial. AC indicates doxorubicin (Adriamycin), cyclophosphamide; ACP, doxorubicin, cyclophosphamide, paclitaxel; NSABP, National Surgical Adjuvant Breast and Bowel Project.

original model used in the UK where paclitaxel was not cost-effective, having a higher estimated ICER of £43 000 per QALY gained (Range: £16 000-dominated). This was due to the difference in cost of paclitaxel and docetaxel as well as the difference in outcome.

For paclitaxel, the difference in the outcome between the UK model and our adapted model can be attributed to the difference in discount rates, among other factors. These factors include the difference in mortality rates with more patients dying earlier in the South African model compared with the UK model. This led to a reduced benefit in the longer term. For example, in the UK model, the incremental QALYs for paclitaxel was 0.14; in the South African model this was reduced to only 0.03. In the adapted model, we have included the annual probability of death in patients with metastatic cancer (breast cancer deaths), which was not replaced with data from South Africa, because we had no new data. In addition, the South African specific mortality rates (death from other causes) for women by age group were used in the adapted model.

The time horizon is a key influence on cost-effectiveness. The costs of the taxane-chemotherapy regimen are incurred in the first few months, whereas QALY benefits due to reduced recurrence occur in the medium to long-term. Reducing the time horizon of the analysis to 5 years (trials follow-up) produces negative cost-effectiveness results in NMB. With a 7-year time horizon, the NMB becomes positive as the accumulated benefits start to offset the higher costs incurred in the first few months. The NMB accumulates to a higher value of about R8 million for docetaxel and R2.5 to R3.0 million for paclitaxel per 1000 women at around the 20-year time horizon. After this point, no significant gains in NMB are expected for either regimen up to a modeled time horizon of 35 years.

Among the strengths of this work is that it was based on a well-validated model, which was adapted from the UK to South Africa using the Mullins checklist. The analysis was based on resource use and cost data collected from the South African health care system, supplemented by our review of evidence from the literature[43] and further informed by clinical experts. The analysis was also informed by updated clinical effectiveness evidence. This increased our confidence in the cost-effectiveness results.

The most significant limitation of this case study was the lack of specific South African data on clinical effectiveness and health state transition probabilities. It may be that clinical effectiveness evidence is largely transferable between jurisdictions[14]; however, this assumption may not hold in this case because breast cancer prognosis has been shown to differ between ethnic groups. Whereas differential effectiveness can be estimated via subgroup analyses or metaregression, this was impossible in our study owing to the lack of comparability between the trial participants and South African ethnic groups.

Specific updated South African data on health state utilities were also lacking. Although several comparisons of utility values and tariffs across HICs are available (eg, Heijink et al[48] and Olsen et al[49]), differences between high- and low-income countries have rarely been investigated. The comparisons across HICs have shown mixed results relating to preference heterogeneity and methodological differences.[48,49] Salomon et al[50] compared Global Burden of Disease disability weights for Bangladesh, Indonesia, Peru, and Tanzania and concluded that across different cultural environments there was "strong evidence of highly consistent results." Although the use of utility values from another country will undoubtedly increase uncertainty, it is difficult to identify any systematic bias that it may introduce.

No available updates in our literature review were relevant to South Africa. Research budget constraints made it necessary to rely on the expert opinion of oncologists for data relating to clinical practice. There is no universally accepted best practice in South Africa that can be used as the baseline; however, this may change with current work done with the National Health Insurance Authority. The cost-effectiveness threshold used has a considerable range, which makes it a far from unambiguous test (ie, 4% to 93% chance of cost-effectiveness using the lower and upper bounds, respectively).

It was a great advantage from the modeling perspective that technologies of interest such as taxanes are already used in clinical practice in South Africa—so here there were more data available, especially for drug costs. Nevertheless, clinical practice did not match the model directly, especially in cycle length, which did not reflect actual practice in South Africa. This is likely to have implications for the estimated total costs and cost-effectiveness of the interventions. Nonetheless, the findings of this study could be used to inform future adoption decisions by considering the cost-effectiveness of all alternative options.

Model adaptation from HICs to LMICs is possible, but it is not easy and may need considerable resources. We spent much more time than originally anticipated. A major need for subsequent studies of taxanes in South Africa is the estimation of health state utilities and clinical effectiveness. Adaptation is certainly easier when clinical practices and cultural conditioners are not too heterogeneous across the countries being compared and where the models used in the source material are not too antiquated.

Conclusions

Based on model adaptation and using resource cost data from South Africa, docetaxel and paclitaxel-containing chemotherapy regimens are predicted to be cost-effective interventions compared with standard treatments as adjuvant treatment for early breast cancer. Model adaptation from HICs to LMICs is possible but not easy and may be context and decision specific.

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Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/0.1016/j.vhri.2019.03.003.

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