PHARMACEUTICAL POLICY IN AUSTRALIA: DEVELOPING METHODS TO MANAGE UNCERTAINTY IN HEALTH TECHNOLOGY ASSESSMENT

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy.

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Signature of Student:

Date:

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ATTRIBUTION STATEMENT FOR ARTICLE PUBLISHED IN THE EUROPEAN JOURNAL OF HEALTH ECONOMICS

I (Bonny Parkinson) conducted the literature review, analysed and critiqued the evaluations, and was the key author of the paper. Associate Professor Sallie-Anne Pearson was involved in the inception of the paper. Associate Professor Sallie-Anne Pearson and Professor Rosalie Viney provided comments on the draft versions of the paper, focusing on style and structure.

A copy of the article published in the European Journal of Health Economics is presented in Appendix 1.

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ETHICS

The analysis of the Herceptin Program data was approved by the NSW Population & Health Services Research Ethics Committee (protocol HREC/10/CIPHS/11), the Medicare Australia External Request Evaluation Committee (2010/CO07329), and is a part of a research program approved by the University of Technology Sydney Research Ethics Committee (UTS HREC REF NO. 2009-143P).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ILLUSTRATIONS

GLOSSARY

Term	Meaning
AC	Anthracycline
ACT	Australian Capital Territory
ACPM	Advisory Committee on Prescription Medicines
ATC	Anatomical Therapeutic Chemical
AE	Adverse event
AEMP	Approved ex-manufacturer price
AIHW	Australian Institute of Health and Welfare
ANZHMD	Australian and New Zealand Hyperbaric Medicine Group
ARC	Australian Research Council, Australia
AR-DRG	Australian Refined Diagnosis Related Groups
ARTG	Australian Register of Therapeutic Goods
ATAGI	Australian Technical Advisory Group on Immunisation
ATC	Anatomical therapeutic chemicals
ARC	Australian Research Council
bd	Twice daily
bDMARDs	Biological disease-modifying antirheumatic drugs
BMD	Bone mineral density
BSA	Body surface area
CADTH	Canadian Agency for Drugs and Technologies in Health
CEAC	Cost-effectiveness acceptability curve
CED	Coverage with Evidence Development
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CISH	Chromogenic in situ hybridization
CT	Computed tomography
CVAD	Central venous access device
DCE	Discrete choice experiment
DPMQ	Dispensed price for maximum quantity
DR	Duration of response
DSPP	Duration of survival post-progression
DUSC	Drug Utilisation Sub-Committee
EBC	Early breast cancer
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDSS	Expanded disability status scale
ENBS	Expected net benefit of sampling
ER	Oestrogen receptor
ESC	Economics Sub-Committee
EVPI	Expected value of perfect information
EVPPI	Expected value of perfect parameter information
EVSI	Expected value of sample information
EUC	Electrolytes, urea and creatinine
FBC	Full blood count
FDA	United States Food and Drug Administration
FISH	Fluorescence in situ hybridization
GP	General practitioner
HBOT	Hyperbaric oxygen therapy
HER2	Human epidermal growth factor receptor 2

Term	Meaning
HR	Hazard rate
HRR	Hazard rate ratio
HRS	Hazard Rate of Progression Following Stable Disease
HRP	Hazard rate of overall progression
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICSP	Intravenous Chemotherapy Supply Program
IHC	Immunohistochemistry
iPAH	Idiopathic pulmonary arterial hypertension
IPCW	Inverse Probability of Censoring Weights
ISH	In situ hybridisation
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intent to treat
IV	Intravenous
kg	Kilograms
LFT	Liver function test
ln	Natural logarithm
LVEF	Left ventricular ejection fraction
LYG	Life years gained
MAUI	Multi-attribute utility instrument
MBC	Metastatic breast cancer
MBS	Medical Benefits Scheme
MES	Managed Entry Scheme
mg	Milligrams
MUGA	Multi gated acquisition scan
MSAC	Medical Services Advisory Committee
n	Number of patients/respondents etc
NA	Not applicable
NHMRC	National Health and Medical Research Council
NHS CRD	National health service Centre for Reviews and Dissemination
NHS EED	National health service economic evaluation database
NHS	National health service
NICE	National Institute for Health and Care Excellence
NIP	National Immunisation Programme
NPS	National Prescribing Service
NSW	New South Wales
NR	Not reported
NT	Northern Territory
OECD	Organisation for Economic Co-operation and Development
OIR	Only in research
OR	Odds ratio
OS	Overall survival
OWR	Only with research
PBAC	Pharmaceutical Benefits Advisory Committee
PBPA	Pharmaceutical Benefits Pricing Authority
PBS	Pharmaceutical Benefits Scheme
PFLY	Progression free life year
PFS	Progression free survival
PgR	Progesterone receptor
PPS	Post-Progression Survival
PSA	Probabilistic sensitivity analysis
q3w	Once three-weekly

Term	Meaning
QALY	Quality-adjusted life year
qd	Once daily
QLD	Queensland
qw	Once weekly
q3w	Once three weekly
r	Response rate
RCT	Randomised controlled clinical trial
RPBS	Repatriation Pharmaceutical Benefits Scheme
RPSFT	Rank preserving structural failure time
RRMA	Rural, remote and metropolitan areas
RR	Relative Risk
SA	South Australia
SE	Standard error
SD	Standard deviation
SMDM	Society for Medical Decision Making
TAS	Tasmania
TGA	Therapeutic Goods Administration
TTO	Time trade-off
TTP	Time to progression
UK	United Kingdom
US	United States of America
VIC	Victoria
VOI	Value of information
WA	Western Australia
WAMTC	Weighted average monthly treatment cost

ABSTRACT

Economic evaluation is a tool used by decision makers to ensure that promising high cost drugs that receive public funding are value for money. Funding decisions are inevitably based on limited data and there is always some uncertainty regarding whether the drug be cost-effective in clinical practice. An incorrect funding decision will reduce society's welfare. The aim of this thesis is to investigate and evaluate current and potential methods to assess and manage uncertainty regarding the cost-effectiveness of a drug in clinical practice.

The thesis undertakes an in-depth case study of a specific high cost drug which captures many of the features common to emerging high cost drugs: trastuzumab (Herceptin) for the treatment for human epidermal growth factor receptor 2 (HER2) positive metastatic breast cancer.

The research had five stages: 1) a systematic review and critique of published economic evaluations was conducted; 2) an economic model was developed using trial evidence; 3) uncertainty was analysed using different methods, including value of information analysis; 4) real-world observational data were analysed to inform modifications to model parameters; and 5) the model was adjusted to estimate the cost-effectiveness in clinical practice.

The systematic review demonstrated the importance of judgements made regarding the structure of the analysis and the data sources used in economic models. The cost-effectiveness of trastuzumab was estimated to be $180,910/Quality Adjusted Life Year (QALY) gained in 2001 (when first considered for PBS-subsidy). This is above the range usually considered cost-effective. The model was used to demonstrate how to estimate the value of collecting real-world observational data to be used in economic evaluations. The case study was extended by exploring a hypothetical coverage with evidence development (CED) arrangement based on observational data collected within the Australian government's Herceptin Program. It was concluded that the hypothetical CED arrangement would not have been appropriate unless the cost of trastuzumab was reduced. The analysis of the observational data lead to policy options for achieving improved cost-effectiveness. In particular, non-adherence to treatment guidelines with respect to concomitant therapies and treatment post-progression was found. This underscores the need for post-market review. It was estimated that there was a net loss from funding trastuzumab via the Herceptin Program due to the high price of trastuzumab and non-adherence to treatment guidelines.

This thesis demonstrates some of the challenges for decision makers regarding high cost drugs with limited evidence, and offers some solutions regarding how uncertainty can be managed.