

## Methods to Manage Uncertainty in Health Technology Assessment



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The cost of new drugs has been increasing overtime and is a major driver of increasing costs in the health system. Economic evaluation is an important tool used by decision makers to ensure that drugs that receive public subsidy represent value for money. A key challenge for reimbursement decision making is the potential gap between the estimated cost-effectiveness at the time of funding decisions, and real-world cost-effectiveness. This can arise because the decisions rely on data from a limited set of clinical studies, and because data from other sources and assumptions are required to estimate health outcomes and resource use in clinical practice. Another growing issue for decision makers is the increasing pressure to make promising new drugs available earlier, when the clinical data may not be mature or are limited in other ways. For high cost drugs, the risks to funders from making decisions under conditions of uncertainty are substantial. The aim of this thesis is to investigate and improve the methods available to decision makers to assess and manage the uncertainty regarding the health outcomes and costs of subsidising high cost drugs. In particular the thesis explores the following questions:

1. How might economic evaluations use different approaches to translate the same clinical trial data and arrive at different conclusions?

2. How is the cost-effectiveness of a treatment likely to differ in clinical practice compared to that predicted using clinical trial data?
3. What is the value of collecting real-world observational data to use as inputs to economic evaluations to reduce uncertainty regarding comparative effectiveness and cost-effectiveness?
4. When should coverage with evidence development (CED) recommendations be considered compared to other risk-sharing arrangements?

The thesis involves an in-depth case study of a specific high cost drug that involves 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. Evidence from trials suggested that trastuzumab is effective; however it is also a high cost drug and whether it represents value for money remains controversial. In Australia the Pharmaceutical Benefits Advisory Committee (PBAC) did not recommend trastuzumab for subsidy for metastatic breast cancer. However, in 2001 the Government established the Herceptin Program, the only program of its kind that funds a specific drug outside of the conditions of the Pharmaceutical Benefits Scheme. The Herceptin program resulted in the availability of a rich observational dataset capturing health outcomes and resource use in clinical practice.

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## Pharmaceutical Policy in Australia: Developing Methods to Manage Uncertainty in Health Technology Assessment (cont.)

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

At its current price, the cost-effectiveness of trastuzumab was initially estimated to be \$222,975/Quality Adjusted Life Year (QALY) – above the range usually considered by the PBAC as being acceptable for subsidy. Various forms of sensitivity analysis demonstrated that, in the context of trastuzumab, a CED recommendation subject to collecting observational data would not have been likely to reduce uncertainty, largely due to the high ICER initially estimated. Using the observational data from the Herceptin Program, the real-world cost-effectiveness was estimated to be \$195,219, lower than the initially estimated cost-

effectiveness, but still supporting the PBAC's initial decision. The cost-effectiveness of trastuzumab could have been improved if: the guidelines for treatment with trastuzumab were more strictly enforced; a stopping rule were applied; risk-sharing arrangements were applied, such as imposing a dose cap; or the price were reduced. Finally, an algorithm is proposed that could be used by the PBAC to inform when a CED recommendation may be appropriate, and what types of evidence would be required to make an informed decision.

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

***This abstract highlights the work Bonny undertook in completing her PhD in Health Economics. We wish Bonny all the best as she submits her thesis!***

## Master Class on the Australian Health System, Policy and Reform

**When:** 2 and 3 of December 2014, to be followed by the Australian and New Zealand Health Services Research Association's Health Policy Symposium and Annual General Meeting on 4 December 2014

**Where:** Sydney, UTS city campus

**Aim:** The master class will provide participants with new insights into the development, implementation and analysis of health care policy

**Who should attend?** Health professionals, Managers, Researchers, Planners and Policy makers


**Presenters:** This intensive two-day course will be taught by a highly experienced multidisciplinary team of policy makers and academics

Registration details as well as a detailed course program will be made available shortly.



**COGNO**  
COOPERATIVE TRIALS GROUP  
FOR NEURO-ONCOLOGY

7<sup>th</sup> COGNO Annual Scientific Meeting  
'Translating science to patient centred trials'  
Friday 24<sup>th</sup> – Saturday 25<sup>th</sup> October 2014  
The Langham, Melbourne, Australia

NHMRC Clinical Trials Centre 

## COGNO ASM UPDATE

[Click here to view the ASM program](#)

**RANZCR CPD Points available:** Up to 10.5 RANZCR CPD points can be claimed for attendance at the 7th COGNO Annual Scientific Meeting.

**COGNO/CINSW Travel Grants for NSW Consumers:** COGNO and Cancer Institute NSW are pleased to announce the opportunity for NSW consumers who are COGNO members to submit an application for a 2014 travel grant to attend the COGNO Annual Scientific Meeting. The travel grant is valued at up to \$850 and is to be used for expenses incurred in attending the Annual Scientific Meeting. There are a number of travel grants available. Eligibility criteria:

- COGNO member
- Must be a consumer residing in NSW with a particular demonstrated interest in neuro-oncology

[Click here](#) for further information.

See you in Melbourne!

Mustafa Khasraw and Zarnie Lwin  
2014 COGNO ASM Co-Convenors

### Important Dates

COGNO/CINSW Travel Grants for NSW Consumers Deadline	19 Sep 2014
COGNO/CINSW Travel Grants for NSW Consumers Recipients Notified	Early Oct 2014
Online Registration Closes: <a href="#">REGISTER NOW</a>	10 Oct 2014
COGNO Annual Scientific Meeting	24-25 Oct 2014

W: [www.cogno.org.au](http://www.cogno.org.au)

E: [cognoasm@ctc.usyd.edu.au](mailto:cognoasm@ctc.usyd.edu.au)

## Concepts in Development...

Over the last quarter, CREST participated in concept development discussions with a number of the CTGs.

The first was at the ANZUP Concept Development Workshop, July 15<sup>th</sup> in Melbourne as part of the ANZUP Annual Scientific Meeting. The oth-

er was the joint ANZCHOG/PoCoG Concept Development Workshop held in Sydney on July 21<sup>st</sup>. Both provided opportunities to hear about potential new trials in development and to offer input to the investigators on things they might like to consider from a health economics perspective, or to make

their trial more amenable for the conduct of future economic evaluations.

If you have an upcoming Concept Development Workshop and would like a CREST representative to attend, please let us know.

## CREST Melbourne Workshops...

In June, CREST held its introductory workshop *Understanding Health Economics in Cancer Research* in Melbourne, hosted by Cancer Australia at the NHMRC facilities in St Kilda. Participants from a mix of backgrounds – including clinicians, clinical trial researchers, charity organisations – and representing half the CTGs attended the workshop to gain an insight into health economics and its use in cancer research. Through a mix of interactive presentations and group exercises, participants were introduced to the key concepts of health economics with respect to defining outcomes, measuring costs and forming comparisons that will be relevant for clinical and

resource allocation decisions. The group exercises allowed the participants to apply these concepts to stylised clinical trial examples, and provided some interesting group discussions. The engagement and feedback from participants was positive, and this workshop will be offered again in 2015 with the location and date to be advised.

Following on from the success of the workshop for consumer representatives held in Sydney, it was repeated in Melbourne in July. Participants were from four trials groups, and had the opportunity to hear about health economic concepts, how pharmaceuticals and medical ser-

vices are reimbursed in Australia, and the role of consumers in that process. Importantly, two of the speakers are currently members of the Pharmaceutical Benefits Advisory Committee and were able to offer participants key insights into the process and the role of consumers and consumer evidence in the process. The feedback from those present was very positive and there are plans to run similar workshops again in 2015.

CREST will endeavour to advertise its 2015 workshop schedule by the end of 2014 to allow sufficient planning by the CTGs.

## Unintended Consequences of Expensive Cancer Therapeutics – The Pursuit of Marginal Indications and a Me-Too Mentality that Stifles Innovation and Creativity

In their recently published piece, Fojo et al (2014) make some potentially controversial, yet nonetheless interesting points regarding the gains in chemotherapy outcomes since 2002 and the corresponding increase in the costs of care. While we often hear of the increasing unit costs of chemotherapy drugs, and the impact this is having on health care budgets, we hear less about what this is buying in terms of clinical outcomes. The authors present a cogent summary of the clinical outcomes (PFS and overall survival) from clinical trials for 71 chemotherapy drugs since 2002; arguing that the gains shown can be described as “marginal benefits”. In their own words...

*“Cancer is expected to continue as a major health and economic problem worldwide. Several factors are contributing to the increasing economic burden imposed by cancer, with the cost of cancer drugs an undeniably important variable. The use of expensive therapies with marginal benefits for their approved indications and for unproven indications is contributing to the rising cost of cancer*

*care. We believe that expensive therapies are stifling progress by (1) encouraging enormous expenditures of time, money, and resources on marginal therapeutic indications and (2) promoting a me-too mentality that is stifling innovation and creativity. The modest gains of Food and Drug Administration–approved therapies and the limited progress against major cancers is evidence of a lowering of the efficacy bar that, together with high drug prices, has inadvertently incentivized the pursuit of marginal outcomes and a me-too mentality evidenced by the duplication of effort and redundant pharmaceutical pipelines. We discuss the economic realities that are driving this process and provide suggestions for radical changes to reengineer our collective cancer ecosystem to achieve better outcomes for society.”*

JAMA Otolaryngol Head Neck Surg. doi:10.1001/jamaoto.2014.1570; Published online July 28, 2014. See the link at: <http://archotol.jamanetwork.com/article.aspx?articleid=1891387>

## TROG Cancer Research report

The Trans Tasman Radiation Oncology Group (TROG Cancer Research) has had a busy quarter with an important study published, preparations for its 2015 Annual Scientific Meeting, and the completion of its Consumer Advisory Panel.

The 5 year follow-up results of the TROG 03.04 'RADAR' trial give Australian and New Zealand men with newly-diagnosed cancer a better chance of survival without increased long term side effects. The powerful prostate cancer treatment regime tested on the RADAR trial has been shown to reduce the spread of aggressive but apparently localised tumours by more than 40 per cent. The study was published this month in the prestigious international journal, The Lancet Oncology.

Registrations are now open for TROG's 2015 Annual Scientific Meeting, which will be held March 24-26, 2015 in Newcastle, NSW. TROG's ASM provides a forum for radiation oncologists, cancer care clinicians, physicists, radiation therapists, data managers, research

nurses, clinical trial coordinators and personnel from allied health fields to meet and discuss TROG's current portfolio of clinical trials, potential new trials and new technologies. Our invited international speaker is Professor Kevin Franks, consultant clinical oncologist at the St. James's Institute of Oncology (SJIO) in Leeds, UK. Registrations are now open at [www.trog.com.au](http://www.trog.com.au).

The call for New Proposals to be presented at the 2015 TROG Annual Scientific Meeting is open and will now be closing on Monday 22nd September 2014 (5pm AEST). Proposals can be submitted to TROG's Trial Development Coordinator, Michelle Hall ([michelle.hall@trog.com.au](mailto:michelle.hall@trog.com.au)). More information is available [www.trog.com.au/New-proposals](http://www.trog.com.au/New-proposals).

TROG would like to thank everyone who applied for a position on our newly formed Consumer Advisory Panel. The following candidates were successful:

- John Stubbs – Consumer Advisor

- Tom Denny – Consumer Advisor
- Aunty Margaret Lawton – Consumer Advocate
- Aunty Bev Powers – Consumer Advocate

They will join existing members Ian Roos, Nicola Bruce, Leonie Young and Joan Torony. Further information can be found on the 'Consumer Advisory Panel' page of our website.

Finally, TROG's Chief Operating Officer, Joan Torony, has been selected as a member of the Best Practice Clinical Trial Model - Project Steering Group. The Best Practice Clinical Trial Model Project Steering Group has been established to act in an advisory capacity to the Cancer Institute NSW. The Project Steering Group comprises a diverse mix of qualified and experienced senior stakeholders from across the clinical trial sector and NSW Local Health Districts.

## Tools for the kitbag...

One of the projects at CREST this year has been to develop a set of pro-forma case report forms (CRFs) that can be used within clinical trials for the purposes of recording health care resource use and health outcomes that might not otherwise be collected, but that are important to the conduct of economic evaluations.

The team at CREST has been working with the investigators of the TROG sponsored SAFRON II trial to develop a set of resource collection CRFs for that trial which can potentially also be adapted for other clinical trials.



## Tools for the kitbag (cont.)...

SAFRON II is a randomised phase II trial investigating the use of stereotactic ablative fractionated radiotherapy compared with radiosurgery for the treatment of patients with oligometastatic neoplasia of the lungs.

One of the planned analyses for SAFRON II is to assess the cost-effectiveness of the use of stereotactic therapy, including its impact on quality adjusted survival. To facilitate this analysis, additional information on the time required for treatment administration and subsequent health care utilisation is being collected. In addition to information collected through access to patients' Medicare Australia data, the resulting health care resource CRFs are focusing on the following parameters: time and specialisation of the individuals involved in radiotherapy planning and delivery; the occurrence and treatment of adverse effects; patient monitoring and diagnostics; and hospital admission status (inpatient or outpatient). These were incorporated into the broader trial CRFs to simplify the data entry and management process.

CREST intends to adapt these pro-formas for other trials to build a suite of CRFs that can be used to show how the resource collection items can be incorporated into the standard clinical data collection.

## What is a QALY Worth? It Depends..

One of the steps when doing an economic evaluation is being able to interpret the results – does the resulting incremental cost-effectiveness ratio represent value for money? Is it cost-effective?

An oft used benchmark or threshold for this purpose is the well-worn standard of \$50,000 per quality adjusted life year (QALY) gained. A recent perspective piece in the NEJM by Neumann et al (2014) ([http://www.nejm.org/doi/full/10.1056/](http://www.nejm.org/doi/full/10.1056/NEJMp1405158)

NEJMp1405158), asks whether adherence to this threshold across time, countries and decision contexts is still relevant. Perhaps such thresholds might more appropriately reflect ability to pay (as reflected by per capita GDP), or increases in expenditure on health – both of which would result in thresholds two to three times that of the \$50,000 mark.

Neumann and colleagues suggest that ideally there would be no one

threshold, but rather the flexibility to use multiple ratios depending on the decision making context and the alternative resource allocations being considered. The authors provide further food for thought in suggesting that in applying thresholds, the decision makers might not only consider granting funding to those interventions that meet the relevant threshold, but perhaps encouraging better substitution or displacement of interventions that don't meet the threshold.

## What has CREST been up to?

### Trial Group Collaborations:

- ◆ Prepared audits on planned clinical trials, and reviewed concepts for concept development workshops (nine in total).
- ◆ Provided advice on the conduct of health economic analyses in ongoing studies (eg. TROG, PC4 and ALLG).

### Health Economics Workshops:

- ◆ One day consumer workshop held in Melbourne, July 2014.

### Website Updates:

- ◆ CREST website has moved: <http://www.crest.uts.edu.au>.

### Other Activities:

- ◆ Presented at a meeting of Sydney Catalyst, Genomics in Cancer, July 2014.
- ◆ Participated in a two day conference on Objectivity and Equity – the dilemmas of high priced drugs access, August 18<sup>th</sup> and 19<sup>th</sup>, Melbourne 2014.