Clinician-Led Improvement in Cancer Care (CLICC): Complementing Evidence-Based Medicine with Evidence-Based Implementation

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Statement of authentication

This thesis is submitted to the University of Sydney in fulfillment of the requirement for the degree of Doctor of Philosophy.

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Signed: 

Date: 15/03/2016

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List of abbreviations

ACI	NSW Agency for Clinical Innovation
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of variance
ANZCTR	Australian New Zealand Clinical Trials Registry
ARIA	Accessibility/Remoteness Index of Australia
ARO	Arbeitsgemeinschaft Radiologische Onkologie und Urologische Onkologie of the German Cancer Society (ARO 96-02/AUO AP 09/95) Trial
ART	Adjuvant radiotherapy
AUA	American Urological Association
AUD	Australian Dollar
BHI	Bureau of Health Information
CaPSURE	Cancer of the Prostate Strategic Urological Research Endeavor
CEC	Clinical Excellence Commission
CI	Confidence interval
CI	Chief Investigator
CL	Clinical Leader
CLICC	Clinician-Led Improvement in Cancer Care
CPG	Clinical Practice Guideline
EORTC	European Organisation for Research and Treatment of Cancer Trial 22911
EPE	Extracapsular extension
EPOC	Cochrane Effective Practice and Organisation Care Group
GEE	Generalised estimating equations
HETI	Health Education and Training Institute
HPN	Home parenteral nutrition
HREC	Human Research Ethics Committee

ICC	intracluster correlation
IQR	Interquartile range
LHD	Local Health District
MBS	Medicare Benefits Scheme
MDT	Multidisciplinary Team
MI	Myocardial infarction
MRN	Medical record number
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NSW	New South Wales
OR	Odds ratio
PCFA	Prostate Cancer Foundation of Australia
PCOS	Prostate Cancer Care Outcomes Study
Post-op	Postoperative
Pre-op	Preoperative
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Prostate Specific Antigen
PSM	Positive surgical margins
PU	Participating urologist
RADICALS	RADICALS - Radiotherapy and androgen deprivation therapy in combination after local surgery
RAVES	RAVES [Radiotherapy Adjuvant Vs Early Salvage] Trial (Protocol Number: TROG.08.03 Salvage
RCT	Randomised controlled trial
RP	Radical prostatectomy
RR	Relative risk
SEER	Surveillance, Epidemiology, and End Results Database
SEIFA	Socio-Economic Indexes for Areas
SES	Socioeconomic status

SRT	Salvage radiotherapy
SSA	Site-specific approval
SVI	Seminal vesicle invasion
SWOG	Southwest Oncology Group Trial S8794
TROG	Trans Tasman Radiation Oncology Group
UK	United Kingdom
URR	Urea reduction ratio
US	United States of America
USANZ	Urological Society of Australia and New Zealand
USD	United States Dollar

Statement of contribution

The candidate developed the series of studies presented in this thesis with guidance from the primary and associate supervisors. Assistance with data collection and statistical analysis where provided, is outlined in the acknowledgements. The candidate alone performed all other work, including all writing.

While it is noted that the CLICC implementation trial was funded as a NHMRC partnership grant prior to commencement of this PhD, the candidate was involved in the project planning and grant submission process. The CLICC intervention was not conceptualised at the time funding was granted and was developed and evaluated by the candidate as outlined below:

Chapter Two

Conceptualised and designed the systematic review protocol

Conducted the literature search

Synthesised results

Drafted the manuscript for publication

Chapter Three

Conceptualised and designed the survey

Analysed and interpreted results

Drafted the manuscript for publication

Chapter Four

Conceptualised the CLICC program logic framework

Conducted the needs and barriers analysis

Synthesised and interpreted results

Developed the CLICC intervention

Chapter Five

Developed the CLICC intervention protocol

Developed CLICC intervention tools, including: the CLICC video; CLICC printed resource; and feedback report templates

Drafted the manuscript for publication

Chapter Six

Conceptualised and developed the CLICC process evaluation framework

Developed process evaluation tools

Developed and conducted semi-structured participant interviews

Synthesised and interpreted results

Chapter Seven

Contributed to data analysis plan

Presented and interpreted results

Chapter Eight

Conceptualised and designed the survey

Informed analyses

Presented and interpreted results

Chapter Nine

Conceptualised and designed the survey

Informed analyses

Presented and interpreted results

Drafted the manuscript for publication

In addition, the candidate coordinated the CLICC implementation trial for its duration, including oversight of ethical and governance approvals, implementation and monitoring of the CLICC intervention, data collection, analyses and write up.

Acknowledgements

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I would also like to thank the other investigators of NHMRC Partnership Grant 1011474 through which this research was co-funded in collaboration with the Prostate Cancer Foundation of Australia. In particular: Andrew Brooks for his unfailing support of the CLICC implementation trial; Andrew Kneebone for his clinical input (and the best out of office replies ever); and Dianne O'Connell, David Smith and the data collection team at Cancer Council NSW for the monumental effort involved in reviewing 3,863 medical records.

Thanks also go to my colleagues at the Sax Institute for their daily project support and invaluable contributions: Cyra Patel for acting as the second reviewer for the systematic review presented in Chapter Two, and for her fabulous editing skills in the production of the CLICC video and printed resource (we wouldn't have got to version 22 without you!); Jane Bois for determinedly (and charmingly) pursuing urologists, pathologists and MDT coordinators in the name of recruitment and data collection; and last, but not least, Amanda Dominello for advice, sanity checks and an endless supply of inappropriate jokes.

Huge thanks also go to Sam Egger for analysis of the data presented in Chapters Seven, Eight and Nine.

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Abstract

Discrepancies between research evidence and clinical practice remain one of the most persistent problems in the provision of high-quality health care. Clinical practice guidelines aim to inform clinical decision-making by providing summaries of recent, credible research evidence with recommendations for clinical practice. However, timely and effective implementation of guidelines into practice is inconsistent.

Prostate cancer is the most common cancer registered in Australia and is the second most common cause of cancer death in males. Radical prostatectomy is the most frequent procedure for locally advanced prostate cancer, however following surgery it is estimated that between 20% and 50% of men are at "high risk" of experiencing progression or recurrence (defined as pT3 disease or having positive surgical margins). Three randomised controlled trials have demonstrated survival, recurrence and disease progression benefits from post-operative adjuvant radiotherapy for these patients. Consistent with other international guidelines, the Australian Cancer Network Clinical Practice Guideline for the Management of Locally Advanced and Metastatic Prostate Cancer (2010) recommends "patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery" (p37). With less than 10% of men with high-risk prostate cancer receiving care in accordance with this guideline, the development of effective strategies to rectify this situation holds potential to improve care processes and outcomes for this group of patients.

This thesis explores whether a multifaceted intervention implemented through a urological clinical network can improve the rates of referral of men for consideration for adjuvant radiotherapy. It comprises seven iterative

studies that address urologists' knowledge, attitudes and equipoise for the use of adjuvant radiotherapy for high-risk prostate cancer, the development of a clinical network embedded intervention and the evaluation of this intervention within a step-wedge cluster randomised trial 'Clinician-Led Improvement in Cancer Care (CLICC)'. The National Health and Medical Research Council (NHMRC) co-funded the CLICC implementation trial in partnership with the Prostate Cancer Foundation of Australia (PCFA), with in-kind support provided by the NSW Agency for Clinical Innovation (ACI). The thesis is presented as a series of journal articles.

Chapter one first provides an epidemiological perspective of prostate cancer including prevalence, tumour staging and grading, treatment modalities and their rates of utilisation, rates and predictors of disease recurrence after primary treatment, and current post-operative patterns of care in Australia and elsewhere. Evidence to support guideline recommended post-operative adjuvant radiotherapy for men with adverse features post-prostatectomy is critically appriased. The remainder of Chapter One introduces the landscape of intervention strategies to promote clinician behaviour change, including evidence specific to the cancer context. Chapter One concludes with a description of the organisation of healthcare and cancer services in New South Wales (NSW), Australia to introduce the setting for the CLICC implementation trial.

Chapter two *(paper published)* is a systematic review of evidence of the effectiveness of clinical networks as an organisational vehicle to improve quality of care and patient outcomes. A systematic search was undertaken in accordance with the PRISMA approach in Medline, Embase, CINAHL and PubMed for relevant papers between 1 January 1996 and 30 September 2014. Established protocols were used to separately examine and assess the evidence from quantitative and qualitative primary studies and then integrate

findings to draw conclusions. A total of 23 eligible studies (10 quantitative; 13 qualitative) were included. Of the quantitative studies, eight focused on improving quality of care and two focused on improving patient outcomes. Studies were limited by a lack of rigorous experimental design. The current best available empirical evidence indicates that clinical networks can be effective vehicles for quality improvement in service delivery and patient outcomes across a range of clinical disciplines. However, the ability to draw conclusions is limited somewhat by relatively low quality quantitative research.

Chapter three *(paper published)* presents the results of a nationwide survey of 157 Australian-based urologist members of the Urological Society of Australia and New Zealand (USANZ) (45% response rate) two years after the publication of the Australian Cancer Network Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer. Just over half of respondents (54%) were aware of the guidelines. Just over half agreed the recommendation for adjuvant radiotherapy is based on a valid interpretation of the underpinning evidence (54.1%, 95% CI [46%, 62.2%]) but less than one third agreed adjuvant radiotherapy will lead to improved patient outcomes (30.2%, 95% CI [22.8%, 37.6%]). Treatment preferences were varied. A positive attitude towards the clinical practice recommendation was significantly associated with treatment preference for adjuvant radiotherapy (rho = 0.520, $p < 0.0001$). There was stronger preference for adjuvant radiotherapy in more recently trained urologists (registrars) while preference for watchful waiting was greater in more experienced urologists (consultants) (b= 0.156, p= 0.034; 95% CI [.048, 1.24]). The results of the survey indicate that there remains clinical equipoise among Australian urologists in relation to adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy.

Chapter four provides an overview of the PRECEDE-PROCEED model of behaviour change and how it was used to develop the CLICC conceptual program logic framework. The chapter then presents the findings of a needs and barriers analysis and outlines how intervention elements were mapped to barriers and facilitators using the CLICC conceptual program logic framework. The needs and barriers analysis included: iterative workshops; results from the national survey of urologists (detailed in Chapter Three); consumer feedback; semi-structured interviews with urologists, radiation oncologists and clinical nurse coordinators at CLICC sites; and consultation with the Cancer Care Action Advisory Group established for the CLICC implementation trial. Barriers were identified at the clinician, patient and hospital system levels and the chapter concludes with a description of how these were addressed through physician- and context-focused intervention elements.

Chapter five *(paper published)* comprises the study protocol for the CLICC implementation trial; a stepped wedge cluster randomised controlled trial involving urological multidisciplinary teams (MDTs) from nine NSW hospitals linked to the NSW Agency for Clinical Innovation (ACI) Urology Clinical Network. The primary outcome was increased referral to radiation oncology for discussion of adjuvant radiotherapy in line with guideline recommended care or referral to a clinical trial of adjuvant versus salvage radiotherapy (RAVES - Radiotherapy Adjuvant Vs Early Salvage; TROG.08.03). Secondary outcomes were: increased discussion of the patient at a MDT meeting within four months after surgery; initial patient consultation with a radiation oncologist; and commencement of radiotherapy.

Chapter six provides the rationale for the process evaluation conducted in parallel with the CLICC implementation trial. This used mixed methods to identify mechanisms of provider and organisational change, which were assessed using three domains (i) whether the intervention was implemented

as intended with fidelity (*implementation*); (ii) why the intervention did or did not result in evidence-based care (*participation and response*); and (iii) why the intervention was or was not implemented or sustained across implementation sites (*context*). Quantitative measures were included to assess *implementation*, *participation* and *response*, combined with qualitative exploration of participants' experience of, and response to, the intervention and the *context*ual characteristics of the participating CLICC sites. Results of the process evaluation demonstrate that CLICC intervention elements were implemented with fidelity across the nine participating sites with all Clinical Leaders and participating urologists meeting the minimum requirement for exposure. Participation was high across eight of nine CLICC sites; all eligible urologists participated from five MDTs and more than three quarters (37 of 55; 76%) of eligible urologists participated overall. One site was an outlier with only 2 of 11 eligible urologists (18%) consenting to participate. Through the process evaluation it emerged that non-participation was considered to be due to lack of willingness to change practice and reluctance to provide access to medical records for review of current practice. Response to the CLICC trial was varied both within and across study sites and a number of contextual factors emerged that impacted on implementation and participation.

Chapter seven presents results of the CLICC implementation trial based on data from independent medical record review to determine whether the CLICC intervention resulted in change in primary and secondary outcomes. After adjustment for potential confounders, there was no significant effect of the intervention on the primary outcome of referral to radiotherapy or the RAVES trial within 4 months after prostatectomy (32% post-intervention versus 30% pre-intervention) (adjusted RR=1.05; 95% CI [0.74, 1.49]; $p = 0.892$). The effect of the intervention on referral was significantly modified by site ($p < 0.001$) with evidence that the intervention worked better in some sites than others. Specifically, the intervention appeared to work best in four

sites, each with similar increases in referral rates: Site 1 (RR=1.37; 95% CI [0.42-4.46]); Site 4 (RR=1.27; 95% CI [0.75-2.17]); Site 7 (RR=1.60; 95% CI [0.80-3.19]) and Site 8 (RR=1.57; 95% CI [1.01-2.43]). There was a significant effect of the intervention on the secondary outcome of discussion of the patient at a MDT meeting within 4 months after prostatectomy (adjusted RR=4.31; 95% CI [2.40, 7.75]; $p < 0.001$). Fifty-nine per cent of intervention patients (240 of 407) were discussed at a MDT meeting within 4 months after prostatectomy compared with 17% of control patients (88 of 505). Amongst those discussed patients with a MDT recommendation for referral to radiotherapy or the RAVES trial, however, less than half (62 of 140; 44%) were subsequently referred to radiation oncology within 4 months after prostatectomy.

To determine whether persisting clinician knowledge or attitudinal barriers were the underlying reason for the lack of a significant effect on the primary outcome of referral to radiotherapy or RAVES within 4 months after prostatectomy **Chapter eight** presents results from baseline and post-intervention participant surveys to measure change in knowledge, attitudes and beliefs. Twenty-nine of 37 participants (78%) completed the baseline survey and 24 of 37 (65%) completed the post-intervention survey; more than half (20 of 37; 54%) completed both surveys. There was no change in CLICC participants' treatment preferences between baseline and post-intervention surveys. When asked to indicate their preferred management approach for three hypothetical scenarios, there was an increase in the proportion who indicated a preference for adjuvant radiotherapy post-intervention for a hypothetical patient with a 19% 10-year risk of biochemical relapse. However, this change was not significant; urologists were on average 0.2 points more favourable towards this patient receiving adjuvant radiotherapy post-intervention than they were at baseline with mean scores of 6.8 and 7.0 respectively (mean difference 0.2; 95% CI [-0.8, 1.2]; $p = 0.666$). There were no

significant changes in participants' understanding of the current literature and evidence for the treatment of prostate cancer between baseline and post-intervention surveys and this was supported by open text survey responses in which a number of participants noted that they had prior knowledge of the evidence from these trials but continued to challenge its veracity. Overall there was no change in agreement with the clinical practice recommendation for adjuvant radiotherapy for locally advanced disease between baseline and post-intervention (mean difference -0.1; 95% CI [-0.3, 0.1]; p = 0.490) reflecting lack of significant change across the majority of underlying attitudes within this domain. The only significant change in attitudes was less agreement post-intervention that the recommendation is consistent with the opinions of respected clinical colleagues (mean difference -0.4; 95% CI [-0.7, 0.0]; p = 0.027). This suggests that within the wider urological community there is potentially less agreement with the recommendation for adjuvant radiotherapy for men with adverse pathological features post prostatectomy than was considered to be the case at baseline.

Chapter nine *(paper published)* presents the results of a follow-up nationwide survey of urologist members of the Urological Society of Australia and New Zealand (USANZ) conducted to determine whether knowledge, attitudes and self-reported practice have shifted nationally among the wider urological community independently of the CLICC implementation trial. Ninety-six respondents completed the 2015 survey (30% response rate) compared with 157 (45% response rate) in 2012. Urologists were significantly less favourable towards adjuvant radiotherapy in 2015 than in 2012 for the hypothetical clinical case with a 19% 10-year risk of biochemical relapse; urologists were on average 1.8 points less favourable towards Case 1 receiving adjuvant radiotherapy in 2015 than they were in 2012 with mean scores of 2.9 and 4.7 respectively (mean difference -1.8; 95% CI [-2.6, -1.0]; p < 0.001. Overall, urologists' were less positive towards the recommendation for post-operative

adjuvant radiotherapy for men with locally advanced prostate cancer in 2015 than in 2012, reflecting a significant change across a number of attitudes and beliefs. Consistent with CLICC participant surveys, urologist members of USANZ were less likely to agree in 2015 than 2012 that the recommendation is consistent with the opinions of respected clinical colleagues (mean difference -0.5; 95% CI [-0.8, -0.3]; $p < 0.001$). Of note, urologists also felt other urologists would more likely be critical if they routinely referred the target patient group for radiotherapy in 2015 compared with 2012 ($p = 0.007$). These results show that while CLICC participant attitudes remained largely unchanged between baseline and the post-intervention survey conducted in 2015, with a slight but non-significant tendency towards being more favourable towards adjuvant radiotherapy for a hypothetical clinical case with 19% 10-year risk of biochemical relapse, the wider urological community was significantly less favourable towards adjuvant radiotherapy for the same hypothetical clinical case in the follow-up survey conducted in the same year.

Chapter ten provides an overview of the studies included in this thesis and discusses the implications of results for clinical practice, and clinical practice guideline implementation more generally.

Due to the inclusion of published and submitted papers, each chapter in this thesis is written to be able to standalone. Therefore, there is some replication in reference lists as some references apply to multiple chapters.

Original contributions arising from this thesis

First author publications

Brown B, Young J, Smith D, Kneebone A, Brooks A, Xhilaga M, Dominello A, O'Connell D & Haines M. Clinician-Led Improvement in Cancer Care (CLICC) - testing a multifaceted intervention to increase evidence-based prostate cancer care: phased randomised controlled trial - study protocol. *Implementation Science* 2014;9:64

Brown B, Young J, Kneebone AB, Brooks AJ, Dominello A & Haines M. Knowledge, Attitudes and Beliefs Towards Management of Men with Locally Advanced Prostate Cancer Following Radical Prostatectomy: An Australian Survey of Urologists. *BJU Int.* 2016; 117 (Supp 4): 35-44. doi: 10.1111/bju.13037.

Brown B, Egger S, Young J, Kneebone AB, Brooks AJ, Dominello A & Haines M. Changing Attitudes Towards Management of Men with Locally Advanced Prostate Cancer following Radical Prostatectomy: A Follow-up Survey of Australian-based Urologists. *Journal of Medical Imaging and Radiation Oncology.* 2016 June 27. doi:10.1111/1754-9485.12483.

Brown B, Patel C, McInnes E, Mays N, Young J & Haines M. The effectiveness of clinical networks in improving quality of care and patient outcomes: A systematic review of quantitative and qualitative studies. *BMC Health Services Research.* 2016; 16:360. DOI: 10.1186/s12913-016-1615-z.

Additional related publications during this PhD candidature

Haines M, **Brown B**, Craig J, D'Este C, Elliott E, Klineberg E, McInnes E, Middleton S, Paul C, Redman S, Yano E on behalf of the Clinical Networks Research Group. Determinants of successful clinical networks: the conceptual framework and study protocol. *Implementation Science* 2012; 7:16.

Atkinson J, Patel C, Wilson A, Mittman B, Dominello A, **Brown B**. Drivers of large-scale change in complex health systems. An Evidence Check review brokered by the Sax Institute for the NSW Agency for Clinical Innovation. September 2013. http://saxinstitute.org.au/wp-content/uploads/Drivers-of-large-scale-change-in-complex-health-systems-a-rapid-review.pdf

Patel C, **Brown B**, Dominello A, Haines M. Knowledge Translation Strategy: A Knowledge Translation Strategy for the dissemination of the revised Australian Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer. The Sax Institute (http://www.saxinstitute.org.au) for the Prostate Cancer Foundation of Australia, 2015.

Brown B, Haines M, Middleton S, Paul C, D'Este C, Klineberg E, Elliott E, on behalf of the Clinical Networks Research Group. Development and validation of a survey to measure features of clinical networks. Under review by *BMC Health Services Research*

Oral conference presentations relating to this thesis

Brown B. Testing an implementation strategy to change practice within hospitals in a clinical network, Network to Network 2012 – the 2nd Australasian Clinical Networks Conference, Sydney, November 2012

Brown B. Implementation Research: A locally tailored intervention to improve adherence to a clinical practice guideline, University of Sydney School of Public Health Research Presentation Day, July 2013

Brown B. Clinician-Led Improvement in Cancer Care (CLICC): Testing an implementation strategy to change practice within hospitals in a clinical network, 2nd Biennial Australian Implementation Conference, Sydney, September 2014

Poster conference presentations relating to this thesis

Brown B. Improving evidence-based care for locally advanced prostate cancer: A randomised phased trial of clinical guideline implementation through a clinical network, ANZUP Annual Scientific Meeting, Sydney, July 2012

Brown B. Testing an implementation strategy to change practice within hospitals in a clinical network, Global Implementation Conference, Washington DC, August 2013

Invited presentations relating to this thesis

Brown B. Testing an implementation strategy to change practice within hospitals in a clinical network, Implementation Science Team Meeting, Kaiser Permanente, Los Angeles, August 2013

Brown B. Testing an implementation strategy to change practice within hospitals in a clinical network, COE Implementation Science Series, VA HSR&D Center for the Study of Healthcare Provider Behavior, VA Greater Los Angeles Healthcare System, Los Angeles, August 2013

Brown B. Clinician-Led Improvement in Cancer Care (CLICC): Testing an implementation strategy to change practice within hospitals in a clinical network, Prostate Cancer Foundation of Australia (PCFA) Patient Support Group, Sydney Adventist Hospital, August 2014

Brown B. Implementation research - complementing evidence-based medicine with evidence-based implementation, HARC Scholars Forum, Agency for Clinical Innovation, Sydney, April 2015.

Brown B. & Haines M. An implementation trial to improve clinician adherence to a prostate cancer guideline - implications for implementing change within the NSW health system, Cancer Institute NSW, Sydney, July 2015

Awards relating to this thesis

Brown B. Recipient of a Hospital Alliance for Research Collaboration (HARC) Scholarship 2013: *Implementation Research – complementing evidence-based medicine with evidence-based implementation*

Chapter 1: Introduction and scope of thesis

1.1 Introduction

1.1.1 Prevalence of prostate cancer

Prostate cancer is the most common cancer registered in Australia and the second highest cause of cancer death in Australian males.(1, 2) The most recently available incidence data from the Australia Institute of Health and Welfare documented 19,993 new cases of prostate cancer in 2011 and in the five years from 2007 to 2011 there were on average more than 20,000 diagnoses per year. This equates to a 1 in 7 risk of diagnosis before 75 years and a 1 in 5 risk before 85 years of age for Australian men, with the peak age for diagnosis being between 65 and 69 years.(2) The most recently available statistics for New South Wales (NSW), Australia from Cancer Institute NSW indicate that there were 7,277 new cases of prostate cancer diagnosed in 2009, accounting for a third of all new cancers in males in that year.(3)

According to figures published by GLOBOCAN, the World Health Organisation International Agency for Research on Cancer, globally, more than 1.1 million new cases of prostate cancer were recorded in 2012, accounting for around 8 per cent of all new cancer cases and 15 per cent in men.(4) Incidence is higher in more rather than less developed countries with age-standardised incidence rates highest in Australia and New Zealand (111.6 per 100,000), North America (97.2 per 100,000), Western Europe (94.9 per 100,000) and Northern Europe (85 per 100,000). This is presumed due to greater detection through widespread prostate specific antigen (PSA) testing and subsequent biopsy in these regions.(5)

1.1.2 Prostate cancer staging and grading

The integration of clinical stage, Prostate-Specific Antigen (PSA) level and

histologic tumour grade can be used to determine the extent or spread of prostate cancer and predict outcomes after treatment. The most widely used staging system for prostate cancer is the American Joint Committee on Cancer (AJCC) TNM system,(6) which is based on 3 key prognostic markers: 1. the extent of the primary tumor (T category); 2. whether the cancer has spread to nearby lymph nodes (N category); and 3. the absence or presence of distant metastasis (M category).

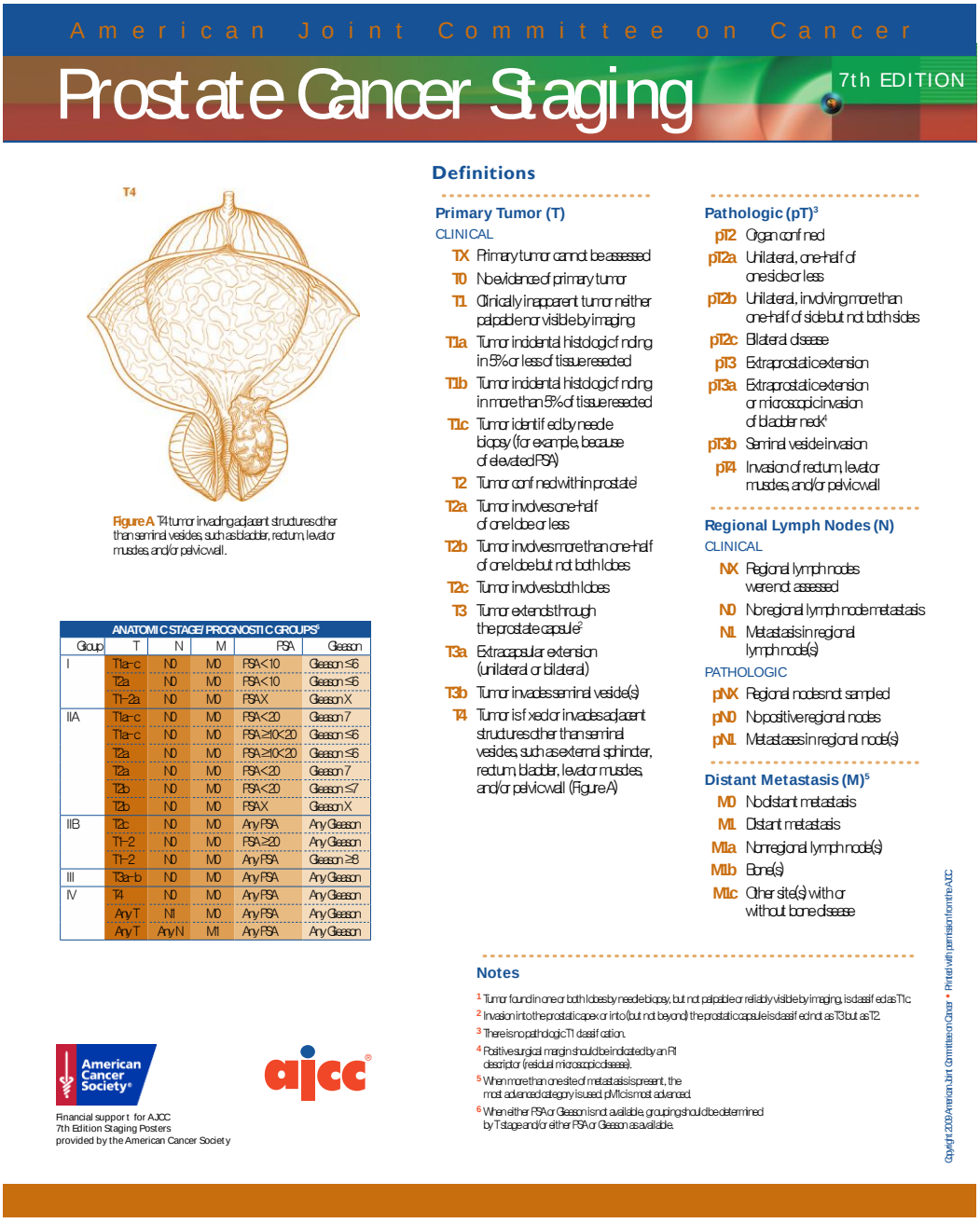
The TNM staging system

In the TNM system for prostate cancer, a simplified summary of staging is as follows:

T1	Tumour so small that it cannot be detected by feeling the prostate or on ultrasound
T2	Tumour can be felt but is still confined within prostate
T3	Tumour extends through the prostatic capsule and may have spread into seminal vesicles
T4	Tumour invades adjacent structures other than seminal vesicles, such as bladder, rectum or pelvic wall
N1	Tumour is found in lymph nodes
M1	Tumour has distant metastases

Within each stage, subgroupings a–d indicate the extent of spread within that stage (Figure 1.1). The PSA level at the time of diagnosis and/or the Gleason score, based on the prostate biopsy or surgery (histologic tumour grade) is used in conjunction with the TNM stage to stratify patients into prognostic groups.

Figure 1.1: American Joint Committee on Cancer (AJCC) TNM system subgroups



Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media.

This thesis is concerned with the management of men with high-risk prostate cancer post prostatectomy. This is defined as anyone with T3 disease (one or

more of extracapsular extension, seminal vesicle invasion, positive surgical margins). Patients with metastatic disease were not included.

The Prostate Specific Antigen (PSA) level at time of diagnosis

The percentage of free PSA in blood serum at the time of diagnosis can be used for risk stratification, providing an estimate of the likelihood of having biopsy-detectable prostate cancer as well as the extent and biological potential of the cancer. While the range of normal PSA values varies with age (Table 1.1), for the average man aged over 50 years, with no suspicious Digital Rectal Examination, the likelihood of having biopsy-detectable prostate cancer with a serum PSA level between 0.0 and 2.0 ng/ml is approximately 10%. This risk increases to 15% to 25% if the PSA level is 2.0 to 4.0 ng/ml; 17% to 32% if the PSA level is 4.0 to 10.0 ng/ml; and 43% to 65% if the PSA level is above 10.0 ng/ml.(7, 8) In addition, the proportion of men with higher volume cancers, extraprostatic disease, higher grade disease, and biochemical failure after treatment all increase as the PSA level increases.(9) When the PSA level at diagnosis is less than or equal to 4.0 ng/ml, 80% of men will have organ-confined disease. This proportion decreases at higher PSA levels to about 70% when the PSA level is between 4.0 and 10.0 ng/ml and about 50% when the PSA level is greater than 10.0 ng/ml.(10) At PSA levels higher than 10.0 ng/ml at diagnosis a significant proportion of men will have incurable, metastatic disease.(11) The PSA level at diagnosis is also significantly associated with the risk of biochemical recurrence after treatment.(12)

Table 1.1: Age specific reference ranges for serum PSA

Age (years)	Normal total PSA range (ng/ml)
40 - 49	0.0 – 2.5
50 – 59	0.0 – 3.5
60 – 69	0.0 – 4.5
70 and older	0.0 – 6.5

Adapted from: Stricker P. (2001) Prostate cancer. Part 1 Issues in screening and diagnosis.(11)

The Gleason score

The Gleason Grading System (13), the most widely used grading system worldwide, is a score of the tumour grade of adenocarcinoma of the prostate i.e. how abnormal, or poorly differentiated, biopsy tissue looks in comparison with well-differentiated normal tissue. Upon pathological examination, the cancer is assigned two Gleason grades based on the histologic pattern of arrangement of carcinoma cells. The primary grade is the most common Gleason pattern while the secondary grade is the next most common Gleason pattern. The primary and secondary grades are added together to derive the Gleason score from two to a maximum ten (for example, 3+4=7). Increasing Gleason grade is directly related to a number of histopathologic end points, including tumour size, margin status, and pathologic stage. Gleason grade has also been linked to a number of clinical end points, including clinical stage, progression to metastatic disease, and survival.(14) Therefore, the higher the Gleason score, the more aggressive the cancer, and the more likely it will grow and spread (Table 1.2). While patients with a Gleason score ranging from 2-6 are considered to have low risk disease, patients with a Gleason score ≥ 7 are at greater risk for extraprostatic extension and biochemical recurrence.(15) For example, in a series of 2404 men who underwent radical prostatectomy at Johns Hopkins Medical Institutions between 1982 and 1999, the biochemical failure rate overall was 17%. For the Gleason 8-10 patients, 10-year disease free survival was 29%, which dropped to 15% by 15 years.(16) In another study of 547 consecutive patients in the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database who underwent radical prostatectomy between June 1988 and September 2000, the 5-year disease-free survival rate for men with a biopsy Gleason score of 8-10 was 38%.(17)

Table 1.2: Gleason score descriptive summary

Gleason Score	Risk	Description
2-6	Low	*Low grade well differentiated tumour.* The cancer is likely to grow and spread very slowly. Treatment may never be needed.
7	Intermediate	*Intermediate grade, moderately differentiated tumour*. The cancer is likely to grow and spread at a modest pace. Treatment is needed to prevent future problems.
8-10	High	*High grade, poorly differentiated tumour.* The cancer is likely to grow and spread quickly. Treatment is needed at diagnosis.

Adapted from National Comprehensive Cancer Network (NCCN) Guidelines for patients. Prostate Cancer, Version 1. 2015.(18)

1.1.3 Treatment modalities and rates of utilisation

United States National Comprehensive Cancer Network (NCCN) guidelines suggest that many men with very low-risk clinically localised disease should be managed with active surveillance. Men with low- and intermediate-risk disease should be managed with active surveillance or with external beam radiation therapy, radical prostatectomy, brachytherapy, or a combination of these treatments. Men with high-risk disease should be managed with external beam radiotherapy plus androgen deprivation therapy with or without high dose rate brachytherapy. Alternatively high-risk disease should be managed with radical prostatectomy and pelvic node dissection.(19)

In Australia, radical prostatectomy is the most frequent procedure for clinically localised and intermediate-risk prostate cancer. NSW Central Cancer Registry data were analysed in the Prostate Cancer Care Outcomes Study (PCOS)(20) for more than 1600 men under the age of 70 years diagnosed with histopathologically confirmed localised prostate cancer (clinical stage T1a to T2c with no evidence of lymph node involvement or distant metastases) between October 2000 and October 2002. Sixty percent (981/1636) had radical prostatectomy as primary treatment. The remainder predominantly had external beam radiation therapy (18% [289/1636]) with or without

androgen deprivation therapy, which was more common in older men with later stage disease, or were kept under active surveillance (12% [280/1636]). More extensive NSW Central Cancer Registry data including 51,341 men diagnosed between 2001 and 2009 showed the frequency of radical prostatectomy in NSW increased progressively each year.(21) Victorian Prostate Cancer Registry data for men diagnosed with prostate cancer from 2008 to 2011 report, overall, 71.0% (1933/2724) received surgery, radiotherapy and/or brachytherapy. Nearly half of men with clinically localised disease (46.1% [1168/2531]) and more than half of those with intermediate-risk of disease progression (54.5% [655/1201]) underwent radical prostatectomy. Just over a quarter (25.6% [698/2724]) had external beam radiotherapy. In total, 558 men (20.5% of those for whom treatment data were collected) were recorded as having received androgen deprivation therapy either alone or in combination with other primary or salvage treatment. Twelve percent (72/594) of those with high-risk localised disease and 40.6% (299/736) of those with low risk of progression received no active treatment.(19) This is consistent with unpublished combined data from clinical registries in South Australia and Victoria for 13,598 men diagnosed with prostate cancer between 2008 and 2013. Sixty percent received radical treatment within 12 months of diagnosis with radical prostatectomy more common than radiotherapy as the curative approach (67% versus 33%). One quarter (25%) were managed using an observational approach with or without androgen deprivation therapy.(22)

These Australian figures reflect those reported in a population-based analysis of contemporary patterns of care in the US. Data from the Surveillance, Epidemiology, and End Results (SEER) database including 12,732 men under 60 years old diagnosed with localised prostate cancer between 2010 and 2011 show that 61.0% (3693/6058) with low-risk and 67.4% (3335/4947) with intermediate-risk had radical prostatectomy while 20.7% (1254/6058) with

low-risk and 21.6% (1071/4947) with intermediate-risk had radiotherapy. 16.8% (1018/6058) with low-risk and 6.4% with intermediate-risk (318/4947) had no active treatment.(23)

1.1.4 Rates and predictors of recurrence after primary treatment

Following radical prostatectomy as the primary curative treatment, it is estimated that 20% to 50% of men are at 'high risk' of experiencing progression or recurrence.(24-27) Rates of recurrence are 40-60% higher among patients with adverse pathological risk factors, namely extracapsular extension, seminal vesicle invasion or positive surgical margins.(28) All three risk factors are independently predictive and in combination yield a worse prognosis.

With regard to extracapsular extension, in a cohort study of 112 patients who underwent radical prostatectomy between 1969 and 1993, with a minimum of 10 years follow up (29), the overall 10-year clinical progression and/or biochemical failure free survival was 63%. For patients with no capsular involvement (n=62) disease free survival was 69%. For men with invasion into, but not through the capsule (n=24), the rate was similar at 67%, while for those men with invasion through the capsule (n=26) the rate dropped to 39% (p=0.017). This statistic is identical to that of another large long-term cohort study of 16,782 patients in the Johns Hopkins database who underwent radical prostatectomy between 1982 and 2008 (30) in which patients with extraprostatic extension (n=5316) had a 39% biochemical failure rate and 11% cancer specific death rate by 12 years. Other studies reporting on the prognosis of extraprostatic positive disease have documented 5-year failure free survival between 48% and 68%.(31, 32) In a study of 2518 Mayo Clinic radical prostatectomy patients with pT2N0M0 or pT3N0M0 prostate cancer, men with extracapsular extension (n=847) had a 5-year progression free survival rate (progression was defined as a PSA level > 0.4ng/ml on at least

one occasion) of 68% compared with 82% in those without extracapsular extension (n=1671), ($p < 0.001$).(31) A further study of 438 patients treated with radical prostatectomy alone between 1987 and 1993 reported 5 year biochemical relapse-free survival rate (relapse was defined as a PSA level > 0.2ng/ml) of 48% in patients with extracapsular extension (n=206) compared with 85% for patients without (n=131), ($p < 0.0001$).(33) It is likely that the higher PSA level for the determination of relapse in the Mayo Clinical study is a factor in the smaller proportion of patients who were considered to have recurrent disease in that cohort.

Multiple studies have demonstrated that extracapsular extension in conjunction with positive surgical margins results in lower disease free survival rates; 5-year failure free survival reported from 33-55% and 10-year failure free survival reported from 20%-53% depending on the definition of failure, median length of follow up and patient selection criteria.(32, 34-36)

Surgical margin status has also been found to be an independent predictor of recurrence. A comprehensive summary of literature by Swanson and Basler (32) concluded that patients with positive margins had double the overall death rate (60%) as those with organ or specimen confined disease (30%) and that margin positive disease had a reported 19-64% recurrence rate, a 5-year failure free survival of 36%-86% and 10-year failure free survival of 26%-61%. The large variation in reported biochemical recurrence and failure-free survival rates across the 17 primary studies was due to a number of methodological differences including variable PSA levels for the determination of biochemical recurrence (range, > undetectable to > 0.4ng/ml) and median follow-up time (range, 25 months to 121 months). For example, the lowest recurrence rate (19%) was defined as PSA >0.3ng/ml at a mean follow-up of 46 months (n=350) (37) and the highest (64%) was defined as PSA ≥0.2ng/ml at median 62 months follow-up (n=60).(38) Furthermore, there were marked

differences in samples sizes that affected the precision of these estimates (range, n=60 to n=1501). Differences in sample size, PSA levels and median follow-up were also evident in the studies reporting the highest and lowest 5- and 10-year survival rates. Of note, the largest study (n=1501, PSA ≥ 0.2 ng/ml on two occasions, median follow-up 38 months) reported 7-year disease free survival in 60% of patients with positive surgical margins.(39) An Australian study that sought to establish predictors of biochemical recurrence by analyzing the pathological characteristics of positive surgical margins found that a higher Gleason grade carcinoma (grade 4 or 5) at a positive surgical margin is significantly associated with biochemical failure after radical prostatectomy.(40) In the study with the lowest reported failure rate of 19% (37), rates of recurrence increased to 20% in the margin positive group with Gleason grade 7 (n=153) and 52% in the margin positive group with Gleason grade 8-10 (n=50).

Seminal vesicle involvement has similarly been linked with increased risk of biochemical failure, and death, in a number of studies. For seminal vesicle positive patients in one study (16), 5-year disease free survival was 48%, dropping to 30% by 10 years and 17% by 15 years. These statistics are similar to those reported for the study of 2518 Mayo Clinic patients; for 5-year progression free survival was 81% for 2183 patients without seminal vesicle involvement compared with 52% for the 335 patients with seminal vesicle involvement ($p < 0.001$). Other studies have shown seminal vesicle positive patients had a 73-75% biochemical failure rate and 23-28% death rate at 10-12 years.(30, 41) For example, of 673 patients in the Johns Hopkins radical prostatectomy database with seminal vesicle involvement, 75% had experienced biochemical recurrence at 12 years follow up.(30) These rates increased if patients also had extraprostatic disease.(41)

1.1.5 Recommendations for post-operative care for men with adverse features post-prostatectomy

Data from three large prospective randomized controlled trials (Table 1.3) involving more than 1800 men have shown the use of adjuvant radiotherapy within 4 months of resection significantly reduces the risk of biochemical recurrence and improves local recurrence and clinical progression free survival compared with surgery alone among patients with adverse pathological risk factors.(42-46) Overall survival was also improved after longer-term follow-up of patients in one trial (47). These trials include the: EORTC Trial 22911 (42, 45); SWOG S8794 (43, 47, 48); and ARO Trial 96–02/AUP AP 09/95 (44, 46).

European Organisation for Research and Treatment of Cancer (EORTC) Trial 22911

EORTC 22911 (42), a multicentre, phase III randomised controlled trial, involved 1005 patients, treated across 37 institutions throughout Europe. Eligible patients were those aged less than 76 years with histopathologically confirmed stage pT2-3 N0M0 prostate cancer with at least one risk factor post radical prostatectomy: tumour growth beyond the capsule (extracapsular extension); positive surgical margins; or invasion of the seminal vesicles. Following surgery as the primary curative treatment, patients were randomly assigned to one of two arms: 1. wait-and-see (n=503); or 2. immediate post-operative radiotherapy (60Gy conventional irradiation delivered over 6 weeks), within 16 weeks of surgery (n=502). The primary endpoint was biochemical progression-free survival. Clinical progression-free survival was defined as survival with no evidence of clinical, sonographic, radiographic or scintigraphic recurrence. Biochemical progression was defined as an increase of more than 0.2 µg/L over the nadir (lowest post-operative PSA value) measured on three occasions at least two weeks apart. Biochemical progression-free survival was counted from the day of randomisation to the

day of first clinical or biochemical progression or start of treatment in absence of progression, if any. Median follow-up was 5 years for both groups. The cumulative rate of locoregional failure was significantly lower in the post-irradiation group (5.4%; 98% CI [2.7% – 8.0%] versus 15.4%; 98% CI [11.2% - 19.6%]; p<0.0001). Clinical progression-free survival was significantly higher in the irradiated group (hazard ratio [HR] 0.61; 98% CI [0.43 – 0.87]; p=0.0009), as was biochemical progression-free survival (hazard ratio [HR] 0.48; 98% CI [0.37 – 0.62]; p<0.0001). At 5 year follow-up there was no significant difference in overall survival for the wait-and-see versus irradiation groups (93.1%; 98% CI [90.1% - 96.2%] versus 92.3%; 98% CI [89.1% - 95.5%; p=0.6796). Any grade and grade 2 (moderate) or grade 3 (severe) late adverse effects, including nausea or vomiting, diarrhea, frequency passage of urine, dysuria, skin and haematuria, were more common in the irradiated group (p=0.0045 and p=0.0005, respectively). Events of grade 3 toxicity were rare and incidence did not differ between groups at five years (2.6%; 98% CI [0.8% – 4.4%] wait-and-see versus 4.2%; 98% CI [3.4% - 5.0%]; p=0.0726).

At longer term follow-up(45) (median 10.6 years; range 2 months – 16.6 years) biochemical progression-free survival was significantly improved in the irradiated group (60.6%; 95% CI [55.7% – 65.2%] over the wait-and see-group (41.1%; 95% CI [36.4% – 45.8%]) (hazard ratio [HR] 0.49; 95% CI [0.41 – 0.59]; p<0.0001). Improvements in clinical progression-free survival, however, were not maintained (70.3%; 95% CI [65.5% – 74.6%] in the postoperative irradiation group versus 64.8%; 95% CI [59.8% – 69.3%] in the wait-and-see group; hazard ratio [HR] for clinical progression or death 0.81; 95% CI [0.65 – 1.01]; p=0.0539). There was no significant difference in overall survival at 10 years (total number of deaths 130 out of 502 patients in irradiated group versus 115 out of 503 patients in the wait-and-see group; hazard ratio [HR] 1.18; 95% CI [0.91 – 1.53]; p=0.20). Late adverse effects (any type, any grade) were more frequent in the postoperative irradiation group than in the wait-

and-see group at 10 years follow-up (cumulative incidence 70·8%; 95% CI [66·6% – 75·0%] versus 59·7%; 95% CI [55·3% – 64·1%]; p=0.001).

Southwest Oncology Group (SWOG) Trial S8794

SWOG S8794 (43, 47, 48) a multi-institutional, randomised controlled trial conducted in the United States, included men diagnosed with T3N0M0 prostate cancer with pathologically determined extracapsular extension, positive margins and/or seminal vesicle involvement between 1988 and 1995. A total of 425 eligible men who had undergone radical prostatectomy within the prior 16 weeks were randomised to: 1. adjuvant radiotherapy (60 to 64 Gy in 30 to 32 fractions), initiated within 10 working days of randomisation (n=214); or 2. observation (n=211). The primary endpoint was metastasis-free survival, defined as the time from randomisation to first evidence of metastasis or death due to any cause. Secondary outcomes included prostate-specific antigen (PSA) relapse, recurrence-free survival, overall survival, freedom from hormonal therapy, and postoperative complications. A post-operative PSA level at enrolment ≤0.2 ng/mL was considered undetectable. Biochemical relapse was defined as a PSA level exceeding 0.4 ng/mL after enrollment for those with a postsurgical PSA level of 0.4 ng/mL or lower. At first publication of results (48), median follow-up was 10.6 years (range 9.2 to 12.7 years). There was no statistically significant difference in metastasis-free survival or overall survival. Seventy-six out of 214 (35.5%) men in the adjuvant radiotherapy group were diagnosed with metastatic disease or died of any cause (median metastasis-free estimate, 14.7 years), compared with 91 out of 211 (43.1%) in the observation group (median metastasis-free estimate, 13.2 years) (hazard ratio [HR] 0.75; 95% CI [0.55 - 1.02]; p=0.06). Neither were there significant between-group differences for overall survival (71 deaths, median survival of 14.7 years for radiotherapy versus 83 deaths, median survival of 13.8 years for observation; hazard ratio [HR] 0.80; 95% CI [0.58 - 1.09]; p=0.16). There were, however, significant reductions in PSA relapse

(median PSA relapse–free survival, 10.3 years for radiotherapy versus 3.1 years for observation; hazard ratio [HR] 0.43; 95% CI [0.31 - 0.58]; p<0.001) and disease recurrence (defined as any evidence of measurable or evaluable disease e.g. bone lesions) in the adjuvant radiotherapy group (median recurrence-free survival, 13.8 years for radiotherapy versus 9.9 years for observation; hazard ratio [HR] 0.62; 95% CI [0.46 - 0.82]; p=0.001). Ten per cent of patients in the radiotherapy group had received hormonal therapy by five years compared with 21% in the observation group (hazard ratio [HR] 0.45; 95% CI [0.29 – 0.68' p<0.001). Post-operative complications were more common in the adjuvant radiotherapy group than the observation group (23.8% versus 11.9%; relative risk, 2.0; 95% CI [1.3 – 3.1]; p=0.002), including rectal complications (3.3% versus 0%; p=0.02), urethral strictures (17.8% versus 9.5%; relative risk, 1.9; 95% CI [1.1 – 3.1]; p=0.02), and total urinary incontinence (6.5% versus 2.8%; relative risk, 2.3; 95% CI [0.9 – 5.9]; p=0.11).

Longer-term results were subsequently published (47), with median follow-up 12.7 years for the radiation arm (range 11.4 to 15.1 years) and 12.5 years for the observation arm (range 11.1 to 14.0 years). At 12 years follow-up 114/211 observation patients (54%) (median metastasis-free survival 12.9 years) had died or had metastatic disease compared with 93/214 irradiated patients (43%) (median metastasis-free survival 14.7 years). The hazard ratio [HR] for metastasis-free survival with adjuvant radiotherapy was 0.71 (95% CI [0.54 - 0.94; p=0.016). At 12 year follow-up overall survival was also significantly improved in the adjuvant radiotherapy arm (hazard radio [HR] 0.72; 95% CI [0.55 - 0.96]; p=0.023). Longer-term rates of post-operative complications were not reported.

Arbeitsgemeinschaft Radiologische Onkologie (ARO) und Urologische Onkologie of the German Cancer Society (ARO 96-02/AUO AP 09/95) Trial

ARO 96-02/AUO AP 09/95 (44) was a German multi-centre phase III

randomised controlled trial conducted between 1997 and 2004 across 22 institutions. Eligible men, aged less than 76 years, with histologically proven adenocarcinoma of the prostate, with a pathological stage pT3-4 N0 and positive or negative surgical margins were randomly assigned to: 1. immediate post-operative radiotherapy (three-dimensional conformal radiotherapy with 60 Gy delivered in 30 fractions) within six to 12 weeks following surgery (n=194); or 2. wait-and-see (n=194). An undetectable post-operative PSA was defined as less than 0.1 ng/ml. PSA progression for patients with previously undetectable PSA was stated after two consecutive determinations with increasing PSA values. The primary end point was biochemical progression-free survival. After exclusion of patients with progressive disease (those who did not achieve an undetectable PSA or who commenced hormonal treatment), 114 patients had adjuvant radiotherapy and 159 patients were observed under a wait-and-see policy. The overall median follow-up period was 53.7 months (radiotherapy group, range, 5.3 to 108.8 months; wait-and-see group, range, 1.3 to 102.5 months). At 5 years follow-up, there was significant improvement in biochemical progression-free survival in patients with undetectable PSA after radical prostatectomy in the adjuvant radiotherapy group (72%; 95% CI [65% - 81%] versus 54%; 95% CI [45% - 63%]; hazard ratio [HR] 0.53; 95% CI [0.37 - 0.79]; p=0.0015). The cumulative rate of grade 1 adverse effects for bladder and rectum was 21.9% in the radiotherapy group and 3.7% in the wait-and-see group (p<0.0001). There were three events for grade 2 genitourinary adverse effects (2%) and two grade 2 gastrointestinal adverse effects in the radiotherapy group compared with none in the wait-and-see group. There was only one event of grade 3 bladder toxicity in the radiotherapy group (0.3%) and no grade 4 events were recorded.

Subsequent analyses were conducted to determine the efficacy of adjuvant radiotherapy at 10-year follow-up with the primary end point of progression-

free survival. (46) Progression was defined as biochemical recurrence, clinical recurrence or death. Median follow-up was 111.3 months for the radiotherapy group (range, 2.3 – 167.8 months) and 112.2 months for the wait-and-see group (range, 1.3 – 161.4 months). Progression-free survival was significantly better in the irradiated group; Kaplan-Meier estimates were 56% in the radiotherapy group versus 35% in the wait-and-see group (hazard ratio [HR] 0.51; 95% CI [0.37 – 0.70]; P<0.0001). The study was underpowered to assess metastasis-free survival or overall survival as end points.

Table 1.3: Evidence from randomised controlled trials for the efficacy of adjuvant radiotherapy (ART) post radical prostatectomy (RP)

RCT	Biochemical Progression Free Survival		Local Recurrence		Clinical Progression Free Survival		Overall Survival	
	RP + ART	RP only	RP + ART	RP only	RP + ART	RP only	RP + ART	RP only
EORTC[38,41]	61%	38%	8.4%	17.3%*	70.3%*	64.8%	76.9%^	80.7%^
SWOG[39,43]	65%	36%	8%	22%	70%	49%	74%	66%
ARO[40,42]	61%	40%	NR	NR	NR	NR	NR	NR

Follow-up time periods: 10-years for all EORTC data; 10 years for all SWOG data except overall survival which was at 12-years; 5-years for all ARO data.
NR = Not reported RP = Radical Prostatectomy *Result was borderline significant ^Not statistically significant, p=0.05

There has been some criticism of these trials, most notably the lack of a well-defined salvage radiotherapy arm which meant many patients in the wait-and-see groups did not ever receive salvage radiotherapy or if given it was delivered with PSA values >1.2ng/ml rather than at low PSA recurrence such as 0.2ng/ml which is the current trigger for salvage radiotherapy. Consequently, in about 40% of cases there was clinically palpable, biopsy-proven, or radiographically evident local failure increasing the risk of concurrent micrometastatic disease and making further local therapy potentially futile.(49) This means it is not possible, from the results of these trials, to make a direct comparison between the efficacies of immediate adjuvant radiotherapy over early salvage radiotherapy at the first sign of a PSA recurrence. It has also been argued that ARO 96-02/AUO AP 09/95, which

exclusively included patients who achieved an undetectable PSA after radical prostatectomy, to prospectively test whether they also benefit from immediate post-surgical radiotherapy, is the only truly adjuvant trial among the three.(46)

Nonetheless, on the basis of the cumulative evidence from these trials, several international clinical practice guidelines (50-54) were published between 2010 and 2013 with a recommendation that men with extracapsular extension, seminal vesicle invasion or positive surgical margins should be offered adjuvant radiotherapy after radical prostatectomy.

Specifically, this thesis is related to a Grade B recommendation in the 2010 *Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer* produced by the Australian Cancer Network (52) that 'patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery' (p37). This recommendation is echoed in the more recently published 2013 American Urological Association Guideline, *Adjuvant and Salvage Radiotherapy after Prostatectomy*, which states 'Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy (Standard; Evidence Strength: Grade A)' (p1).(51)

1.1.6 Current post-operative patterns of care

A number of patterns of care studies demonstrate historically low rates of utilisation of adjuvant radiation in patients with adverse pathological features post-prostatectomy. These studies consistently report only approximately 10-20% of eligible patients receive treatment in Australia (19, 20, 55, 56), Canada (57, 58) and the United States (59-62) and rates of adjuvant radiotherapy did not increase following publication of randomised controlled trial data. For example, in NSW, Australia's most populous state with 7.4 million inhabitants,

less than 10% of men diagnosed with locally advanced prostate cancer between 2000 and 2002 received adjuvant radiotherapy within the recommended timeframe.(20) This figure is consistent with more recent Victorian Cancer Registry Data including men diagnosed with prostate cancer between August 2008 and February 2011 of whom only 8% with high-risk clinically localised disease received external beam radiotherapy following radical prostatectomy.(19) Other analyses of the same Registry data (56) found that 9.4% of men with at least one adverse pathologic feature (any of positive surgical margin, extracapsular extension, or seminal vesicle invasion) and no evidence of lymph node metastases received adjuvant radiotherapy. Further, a retrospective analysis of data from the US National Cancer Data Base indicates declining use of radiotherapy for adverse features after radical prostatectomy. That study, including 97,270 patients diagnosed with prostate cancer between 2005 and 2011, found receipt of postoperative radiotherapy significantly decreased from 9.1% to 7.3% ($p < 0.001$).(63) These figures identify a significant gap between evidence-based guideline recommended care and actual clinical practice.

1.1.7 How to address the evidence-practice gap?

This type of disconnect between research evidence and clinical practice is not unique (64), and remains one of the most persistent problems in providing high-quality healthcare.(65) Clinical practice guidelines such as the one that is the focus of this thesis have been extensively developed as a means to disseminate best practice and ensure clinical decision-making is informed by recent, credible research evidence, thereby improving healthcare processes and outcomes. However, timely and effective uptake of evidence-based guideline recommendations into clinical practice is haphazard (66), and it is often difficult to make changes across the health system even when there is compelling evidence.(67) The difficulty in achieving large scale adoption of proven innovations and recommended care (as well as discontinuing

ineffective or harmful practices) has been characterised as a 'translation block'.(68-71)

A number of steps are necessary to translate innovations from basic research into routine health service delivery. Cancer Institute NSW classifies the stages of translational research as follows:

- T1 - *Translation to humans*: developing treatments and interventions from basic research through observational studies, case studies, and Phase 1 and II clinical trials
- T2 - *Translation to patients*: testing the efficacy and effectiveness of treatments and interventions and translation of new clinical science and knowledge into routine clinical practice and health decision making through observational studies, evidence synthesis and guidelines development and Phase III clinical trials
- T3 - *Translation to practice*: dissemination and implementation for system-wide change by embedding evidence-based guidelines into health practice through dissemination research, implementation research, diffusion research, and Phase IV clinical trials

This thesis relates to a National Health and Medical Research Council (NHMRC) Partnership Project co-funded by the Prostate Cancer Foundation of Australia (PCFA) titled *'Improving evidence-based care for locally advanced prostate cancer: A randomised phased trial of clinical guideline implementation through a clinical network'* (working title Clinician-Led Improvement in Cancer Care (CLICC)) an implementation research study that sits within the T3 phase of the translation spectrum.

Established research indicates that successful implementation of evidence-based care depends critically on the extent to which strategies address prospectively identified barriers, through theoretical frameworks of behaviour

change.(72, 73) Therefore, a conceptual program logic model was developed to underpin the design of a multi-faceted guideline implementation strategy based on the PRECEDE-PROCEED model, which comprises eight steps for the planning, implementation and evaluation of behaviour change interventions.(74, 75) The four phases of PRECEDE represent the pre-intervention diagnostic planning process, encompassing *P*redisposing, *R*einforcing, and *E*nabling Constructs in *E*ducational/*E*nvironmental *D*iagnosis and *E*valuation. The additional four phases of PROCEED guide the implementation and evaluation of intervention programs designed through the PRECEDE process through *P*olicy, *R*egulatory, and *O*rganizational *C*onstructs in *E*ducational and *E*nvironmental *D*evelopment. Taken as a whole, PRECEDE-PROCEED relates interpersonal factors and system characteristics into one model to inform change in practice and enables the integration of context-specific barriers into 'predisposing factors' (e.g. knowledge and attitudes of the target group); 'reinforcing factors' (e.g. opinions and behaviour of peers); and 'enabling factors' (e.g. capacity of the system and hospital processes). PRECEDE-PROCEED was the most widely used theory in a systematic review of the use of theory in the design of guideline dissemination and implementation strategies, and interpretation of the results of rigorous evaluations.(76) Further systematic reviews have shown that trials that intervene to alter these three factors are the most successful.(77) Details of how PRECEDE-PROCEED was used to develop the conceptual program logic model for this study and the intervention mapping process are provided in Chapter 4.

1.1.8 The landscape of intervention strategies for clinician behavioural change

Recommendations from clinical guidelines are more likely to become embedded within practice when they: are initiated and led by local clinical leaders; are tailored to the local context; and engage clinicians in the design of

the implementation strategy.(64, 66, 77-79) Richard Grol (80) argues that to effectively implement evidence-based practice, research has to change so that it develops through collaborations between clinicians, researchers, patients, policy makers, and quality improvement experts.

Specifically, the growing body of evidence suggests several core implementation strategies are effective in bringing about system-wide and sustained change (64, 76, 79, 81):

1. Local clinical champions/opinion leaders supporting change within their practices and settings
2. Systems, structural, and organisational support for system-wide changes to enable implementation strategies to be rolled out and scaled up (e.g. legislation, resources, mechanisms for communication and collaboration between health sectors)
3. Ongoing monitoring, evaluation, and feedback of changes as they are implemented

There is further evidence from a number of Cochrane reviews and overviews or syntheses of systematic reviews supporting these intervention strategies as the most effective in terms of impact on professional practice and healthcare outcomes:

Local clinical champions/opinion leaders supporting change within their practices and settings

A review of 18 randomised controlled trials investigating the effectiveness of opinion leaders (either as a single intervention or as part of multiple interventions) to disseminate evidence-based practice using objective measures of professional performance and/or health outcomes reported a 12% absolute increase in compliance with best evidence overall. Further, when local opinion leaders were utilised within the context of a

multidisciplinary team, thereby improving collaboration between health sectors, compliance increased by 18%.(82)

A synthesis of 33 systematic reviews, reporting 714 primary studies, examined the effectiveness of several clinical guideline implementation strategies. The authors concluded that there was variable evidence of moderate quality, for the effectiveness of local opinion leaders in the promotion of behaviour change and guideline adherence. Improvements of up to 39% were reported, with a median adjusted risk difference of 0.10, representing 10% greater compliance in intervention groups. (83)

Systems, structural, and organisational support for system-wide changes to enable implementation strategies to be rolled out and scaled up

A number of systems, structural or organisational interventions have been the subject of systematic review including: point of care reminders (84) and decision support systems (83); and interactive educational meetings (85) or educational outreach as mechanisms for improved communication.(83)

The effects of on-screen, point of care computer reminders were assessed in a review of 28 randomised or quasi-randomised studies reporting at least one outcome involving a clinical endpoint or adherence to a recommended process of care.(84) Point of care computer reminders generally achieved small to modest improvements in provider behaviour: median improvement in process adherence of 4.2% (interquartile range (IQR): 0.8% to 18.8%) across all reported process outcomes; 3.3% (IQR: 0.5% to 10.6%) for medication ordering; 3.8% (IQR: 0.5% to 6.6%) for vaccinations; and 3.8% (IQR: 0.4% to 16.3%) for test ordering.

In the synthesis of systematic reviews mentioned previously (83), the use of reminder and clinical support systems consistently resulted in significant practice improvements in process or compliance of up to 71.8%. Interactive

educational sessions (effects ranging from 1% to 39%), and educational outreach or academic detailing (up to 68% relative improvement in process or compliance), which actively engaged clinicians, were generally effective while didactic education and passive dissemination strategies were largely ineffective.

The effects of continuing medical education meetings and workshops on professional practice and health care outcomes were further evaluated in a review of 81 trials involving more than 11,000 health professionals.(85) Educational meetings alone or combined with other interventions resulted in a 6% median adjusted improvement in compliance (interquartile range 2.9% to 15.3%). Univariate meta-regression indicated didactic (risk difference 6.9) or interactive (risk difference 3.0) meetings alone were less effective than mixed interactive and didactic meetings (median adjusted risk difference 13.6). Educational meetings were less effective for more complex compared with less complex behaviours (adjusted risk difference -0.3). Conversely, they appeared to be more effective for more versus less serious outcomes (risk difference 2.9).

Ongoing monitoring, evaluation, and feedback of changes as they are implemented

The provision of performance feedback as a strategy to improve professional practice was assessed in a review of 140 primary studies.(86) Across 49 included studies featuring dichotomous outcomes, the weighted median adjusted risk difference was a 4.3% (interquartile range (IQR) 0.5% to 16%) absolute increase in healthcare professionals' compliance with desired practice. Multivariable meta-regression suggested that feedback may be more effective when baseline performance is low, the source is a supervisor or colleague, it is provided more than once, it is delivered in both verbal and written formats, and when it includes both explicit targets and an action plan.

The synthesis of systematic reviews reported moderate evidence for the effectiveness of audit and feedback on process or compliance measures with effect sizes ranging from a 17% decline, through no effect, to a 63% improvement. More consistent effects were seen for cost outcomes with decreases of up to 37% following guideline implementation coupled with audit and feedback, typically achieved through a reduction in the number of diagnostic tests being performed, with no reported detrimental patient outcomes.(83)

Multifaceted versus single intervention strategies

The synthesis of systematic review findings additionally reported that multifaceted intervention strategies had greater evidence of effects than single intervention strategies with significant improvements in guideline compliance and behavioural change (reported effects up to 60%).(83) This is consistent with an earlier overview of systematic reviews of interventions to change provider behaviour which concluded that while single interventions are of variable effectiveness, with none clearly more effective than another, multifaceted interventions based on assessment of potential barriers to change are more likely to be effective.(87) Another overview of systematic reviews of implementation of research into practice similarly concluded that while opinion leaders, systems, structural and organisational support, and audit and feedback can achieve small to moderate impacts in isolation, they are far more effective when combined in more complex interventions that include multiple strategies, which consider both context and process.(88)

It should be noted however, that the most recent overview of 25 systematic reviews of moderate or strong methodological quality directly comparing the effectiveness of multifaceted interventions with single interventions in changing health care professionals behaviour (89) reported mixed results and concluded that, based on three levels of analyses, there was no compelling

evidence multicomponent interventions were more effective. Direct statistical analyses of effect size/dose-response in three reviews found no significant association between the number of intervention components and the effect size. Four out of eight reviews reporting direct (non-statistical) comparisons of the effectiveness of multifaceted compared with single interventions found multifaceted interventions to be generally effective compared with single interventions, while the remaining four found that multifaceted interventions had either mixed effects or were generally ineffective compared with single interventions. Twenty-three reviews indirectly compared the effectiveness of multifaceted compared to single interventions (by comparing multifaceted interventions to controls versus single interventions to controls). Fifteen of these showed similar effectiveness for multifaceted and single interventions when compared to controls. Of the remaining eight reviews, six found multifaceted interventions had mixed effectiveness while single interventions were reported to be generally effective. The authors conclude that 'a single or less complex multifaceted intervention that is tailored to overcome the barriers and enhance the enablers of the behaviour that needs to be changed may be appropriate'.

Intervention strategies for clinician behavioural change in the cancer context

It is widely accepted that context is fundamental in the design and implementation of quality improvement behavioural change interventions.(90, 91) It is therefore, necessary to consider whether cancer specialists are a discrete clinical group that might require a different approach given that there are some evidence-based practices, such as post-prostatectomy referral to radiation oncology for consideration of adjuvant radiotherapy, over which they solely have control.

A review of 34 systematic reviews, published between 2005 and 2010, considered the evidence for interventions tested in cancer-specific

environments.(92) Clinician focused interventions included: education; audit and feedback; information technology/information management/informatics; clinical decisions support systems, computerised order entry and reminders; local opinion leaders; tailored interventions; clinical pathways; guidelines; and discharge planning. The reviewers concluded that evidence of effectiveness for improvement in professional practice and clinical outcomes was most promising for educational outreach (5% median improvement on dichotomous outcomes, IQR 1% to 20%; 23% median improvement on continuous outcomes, IQR 0% to 617%); and, audit and feedback interventions (4% median improvement on dichotomous outcomes, IQR -16% to 70%; 11.9% median improvement on continuous outcomes, IQR 10.3% to 67.5%). Local opinion leaders were most effective for reduction in clinician non-compliance (median decrease in rates of non-compliance 7%; IQR -6% to 12%). Tailored interventions also improved some clinical outcomes with 8/14 studies demonstrating a benefit of tailoring (pooled odds ratio 1.54; 95% CI [1.16, 2.01]). Educational outreach and audit and feedback were both more effective as part of multifaceted interventions than when used as single interventions. Further audit and feedback was more effective when baseline compliance was low and when delivered more frequently.

Another systematic review of quality improvement interventions directed at cancer specialists (93) included 12 studies, including three randomised controlled trials (RCTs) conducted in response to concerns about quality of care in common cancers including breast, colon, rectum, ovarian and prostate. The majority of interventions included more than one quality improvement strategy, most commonly utilising a combination local opinion leaders, education and an audit and feedback component that varied between feedback at the clinician level and at the group level. None of the three RCTs demonstrated a consistent benefit of the intervention strategies tested. A combination of local opinion leaders, educational meetings,

observational/learning practice and individual level audit and feedback had no effect on outcomes for patients with rectal cancer. Similarly academic detailing led by local opinion leaders, coupled with educational meetings and printed materials had no impact on outcomes for stage II colon cancer. One RCT did, however, report that an educational outreach program involving a meeting with an expert was more effective than group level feedback for adherence to antiemetic guidelines across some but not all chemotherapy categories. Uncontrolled before and after studies tended to report more benefits of the tested intervention strategies. Across all types of study process measures were more commonly reported, with larger effect sizes (mean risk difference 17.3%; -1.7% to 48.6%), than outcome measures (mean risk difference 4.5%; 1.4% to 9%).

Variability in quality, reporting and outcomes of the primary evidence was common across systematic reviews, with limited descriptions of different intervention components that would enable replication by other cancer specialists. The few randomised controlled trials are outweighed by studies of lower quality observational design resulting in the potential for uncontrolled confounding, such that it is not possible to draw definitive conclusions about the most effective clinician-focused interventions. Further most interventions included multiple components but few assessed their effectiveness separately. Therefore, there is a need for more rigorous study design, execution and reporting of quality improvement intervention studies to increase knowledge about the most effective strategies for the uptake of evidence-based practice in the cancer context.

1.1.9 Organisation of health care services in New South Wales (NSW), Australia

Given the importance of context, in order to determine which of the multitude of potential behaviour change intervention strategies might be the

most effective for the current purpose, it is necessary to consider the organisation of health- and cancer-care services in NSW.

Overall coordination of the public health system within Australia is the responsibility of the Commonwealth in combination with the state and territory governments. The Commonwealth focuses on public health, research and national information management while the states and territories are largely responsible for the delivery of public sector health services and the regulation of health workers in the public and private sectors.(94)

NSW Health

NSW Health is comprised of the Ministry of Health (the Ministry), statutory health corporations (the Pillars), Local Health Districts (LHDs), and affiliated health organisations.(95)

The Ministry focuses on policy, funding and performance across the health system and has regulatory functions, public health functions (disease surveillance, control and prevention) and system management functions (state-wide planning, purchasing and performance monitoring of hospitals and health services).

The five pillars, namely, the: Agency for Clinical Innovation (ACI); Bureau of Health Information (BHI); Cancer Institute NSW; Clinical Excellence Commission (CEC); and Health Education and Training Institute (HETI) provide support to the LHDs. The five pillars cover the following functions:

- Agency for Clinical Innovation (ACI) - responsibility for state-wide clinician engagement through clinical service networks with responsibility for clinical redesign, and development and implementation models of care to make the public health system more efficient, better performing and sustainable over the longer term.

- Bureau of Health Information (BHI) - responsibility for reporting of health care quality information to the community, healthcare professionals and policymakers.

- Cancer Institute NSW – responsibility for cancer control, including reducing the incidence of cancer, increasing survival from cancer and improving the quality of life for people with cancer and their carers.

- Clinical Excellence Commission (CEC) - responsibility for system quality and safety, including critical response management for adverse clinical incidents and clinical risk management, and providing leadership in clinical governance with LHDs.

- Health Education and Training Institute (HETI) – responsibility for development and training for clinicians and health administrators.

There are 15 LHDs in NSW with responsibility and accountability for governing hospital and health service delivery for their local population. These LHDs cover a wide range of settings, from primary care posts in the remote outback to metropolitan tertiary health centres. There are also two specialist networks focusing on children's and paediatric services, justice health and forensic mental health. A third specialist network covers public health services provided by St Vincent's Health, a Catholic not-for-profit health and aged care provider.

1.1.10 Cancer care in NSW

Multidisciplinary care, involving a team of surgeons, radiation oncologists, medical oncologists, nurses, pathologists, radiologists and allied health professionals, is widely accepted as best practice in cancer care. A multidisciplinary approach can help to refine treatment recommendations, coordinate care and achieve optimal cancer outcomes for people with cancer. The establishment of multidisciplinary teams (MDTs) has been advocated for

widely internationally (96) and in Australia (97, 98), including the introduction of two Australian Commonwealth Government Medical Benefit Scheme (MBS) payment items in 2006 (99) enabling Medicare rebate claims to encourage and support clinicians participating in cancer case conferences. In a review of published literature, (100) MDT discussion was demonstrated to have a significant impact on clinical decision-making for various cancer types.
The NSW government cancer control agency, the Cancer Institute NSW, works with LHDs within the NSW Health system to assist them in providing cancer services. As part of this role the Cancer Institute NSW has supported the development MDTs across NSW through a number of different grant, project and evaluation activities.(101)

1.1.11 A clinical networks approach to implementation

Networks of clinical experts are increasingly being implemented as a strategy to improve health care processes and outcomes and achieve change in the health system. Formalised managed clinical networks have been established in the United States, United Kingdom and other parts of Europe, Australia and Canada with significant financial investment.(102-111) These clinical networks of volunteer health professionals provide a framework for doctors, nurses, allied health professionals, managers, and consumers to collaborate across regional and service boundaries to drive improvements in service delivery and care outcomes through innovation in clinical practice.

While there are numerous different models of clinical network from fully integrated service delivery systems, such as Kaiser Permanente or the Veterans Health Administration in the United States, to informal communities of practice, all have the shared aim of engaging clinicians in the implementation of quality improvement initiatives.(103, 104, 106, 109, 112) These clinical networks can uniquely provide 'bottom up' views on the best ways of tackling complex healthcare problems within the local context

coupled with the strategic and operational 'top down' support necessary to facilitate and champion changes in practice at the clinical interface.(113, 114)

Clinical networks embody, or have the potential to enable, the core features of successful implementation strategies and therefore are a mechanism for health system change and increasing the uptake of evidence-based care for three reasons:

1. Clinical networks include clinical leaders who can design and champion change to improve care within their practices and influence wider culture change within their healthcare settings
2. Clinical networks are a 'ready-made' organisational structure through which innovations may be promulgated and accelerated by clinicians
3. Clinical networks provide a structure to monitor and evaluate changes as they are implemented to answer questions about effectiveness and the success of implementation strategies

There are data suggestive of networks being effective in improving the quality of patient care (103, 106, 108, 115) and there is evidence from 'before and after' controlled studies that when clinical practice guidelines are implemented through clinical networks there are improvements in compliance with guideline recommendations.(116, 117) However, much of the evidence for the effectiveness of clinical networks is anecdotal and the relatively few quantitative studies are limited by lack of a rigorous experimental design (a systematic review of the clinical networks literature is provided in Chapter 2). Subsequently there remains a need to more formally test the efficacy of a network approach to health care quality improvement.

The Agency for Clinical Innovation (ACI) in their capacity as the agency responsible for clinician engagement has established a coordinated program of 30 managed clinical networks, institutes and taskforces in NSW. The

networks are formed around a diverse range of specialty health service areas and serve a population of 7.5 million people.(118) State-funded, they have a system-wide focus where members identify and advocate for models of service delivery (e.g. outreach services, new equipment, using technology to improve diagnosis) and quality improvement initiatives (e.g. guideline development and dissemination, training and education for health professionals).(119-122)

The implementation trial that is the focus of this thesis was funded to test a range of strategies to increase the uptake of a clinical practice guideline recommendation into routine care for patients with prostate cancer in hospitals within the ACI Urology Network, with in-kind support provided by the Network. The Urology Network was established to improve equity of access, promote high quality care and improve outcomes for NSW patients with urological conditions. Led by an executive committee, which includes doctors, nurses, academics, allied health staff and consumers, the network has more than 80 members and includes representatives from the NSW Ministry of Health, local health districts (LHDs), specialty network governed health corporations, Clinical Excellence Commission (CEC) and the Cancer Institute NSW.

Specifically, the study involves nine urological MDTs, linked to the ACI Urology Network, responsible for the treatment of patients with prostate cancer in hospitals spread across eight LHDs. Full details of hospital and patient eligibility criteria are provided in the published study protocol (Chapter 5).

1.2 Scope of thesis

This thesis presents a series of studies conducted within the overarching framework of a stepped-wedge prospective phased randomised controlled trial 'Clinician-Led Improvement in Cancer Care (CLICC)' funded by the

National Health and Medical Research Council (NHMRC) in partnership with the Prostate Cancer Foundation of Australia (PCFA), with in-kind support provided by the NSW Agency for Clinical Innovation (ACI).

This thesis includes those components for which I have had primary conceptual, methodological, analytical and interpretative responsibility, except where explicitly acknowledged in the text, and I am the first author of all publications arising from this work.

1.3 Thesis statement

This thesis addresses the following aims:

(a) To develop and trial a locally tailored, multifaceted implementation strategy that harnesses the NSW Agency for Clinical Innovation (ACI) Urology Clinical Network to increase evidence-based care for men with high-risk prostate cancer following radical prostatectomy in selected NSW hospitals.
(b) To identify reasons why changes in behaviour and outcomes occurred or did not occur in CLICC hospitals and why the implementation strategy did or did not result in increased compliance with guideline recommended care.
(c) To consider how findings could be translated to the implementation of other clinical practice guideline recommendations.

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Chapter 2: The effectiveness of clinical networks in improving quality of care and patient outcomes: a systematic review of quantitative and qualitative studies

Publication arising from this chapter

Brown B, Patel C, McInnes E, Mays N, Young J & Haines M. The effectiveness of clinical networks in improving quality of care and patient outcomes: A systematic review of quantitative and qualitative studies. *BMC Health Services Research.* 2016; 16:360. DOI: 10.1186/s12913-016-1615-z

2.1 Abstract

Background: Reorganisation of healthcare services into networks of clinical experts is increasing as a strategy to promote the uptake of evidence-based practice and to improve patient care. This is reflected in significant financial investment in clinical networks. However, there is still some question as to whether clinical networks are effective vehicles for quality improvement. The aim of this review was to ascertain the effectiveness of clinical networks and identify how successful networks improve quality of care and patient outcomes.

Methods: A systematic search was undertaken in accordance with the PRISMA approach in Medline, Embase, CINAHL and PubMed for relevant papers between 1 January 1996 and 30 September 2014. Articles were included if the primary focus was on clinical networks as defined in Table 2.1. Both quantitative and qualitative studies were included. Established protocols were used separately to examine and assess the evidence from quantitative and qualitative primary studies, including risk of bias, then synthesise and integrate findings.

Results: A total of 22 eligible studies (9 quantitative; 13 qualitative) were included. Of the quantitative studies, seven focused on improving quality of

care and two focused on improving patient outcomes. Quantitative studies were limited by a lack of rigorous experimental design. The existing evidence indicates that clinical networks may be effective vehicles for quality improvement in service delivery and patient outcomes across a range of clinical disciplines. However, there was variability in the networks' ability to make meaningful network- or system-wide change across more complex measures for processes that required intensive professional education or more comprehensive redesign of the care pathway. Findings from quantitative studies were supplemented with insights from qualitative studies to explain why some networks were more successful than others. Specifically, networks that had a positive impact on quality of care and patients outcomes had adequate resources, credible leadership and efficient management coupled with effective communication strategies and collaborative trusting relationships.

Conclusions: There is evidence that clinical networks may improve the delivery of healthcare though there are few high quality quantitative studies of their effectiveness. Our findings can provide policymakers with some insight into how to successfully plan and implement clinical networks by ensuring strong clinical leadership, an inclusive organisational culture, adequate resourcing and localised decision-making authority.

2.2 Background

Networks of clinical experts are increasingly being established as a strategy to promote the uptake of evidence-based practice and drive improvements in standards of patient care. These clinical networks are argued to represent a shift away from hierarchical, bureaucratic organisation of healthcare services to one which engages clinicians more in the development of improved models of care, integration of services and multidisciplinary collaboration.[1, 2] Broadly, clinical networks provide a structure for clinicians to work more

closely across institutional and professional boundaries, and allow for continuous working relationships and flow of knowledge about best practice between individuals and organisations, thereby improving the quality of and access to care for patients, including those who require coordination of care across a range of settings. With this shared aim, clinical networks have been established in the United Kingdom (UK) [3-5], other parts of Europe [6, 7], Australia [1, 8-10], Canada [11], and the United States (US).[12]

The use of networks to reduce fragmentation, and increase efficient and seamless integration of service delivery is well established in other public services.[13, 14] There has already been significant financial investment. For example, in the UK the NHS England allocated £42 million in the 2013/2014 financial year (approximately $27.7m USD) to the establishment of strategic clinical networks to strengthen the existing less formalised clinical networks.[15, 16] In Australia, $58 million AUD (approximately $48.7m USD) was allocated in the 2010/11 Budget for the establishment of Lead Clinicians' Groups in Local Hospital Networks.[17] However, the question remains: does the planning and delivery of services through clinical networks improve quality of care?

The term "clinical network" has been used to describe many variants of networks [2, 18] (see Table 2.1). For this review, we excluded studies of fully integrated service delivery systems because they are very contextually specific with overarching administrative structures through which networked services are delivered (e.g. Kaiser Permanente or the Veterans' Health Administration in the US). We also excluded 'communities of practice' because there has been a systematic review published which assessed the evidence of whether they improved the uptake of best practices and mentoring of new practitioners in the health sector.[19] That review identified 13 primary studies, none of which met the eligibility criteria for quantitative analysis to

evaluate effectiveness. Consequently, the effectiveness of communities of practice in the healthcare sector remains unknown.

Previous systematic reviews [2, 19] of other models of clinical networks were not able to draw conclusions because of limited and poor quality research. This is a fairly common conclusion for reviews of newly established, innovative healthcare structures, processes and systems.[20-22] A large-scale systematic review of clinical networks published in 2004 described models and functions of networks across multiple public service sectors.[2] That review had a broad focus in order to derive implications for management, governance, leadership and policy of networks in health and social care. In relation to healthcare, this review concluded that there was no evidence of how effective networks were in improving patient care. A more recent review focused on the structure of social networks of health professionals concluded, "cohesive and collaborative health professional networks can facilitate the coordination of care and contribute to improving quality and safety of care".[23] As defined in that review, social networks could be considered to share the characteristics of communities of practice, typified by natural structural network features and fluid interactions, rather than the more hierarchical structure of clinical networks and their associated governance arrangements.

The current review focuses on managed and non-managed clinical networks, defined as voluntary clinician groupings that aim to improve clinical care and service delivery using a collegial approach to identify and implement a range of quality improvement strategies [8] (see Table 2.1 for further definitions). The primary aim was to investigate the effectiveness of these clinical networks to improve: a) quality of care (defined as increased uptake of evidence-based practice); and b) patient outcomes (based on objective outcome measures). Sub-aims of the review were to: i) assess the quality of the methods used in each of the studies; and ii) identify how clinical networks achieved their

Table 2.1: Typology of clinical networks

	Community of practice	Information network	Clinical network (non-managed)	Clinical network (managed)	Integrated service delivery
Definition	Groups of people who share a concern or passion for something they do and learn how to do it better as they interact regularly. Communities of practice are characterised by voluntary and transitory memberships without a hierarchical structure.	Soft networks are largely referral systems whereby members list themselves in an electronic directory to receive information and resources.	Groups of voluntary experts who work together on common concerns to develop solutions that involve transcending traditional boundaries. These networks are characterised by a hierarchical structure with governance arrangements. These tend to be organised by clinical discipline.	Groups of clinicians who deliver services across boundaries between healthcare professions and the different sectors of the health system. These tend to be organised by clinical discipline.	Networks made up of healthcare organisations as well as individuals within them with an overarching administrative structure with a focus on integration and coordination of clinical services. These tend to be organised by geographical region.
Membership	Individuals	Individuals	Individuals	Individuals and healthcare organisations	Healthcare organisations
	Flexible and unrestricted	Flexible and unrestricted	Flexible and voluntary	Formal	Contractual arrangements about service delivery
Governance and management	Non-hierarchical and informal	Non-hierarchical and informal	Semi-hierarchical	Hierarchical	Hierarchical
	"Bottom up"	"Bottom up"	"Bottom up"	"Mix of bottom up and top down"	"Top down"
Overlap with other typology	Enclave*	Enclave	Individualistic	Individualistic	Hierarchical

	Community of practice	Information network	Clinical network (non-managed)	Clinical network (managed)	Integrated service delivery
Example	Canadian Health Services Research Foundation - The Executive Training for Research Application (EXTRA) program alumni community of practice, Canada http://www.cfhi-fcass.ca/sf-docs/default-source/extra/cfhi-extra_brochure-2015-e.pdf	NHS UK – CHAIN: Contact, Help, Advice and Information Network, UK http://chain.ulcc.ac.uk/chain/index.html	NSW Agency for Clinical Innovation's networks, Australia http://www.aci.health.nsw.gov.au/	NHS National Services Division Scotland Managed Clinical Networks, UK http://www.nsd.scot.nhs.uk/%5C%5C/services/nmcn/index.html	Veterans Integrated Service Networks, Veterans' Health Administration, US http://www2.va.gov/directory/guide/division_flsh.asp?dnum=1
Included in this review	**NOT INCLUDED**	**NOT INCLUDED**	**INCLUDED**	**INCLUDED**	**NOT INCLUDED**

*Enclave is defined where members are individuals rather than organisations whose participation is voluntary and often transient

impacts. Evidence of impact on quality of care and patient outcomes from quantitative studies was supplemented with findings of qualitative research to aid interpretation of results and facilitate understanding of the process of network implementation, network structure, the ways in which networks have been used to improve knowledge sharing and coordination of services, and key features necessary for success. This is the first systematic review that has explicitly focused on the effectiveness of clinical networks to improve quality of care and patient outcomes.

2.3 Methods

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach to ensure the transparent and complete reporting of the searching, systematic screening and independent quality assessment.[24] The concepts and overarching methods for systematic reviews [25] have been adapted for a mixed methods systematic review using the framework outlined by Thomas and colleagues [26, 27] which allows independent syntheses of quantitative and qualitative studies followed by integration of findings. Given the lack of high quality evidence from randomised controlled trials, we adopted a pragmatic approach examining all available evidence, from primary observational studies, and assessing study quality within this lower level of the evidence hierarchy using established protocols. A detailed description of the search can be found in Appendix I. Articles were eligible for inclusion in this review if:

i) The primary focus of the paper was on clinical networks in any healthcare setting (e.g. acute, primary, community, vertical integration)

ii) The networks corresponded with the category of network that would be included - that is a managed or non-managed clinical network

iii) The paper reported an outcome related to improvement of quality of care or patient outcomes (based on objective measures)

Excluded were:

i) Abstracts and titles with the term 'clinical network' that were not referring to actual clinical networks (e.g. clinical network guidelines, simulation studies for proposed networks, protocol papers detailing study plans of networks, information technology or infrastructure networks)
ii) Research networks
iii) Clinical trial networks
iv) Clinical guideline networks
v) Integrated service delivery networks (sometimes called regional networks or networked hospitals, Health Management Organisations and managed care organisations in the United States)
vi) Articles that used clinical networks as vehicles for samples for studies
vii) Articles that were not published in peer review journals (e.g. conference proceedings)

2.4 Search Strategy

Papers were identified in two stages and selected for inclusion using the PRISMA steps (see Figures 2.1 and 2.2). Two researchers (BB, MH) initially searched Medline, Embase and CINAHL for relevant papers between 1996 and 2010. In the second stage of the literature search, two researchers (BB, CP) performed an updated literature search in PubMed and CINAHL for the period covering 1 January 2011 to 30 September 2014. Details on search terms can be found in Appendix I. Full text publications identified through reference lists were screened for eligibility using the screening criteria. The reviewers independently reviewed abstracts and selected full text articles to confirm

whether the publication should be included in the analysis. Discrepancies were resolved through discussion and consensus. After discussion, there was 100% agreement on which articles met the eligibility criteria for inclusion. With 17 articles from the initial search and 5 from the updated search, a total of 9 quantitative and 13 qualitative eligible studies were identified from the search period 1 January 1996 to 30 September 2014.

Figure 2.1: PRISMA Flow Diagram – Initial search 1996-2010

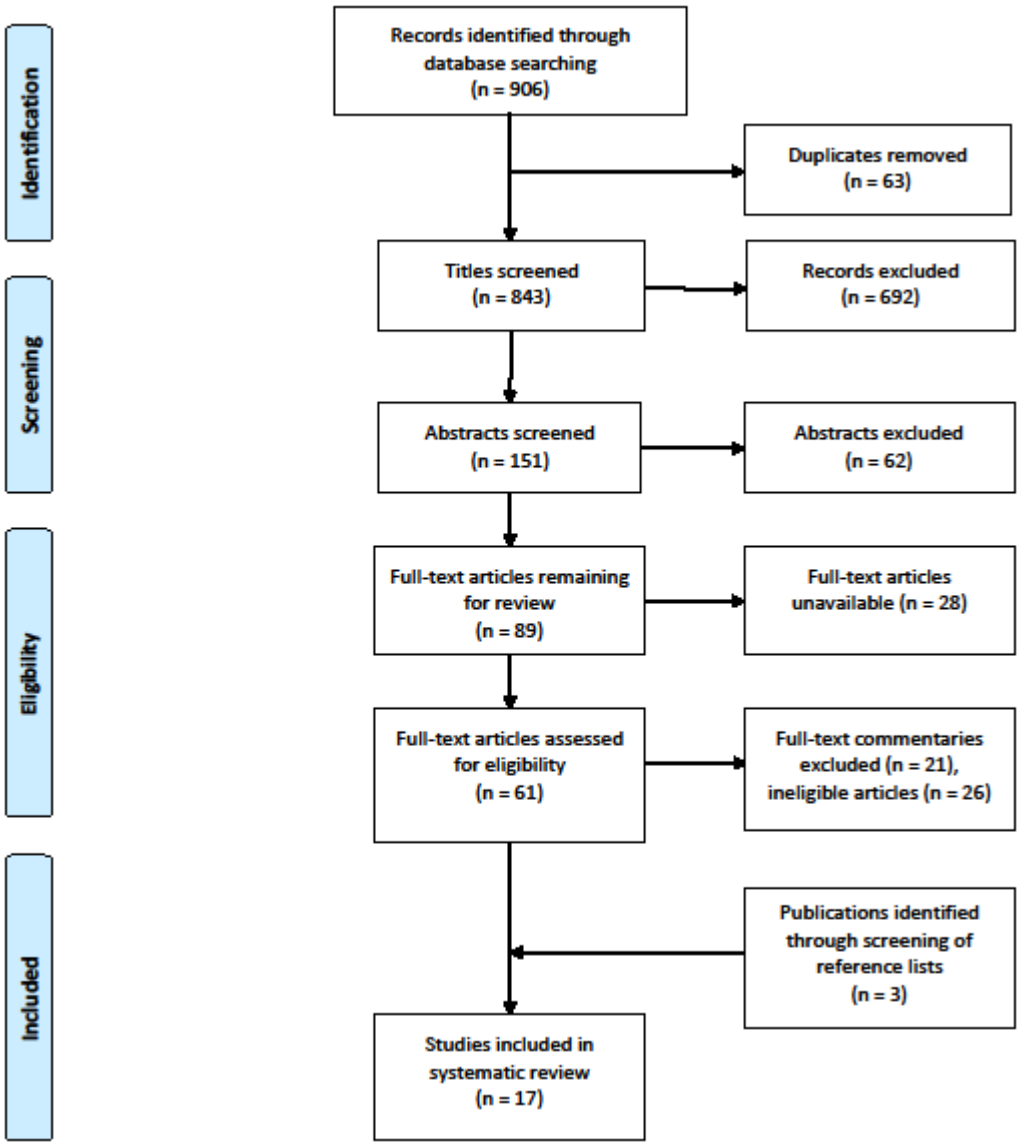
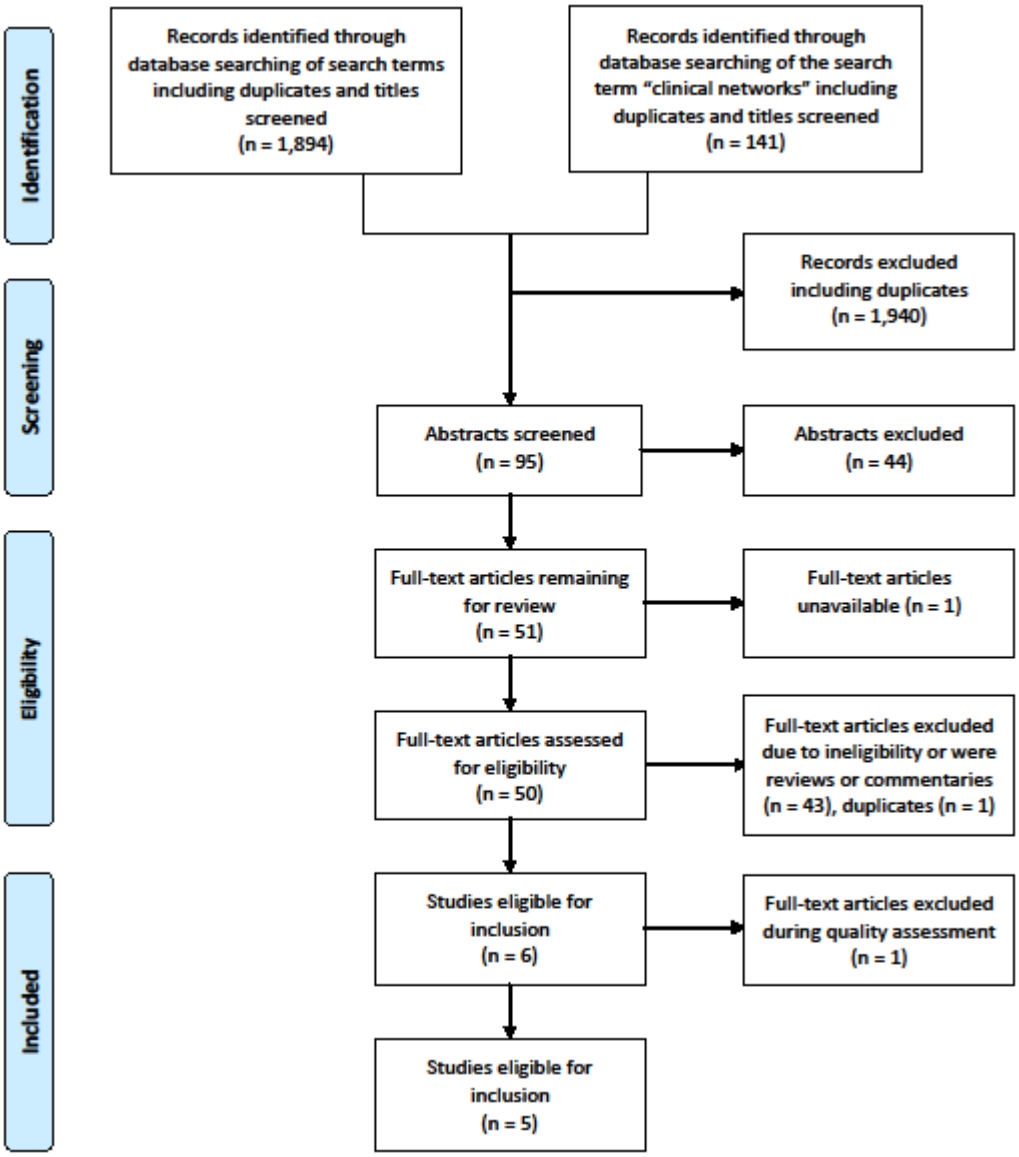


Figure 2.2: PRISMA Flow Diagram – Updated search 2011-September 2014



2.5 Quality and assessment of risk bias

The quality assessments of quantitative and qualitative studies were conducted separately.[25, 28]

Quantitative Studies

The quantitative study designs were assessed on the basis of whether they would meet the study design acceptable for a Cochrane Effective Practice and Organisation of Care Group (EPOC) review with those being: a) patient or cluster randomised control trials; b) non-randomised cluster control trials; c) controlled before and after studies; and d) interrupted time series [29, 30]. Given the lack of high quality study designs found in the included articles, study designs were coded into the followed grades of evidence used previously for a communities of practice review [19]:

1. Experimental
2. Quasi-experimental studies (controlled trials, time series, controlled before and after designs)
3. Observational designs (before and after studies, cross-sectional studies).

The assessment of the quality of the methods and reporting drew on elements of EPOC and the Agency for Healthcare Research and Quality [29, 31]:

- Was the study free from selective outcome reporting? (yes/no/unclear)
- For comparative studies, was the control/comparison group used equivalent to the intervention group? (yes/no) (where appropriate)
- For non-comparative studies, were the cases representative (i.e. all eligible cases over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital, clinic or group, or an appropriate sample of those cases)? [32] (yes/no) (where appropriate)
- Was there a clear description of the exposure or intervention? (yes/no)
- Was the study adequately protected against contamination? (yes/no/unclear) (where appropriate)

- Statistical analysis – were the methods appropriate and was reporting adequate? (yes/no)
- Was there a declaration of funding or sponsorship? (yes/no)
- Was the study free from other risks of bias? (yes/no)

The studies were grouped into three categories on the basis of quality of methods and reporting [33]:

- High quality – design and conduct of study address risk of bias, appropriate measurement of outcomes, appropriate statistical and analytical methods, low drop-out rates, adequate reporting;
- Moderate quality – do not meet all criteria for a rating of good quality but no flaw is likely to cause major bias, some missing information;
- Low quality – significant biases including inappropriate design, conduct, analysis or reporting, large amounts of missing information, discrepancies in reporting.

Qualitative Studies

There is lack of consensus about how to assess risk of bias for qualitative studies [9]. For this review we considered that assessing the validity of the methods and quality of the reporting was the most appropriate approach to take [10, 11]. To do this, we used nine criteria to assess the quality of qualitative studies recently developed by Harden and colleagues [12] and two criteria on the extent to which the 'participant voice' [13] was elucidated using a definition suggested by Mays and Pope [10] (see Box 2).

Arbitrary cut offs were selected as:

- High quality – those meeting 8 or more criteria
- Medium quality – those meeting between 5 and 7 criteria

- Low quality – those meeting fewer than five criteria

Box 2 - Criteria used to assess the quality of the qualitative studies.

Quality of reporting [26]

1. Were the aims and objectives clearly reported?
2. Was there an adequate description of the context in which the research was carried out?
3. Was there an adequate description of the network and the methods by which the sample was identified and recruited?
4. Was there an adequate description of the methods used to collect data?
5. Was there an adequate description of the methods used to analyse data?

Use of strategies to increase reliability and validity [26]

6. Were there attempts to establish the reliability of the data collection tools (for example, by use of interview topic guides)?
7. Were there attempts to establish the validity of the data collection tools (for example, with pilot interviews)?
8. Were there attempts to establish the reliability of the data analysis methods (for example, by use of independent coders)?
9. Were there attempts to establish the validity of data analysis methods (for example, by searching for negative cases)?

Quality of the application of the methods [35]

10. The extent to which qualitative studies are grounded in and reflect study participants' perspective and experiences (as evidenced by the use of supporting quotes)
11. Whether the studies produce also rich or 'thick' descriptions of the investigation and explanatory insights rather than 'thin' descriptions or flat summaries of the findings.

Two review authors (BB, CP) independently assessed the risk of bias of each study; discrepancies were resolved by consensus with a third author (MH) as needed. Studies were grouped into three categories (high, medium and low).

For the quantitative studies, the reviewers agreed that observational articles would not be given a "high" quality rating even when bias was minimised in the study due to the difficulty in controlling confounding and attributing causality when using an observational design for effectiveness studies. Following discussion, there was 100% agreement on the quality assessment rating of the included articles between the three researchers (see Table 2.2). Quality ratings were used descriptively to assess the strength of evidence.

2.6 Data extraction and synthesis

Data relating to each eligible study were extracted in a standard way directly into a data extraction table (see Appendix II). Studies were first categorised as either qualitative or quantitative. Quantitative papers were then further categorised independently by two reviewers (BB, CP) according to the focus of the study: 1. improving quality of care; or 2. improving patient outcomes (see Table 2.2). The two reviewers independently used content analysis to identify and categorise the qualitative papers into four agreed themes: 1. features and outcomes of effective networks; 2. network implementation; 3. organisational structure; or 4. organisational learning and knowledge (see Table 2.3). The main findings of the quantitative and qualitative studies were first examined separately. Due to the heterogeneity of the included quantitative studies and their outcomes, results were reported in narrative form. Qualitative methods were used to thematically analyse and synthesise textual data extracted from the qualitative studies. Results from the quantitative narrative analysis were then integrated with the qualitative synthesis in the discussion to identify recurrent themes and explain how successful networks achieved their outcomes.

2.7 Results

Appendix II presents an overview of the 22 studies including details of context, sample, research aim, study design, methods, outcomes, and main results.

Synthesis of quantitative studies

Table 2.2 summarises study characteristics and quality ratings. With the exception of one study published in 1999, the remainder (eight) were published after 2000, with four published since 2011. Four were undertaken in the UK, two in France, two in Australia and one in the US. The studies involved networks covering diverse clinical specialties including: cancer (three); cardiac services (two); diabetes (one); end stage renal disease (one); and neonatal services (two).

Of the nine included quantitative studies, seven focused on improving quality of care and two focused on improving patient outcomes (see Appendix II for measures used in each study). Based on our quality assessment criteria, six studies (67%) were of moderate quality and three studies (33%) were of low quality (Table 2.2). Studies were limited by the use of observational rather than experimental designs (7 of 9).

Four studies (3, 4, 39, 43) described the impact of the establishment and reorganisation of healthcare into clinical networks, while five studies (6, 7, 40-41) described the impact of network initiatives. Network initiatives included development and dissemination of clinical practice guidelines and protocols, educational activities (e.g. workshops), clinical audit and provision of feedback, care pathway redesign, facilitation of multidisciplinary team care, patient education, and other interventions to improve clinical care (such as point-of-care reminders and availability of new technology).

Table 2.2: Summary of included quantitative articles

Authors	Country	Type of Network	Theme	Study Design	Quality Rating*
Gale et al 2012 (3)	UK	Managed clinical network for neonatal services	Improving quality of care	Observational – before and after	Moderate
Greene et al 2009 (40)	UK	Tayside Diabetes Managed Clinical Network	Improving quality of care	Observational – cross-sectional	Moderate
Hamilton et al 2005 (4)	Scotland	Managed clinical network for cardiac services	Improving quality of care	Quasi-experimental – interrupted time series	Moderate
McClellan et al 1999 (42)	USA	End Stage Renal Disease Networks	Improving patient outcomes	Observational – before and after	Low
McCullough et al 2014 (39)	Scotland	Scottish Sarcoma Managed Clinical Network	Improving quality of care	Observational – retrospective before and after	Low
Ray-Coquard et al 2002 (6)	France	Regional cancer network of hospitals	Improving quality of care	Quasi-experimental – controlled before and after	Moderate
Ray-Coquard et al 2005 (7)	France	Regional cancer network of hospitals	Improving quality of care	Observational – before and after	Moderate
Spence & Henderson-Smart 2010 (41)	Australia	Australian and New Zealand Neonatal Network	Improving quality of care	Observational – before and after	Low
Tideman et al 2014 (43)	Australia	Integrated cardiac support network	Improving patient outcomes	Observational – retrospective before and after	Moderate

*Quality rating definitions:

- High quality – design and conduct of study address risk of bias, appropriate measurement of outcomes, appropriate statistical and analytical methods, low drop-out rates, adequate reporting
- Moderate quality – do not meet all criteria for a rating of good quality but no flaw is likely to cause major bias, some missing information
- Low quality – significant biases including inappropriate design, conduct, analysis or reporting, large amounts of missing information, discrepancies in reporting

Effectiveness of clinical networks to improve quality of care

A total of seven studies examined quality of care indicators, all of which achieved significant improvements on some or all indicators. Studies are listed by clinical specialty.

- *Cancer*

Three observational studies (two moderate and one low quality) reported improvements on quality of care indicators related to previous provision of cancer services. In a controlled before and after study, Ray-Cocquard et al [6] reported an increase in the observed compliance rate for overall treatment sequences post-implementation of clinical practice guidelines established and disseminated by a regional cancer network for hospitals in the network; 36% (126 out of 346) vs 12% (34 out of 282) and 46% (56 out of 123) vs 14% (14 out of 103) ($p<0.001$) for breast and colon cancer, respectively. In the control group of non-network hospitals, there was no difference in the observed compliance rate pre-and post-implementation. In a three-year follow up repeated controlled before and after study, Ray-Cocquard et al [7] observed that compliance of medical decisions with clinical practice guidelines was higher at follow up for colon cancer (73%; 95% CI [67%, 79%] v 56%; 95% CI [49%, 63%], respectively; $p=0.003$) and similar for the two periods for breast cancer (36%; 95% CI [31%, 41%] v 40%; 95% CI [35%, 44%], respectively; $p=0.24$). In the control group, compliance was higher at three-year follow up for colon cancer (67%; 95% CI [58%, 76%] v 38%; 95% CI [29%, 47%], respectively; $p=0.001$) and identical for the two periods for breast cancer (4%; 95% CI [1%, 7%] v 7%; 95% CI [3%, 11%], respectively; $p=0.19$). These findings indicate that clinical network-led improvements can be sustained over time. While there was improvement in compliance for colon cancer in both networked and non-networked hospitals at three-year follow-up, behaviour change was more rapid in the region within the cancer network suggesting

that valid evidence-based information was disseminated more expeditiously through the network.

In a retrospective observational study, McCullough et al [39] conducted a cohort analysis of patient records and administrative datasets before and after establishment of the Scottish Sarcoma Managed Clinical Network. More patients were seen by more specialties after establishment of the network and the time interval from receipt of referral to initial assessment by the service improved from a median of 19.5 days to 10 days. However the interval between initial GP consultation and initial assessment by the service increased from 35 to 41 days (p=0.57). Patients undergoing investigation with a magnetic resonance imaging (MRI) scan prior to excision of the sarcoma increased from 67% to 86% after the establishment of the network (p=0.0009). The proportion of patients undergoing appropriate biopsy increased from 57% to 79% (p=0.006), while complete resection margins increased from 48% to 81% (p<0.001).

- *Cardiac services*

In one quasi-experimental interrupted time series study (moderate quality), Hamilton et al [4] reported statistically significant improvement in two out of 16 clinical care indicators (pain to needle time <90min; p=0.05 and 70% on beta-blockade at 6 months post myocardial infarction; p=0.05) and non-significant improvement in nine others following the set-up of a managed care network for cardiac services in Scotland. Five indicators showed no improvement and there was no impact on resource costs.

- *Diabetes*

One study (moderate quality) [40] retrospectively evaluated the impact of quality improvement initiatives undertaken by the Tayside Diabetes Managed Clinical Network in the UK using data extracted from the regional diabetes register. Simple process indicators such as measuring glycated haemoglobin,

blood pressure and cholesterol rapidly improved, while there was slow continuous improvement on others such as recording of smoking status, measurement of creatinine, assessment of foot vascular and neurological status and retinal screening (all significance levels $p<0.001$). Improvements were greater for type 2 than type 1 diabetes for which three indicators did not change significantly. Significant shifts of care for type 2 diabetes into primary care were achieved. Network organisation and leadership with a clear vision for best care were important facilitators in implementing quality improvement initiatives and achieving widespread clinical engagement, with information technology playing a supportive role.

- *Neonatal Care*

Two observational before and after studies, one in Australia (low quality) [41] and one in the UK (moderate quality) [3] reported neonatal care outcomes of neonatal care networks. The previously established Australian and New Zealand Neonatal Network [41] drove the implementation of multiple intervention strategies to increase evidence-based practice for the treatment of newborn pain, resulting in improvements across three outcomes. Increased use of a pain assessment tool for ventilated neonates, an increase in the percentage of infants receiving sucrose for procedural pain (41% to 61%; $p<0.005$) and increased staff awareness of a clinical practice guideline for the management of newborn pain (61% to 86%; chi square =73.8, d.f. 1, p=0.000) were reported. Family awareness of infant pain and strategies to manage the pain also increased from 19% to 48% (chi square =52.3, d.f. 1, p=0.000).

In the UK, the impact of reorganisation of neonatal specialist care services for high-risk pre-term babies into managed clinical networks for neonatal services achieved improvements [3]. The proportion of babies born at 27-28 weeks gestation at hospitals providing the highest volume of specialist care increased from 18% to 49% (risk difference 31%, 95% CI [28, 33]; OR: 4.30, 95% CI [3.83,

4.82]; p<0.001). The proportion of babies undergoing acute and late postnatal transfer in England increased (7% v 12% and 18% v 22%, respectively; p<0.001). There was no reduction in the number of infants from multiple births separated by transfer.

Effectiveness of clinical networks to improve patient outcomes

Two observational (one prospective and one retrospective before and after) studies (one moderate and one low quality) assessed patient outcome measures, both reporting improvements on primary indicators. A study in the US [42] assessed the effects of a quality improvement intervention on network-specific Urea Reduction Ratios (URRs) driven by the End Stage Renal Disease Network. URRs improved during the intervention period (63% to 67%; p<0.001) and the proportion of under-dialysed patients in the networks decreased from 56.6% to 31.7% (chi-squared for trend, p<0.0001). Successful intervention strategies included audit and feedback coupled with educational interventions, involvement of a diversity of physicians and clinical leaders, and persistence over several years.

In Australia, the regionalised Cardiovascular Clinical Network (ICCNet) was established to improve outcomes of patients with myocardial infarction (MI) in rural settings.[43] Among rural hospitals, 30-day mortality decreased among patients presenting to hospitals integrated into the clinical network (13.93% before ICCNet vs 8.92% after ICCNet; p<0.001). After adjustment for temporal improvement in MI outcome, baseline comorbidities and MI characteristics, availability of immediate cardiac support (i.e. presentation to an ICCNet hospital) was associated with a 22% relative odds reduction in 30-day mortality compared with patients presenting to rural centres outside the clinical network (OR, 0.78; 95% CI [0.65, 0.93]; p=0.007). A strong association between network support and increased rate of transfer of patients to metropolitan hospitals was observed (before ICCNet, 1102/2419 [45.56%] vs

after ICCNet, 2100/3211 [65.4%]; p<0.001). Increased transfers were associated with a lower total length of stay compared with admissions before implementation of the network. Rates of angiography increased among rural patients, but remained lower than in metropolitan patients.

Synthesis of qualitative studies

Table 2.3 summarises key study characteristics and quality ratings. All of the 13 studies were published in 2005 or later. Eight were undertaken in the UK, two in Australia, two in Canada, and one in Sweden. The majority of studies used a case study or comparative case study approach to examine clinical networks. A summary of findings is available in Appendix II. According to our criteria, nine of the 13 studies were given a high quality rating while four were given a moderate quality rating. Although none were rated low quality, studies were limited by their lack of use of sufficient strategies to establish reliability (e.g. independent coding) or validity of data analysis (e.g. reporting of negative cases).

While five articles (44-48) specifically addressed the features and outcomes of effective networks, articles that fell in the other three subcategories similarly identified leadership, interpersonal relationships, organisational structure and resourcing as factors that contribute to the network effectiveness.

Features and outcomes of effective networks

Five papers (one high and four moderate quality) [44-48] identified the following characteristics as enabling a network to be successful:

- Supportive policy environments and links with government agencies;
- Sufficient resources – in particular, having a project/network leader or coordinator provided a clear advantage, as did the availability of information and communication technologies;

Table 2.3: Summary of included qualitative articles

Authors	Country	Type of Network	Theme	Study Design	Quality Rating*
Addicott 2008 (50)	UK	Managed clinical network for cancer services	Organisational structure	Comparative case study	High
Addicott & Ferlie 2007 (51)	UK	Managed clinical network for cancer services	Organisational structure	Comparative case study	High
Addicott et al 2007 (52)	UK	Managed clinical network for cancer services	Organisational structure	Comparative case study	High
Addicott et al 2006 (53)	UK	Managed clinical network for cancer services	Organisational learning and knowledge	Observational, cross-sectional organisational process study	High
Ahgren & Axelsson 2007 (44)	Sweden	'Chains of care' (managed clinical networks) for patients having the same illness or symptom	Features and outcomes of effective networks	Cross-sectional embedded multiple-case study	High
Baker & Wright 2006 (45)	UK	Managed clinical network for paediatric liver services	Features and outcomes of effective networks	Appreciative Inquiry methodology (case study)	Moderate
Burnett et al 2005 (54)	UK	Various managed clinical networks (cancer, coronary heart disease, stroke, mental health)	Organisational learning and knowledge	Qualitative information and knowledge needs analysis (comparative case study)	Moderate
Cunningham et al 2012 (46)	Australia	Advisory clinical networks – two networks for musculoskeletal health (NSW and WA)	Features and outcomes of effective networks	Longitudinal comparative case study	High
Fleury et al 2002 (49)	Canada	Mental health integrated service network	Network implementation	Case study and multi-dimensional analytic model	Moderate
Hogard & Ellis 2010 (47)	UK	Managed clinical network for personality disorder	Features and outcomes of effective networks	Evaluation Trident methodology (case study)	Moderate

Authors	Country	Type of Network	Theme	Study Design	Quality Rating*
McInnes et al 2012 (48)	Australia	Voluntary collegial clinical networks in NSW established by the NSW Agency for Clinical Innovation	Features and outcomes of effective networks	Comparative case study	High
Tolson et al 2007 (5)	Scotland	Managed clinical network (Palliative Care), linking primary, secondary and tertiary care	Network implementation	Realistic Evaluation methodology (qualitative pilot case study)	High
Touati et al 2006 (13)	Canada	Managed clinical network (cancer)	Network implementation	Longitudinal qualitative case study	High

*Quality rating definitions:

- High quality – those meeting 8 or more criteria
- Medium quality – those meeting between 5 and 7 criteria
- Low quality – those meeting fewer than five criteria

The full list of 11 criteria can be found in Appendix I.

- A bottom-up, locally-initiated and driven approach to network implementation, with subsequent formalisation to increase the adoption of new processes;
- A positive, trusting culture where networks are seen as desirable and perceived to be necessary to sharing knowledge, and where there is open and inclusive communication, clinician engagement and widespread stakeholder participation;
- The norms and values of the network are compatible with those of the organisations involved;
- Strong leadership, particularly by clinical leaders and network managers;
- Inclusive membership in the network, including representation of patients and other stakeholders;
- Evidence-based work plans and projects that address issues identified by network members, particularly gaps in current practice, with goals that are feasible and can be objectively measured.

The studies noted that success was dependent on a combination of these factors being present rather than just a few isolated features. In particular, commitment to a set of shared values and objectives was necessary but insufficient for clinical effectiveness in the absence of other factors.[47]

The following characteristics of ineffective clinical networks were identified as hindering their success:

- Lack of funding and resources;
- Tension, distrust and competition (particularly over resources) between network members;
- Poor communication and unwillingness to collaborate;
- Lack of confidence in the ability of network leaders and managers;

- Lack of representation of key stakeholders in certain contexts (e.g. rural and indigenous interests);
- Poor record keeping and documentation, which made it difficult to measure the impact of network initiatives and track progress.

Outcomes of effective networks included the development or reorganisation of service delivery into clear clinical pathways, provision of holistic services, improved working relationships and collaboration within the network, and improved clinical knowledge and skills of network members.

Network Implementation

Three articles (two high and one moderate quality) described the process of implementing a clinical network and the key lessons learned from the implementation process [5, 13, 49]. Two of the studies described positive steps towards the implementation of clinical networks [5, 13], while one study described a negative experience.[49] The overarching lesson was that the implementation of a network is extremely complex and requires "considerable time, resources and initiatives at different levels of the healthcare system".[13] Successful implementation required strong leadership, coordination and a sense of shared values and trust between network members. While vital, clinical leadership alone was insufficient.[13] Trust between network members, whether inter-organisational or inter-professional, was regarded as being vital to the implementation process. Members had to be receptive to the concept of the network. For this, the values of the network must match the values of the organisation and the individual's practice. Power imbalances between institutions in a network were observed to hinder the implementation process, as larger institutions were viewed as "hoarding resources" leaving smaller practices at a disadvantage, resulting in their disengagement.[49]

The availability of adequate resources for the network was also essential. This included funding, administration and human resources. The formalisation of processes was seen as a positive step, but only when done under the direction of the clinical teams. Inexperience in change management and unfamiliarity with leading development projects were cited as barriers to implementation.[5] It was essential for network members to have confidence in the expertise and ability of the people leading the changes to the system; where leaders lacked legitimacy and were perceived to lack the required knowledge and expertise, implementation was slow. Having clinical leaders who championed change was essential for buy-in from other clinical staff.[5, 13] Implementation of the network was also unsuccessful when a top down approach was used, where the network was mandated and led by external organisations rather than having clinicians set priorities and driving the implementation process. Without genuine participation of the physicians involved, implementation was difficult and did not appear to affect practice.[49]

One study reported briefly on some of the outcomes of the implementation process which were generally viewed as positive.[5] There were better working relationships between teams, enhanced knowledge, and a greater commitment to the practice of evidence-based care. There also appeared to be improved patient outcomes – interviewed patients reported better management of their symptoms and had greater knowledge about how to manage their condition.

Organisational Structure

Three articles (all high quality) looked at how networks were structured and how network structure affected the ability to function in the local context.[50-52] All three articles referred to a single study of five managed clinical networks for cancer in the UK. Due to the top down approach used to set up

these networks by the government, the networks achieved limited success in organising and working together effectively, with only one network emerging as a successful anomaly. Despite attempting to delegate authority to the local level, the organisational structure of the networks maintained decision-making power at a centralised level. Boards had limited strategic influence, with decision making power and budgetary responsibilities ultimately ascribed to the Strategic Health Authorities and Primary Care Trusts; only one board was able to have a noteworthy impact due to the seniority of its members.[50] At all levels, network members in positions of less influence struggled to make an impact. Network Management Teams relied on interpersonal skills to influence members to cooperate, and were unsuccessful in all but one network.[51] Medical staff overwhelmingly dominated decision-making in all networks, often with the intention of acquiring resources and/or accreditation status for their own institutions.[51] An imbalance of power between medical staff meant that those with less power (typically those clinicians with smaller district hospital units as opposed to those working at a major cancer centre) frequently resisted decisions and implementing changes due to a perception that their interests were not taken into consideration.[51]

The organisation of the networks also limited their ability to implement knowledge sharing and educational activities.[52] Because power and influence remained centralised and there was strong resistance to any changes being implemented, there was little impact on organisational processes. Only one network, where the Network Management Team was viewed positively and had an open and facilitative approach to implementing changes, was able to implement some education and training activities. The Team was able to successfully leverage pre-existing relationships to build support for and engagement in the network, and adapt interventions to the local context.

Organisational learning and knowledge

Two papers (one high and one moderate quality) [53, 54] focused on organisational learning and the transfer of knowledge within networks. Members of clinical networks identified organisational learning as a desirable outcome that could increase individual knowledge and improve patient outcomes. They recognised that easy access to timely information would enable them to work more efficiently.[54] However not all networks were able to successfully implement educational measures. Those that were successful had adequate resources, good network management, appropriate organisational structure that facilitated inclusive and open participation, enthusiastic network members and a positive learning environment. Networks where educational initiatives were unsuccessful were characterised by organisational structures that impeded knowledge sharing, poor relationships between network members, weak management and the perception of increasing competition among members. Due to the uneven distribution of resources, individuals competed over resources, which fostered distrust and a lack of willingness to collaborate. Several respondents believed education would become more of a priority when structural issues were addressed.[53]

2.8 Discussion

Testing the effectiveness of clinical networks

There is an emerging, albeit limited, body of empirical quantitative research into the effectiveness of clinical networks. Amongst the nine studies included, the majority (seven) focused on improvement in service delivery. Only two reported on clinical networks' impacts on patient outcomes. None of the quantitative studies were of high quality, and several (3 of 9) were of low quality. All except two used observational study designs; none used a randomised controlled trial. The lack of studies with a rigorous design limits

the conclusions that can be drawn. Although the vast majority (9 of 13) of the qualitative studies were rated “high quality” and their findings complement those of the empirical studies, they are not designed to determine whether clinical networks can successfully improve health service delivery and patient outcomes.

The best available empirical evidence indicates that clinical networks may be effective vehicles for quality improvement. Among the studies reviewed, networks were judged to improve quality based on several endpoints relating to both service delivery (such as adherence to clinical guidelines and protocols, development of clear patient pathways, and use of clinical tools) and patient outcomes (such as reduced mortality, improvement in biomarkers, and improved time to treatment). Desirable intermediate outcomes were also reported in both the quantitative and qualitative studies, such as improved knowledge amongst clinical staff and patients, greater clinical collaboration and greater availability of resources. There is some evidence that clinical networks may be effective in engaging clinicians in service redesign and reform [55], and developing and implementing protocols and clinical practice guidelines.[56] Quality improvement programs undertaken by networks largely report significant improvements across several quality of care indicators for a range of clinical disciplines including cancer [6, 7, 39], diabetes [40], and neonatal care.[3, 41] The two studies reporting patient outcome measures similarly demonstrated positive effects of network-specific interventions for end stage renal disease [42] and reorganisation of cardiac services.[43] There is some evidence to demonstrate that improvements may be sustained over time.[7, 42]

Although these findings generally indicate that clinician-led networks may improve care, other studies have not reported such consistent results. One study examining the impact of a managed clinical network for cardiac services

on patient care found that only two out of sixteen clinical care indicators significantly improved.[4] The authors note that changes were not noticeable until two years after network start up, which was an intensive process. This resonates with the findings of other studies [40, 57], which found simple process measures rapidly improved but that there was slower improvement across more complex measures that required intensive professional education or comprehensive redesign of the care pathway. There was also variability in the ability of networks to make meaningful network- or system-wide change. A qualitative comparative case study of five cancer networks in the UK conducted by Addicott et al [53] highlighted a great degree of variability in the extent to which networks successfully implemented planned activities and the consequent success of the network. This would suggest that some quality improvements are likely to be incremental and that complex changes may take longer to be successfully embedded into routine care. Therefore, while clinical networks can be effective in improving care, this is not always the case.

Features of effective networks

Variability in networks' success in improving healthcare is multifactorial and dependent on the local context. Implementation of a clinical network and its initiatives is a time- and resource-consuming process.[4] Critical factors for success identified across the quantitative and qualitative studies were strong leadership by clinical leaders and managers, availability of sufficient resources, and involvement of a broad range of people from different healthcare professions to patients and other stakeholders. Successful networks and their initiatives were typically driven by a few individual clinical leaders and dedicated managers who were widely respected by their colleagues and deeply committed to the purpose and values of the networks. Furthermore, networks without adequate administrative, human and technological

resources were less effective. Several qualitative studies reported that lack of a network manager or project coordinator and insufficient administrative and technological support to improve communication, collect relevant data and share educational tools reduced the effectiveness of networks.

Network structure was also perceived to impact upon success. Networks where decision-making power was decentralised to the local level were more successful.[44, 48, 50-52, 58] Several participants in the qualitative studies noted that without an appropriate organisational structure, the networks were unlikely to be able to change organisational processes and implement quality improvement measures. This could partially explain why some networks were able to change simple process measures like ordering additional laboratory tests, but were unsuccessful at changing more complex processes and systems, like clinical pathways, that may have required the support of a strong network structure.

These findings are in agreement with those of two reports that included an examination of what makes an effective managed clinical network. The first of these by Guthrie et al [59] in the UK identified the following key factors: *inclusiveness* to ensure that all relevant stakeholders are actively engaged with the network; strong credible *leadership* and *effective management* based on negotiation, facilitation and influence; *adequate resourcing* for network coordination; strong two-way *communication strategies* within the network; and collaborative *relationships with wider organisational context* to ensure network priorities are aligned with those of individual network members as well as local, regional and national organisations and agencies. Respondents in that study additionally agreed that 'networks should start with relatively small, non-contentious issues to achieve some "early wins" in order to demonstrate the benefits of networks and secure broader engagement and ownership'. The current review identified the same. The second report by

Cancer Australia [60] similarly identified the need for *clear and structured management arrangements* with one person acting as the overall lead coupled with inclusive multidisciplinary representation. Emphasis was also placed on *patient involvement* to ensure alignment of network priorities with the wider context and the need for *formalised reporting requirements* to evaluate network quality improvement initiatives. This report further stressed the role of clinical networks in the dissemination of *evidence-based practice* and promotion of *continuing professional development*, similar to our category of organisational learning and knowledge.

Strengths and limitations of the review

This is the first systematic review that has explicitly focused on the effectiveness of clinical networks to improve quality of care and patient outcomes. Like all systematic reviews, the conclusions of this review are limited by its scope and the range and quality of the research we have been able to uncover. Clinical networks are a relatively new phenomenon and it is difficult to identify relevant papers in any emerging field. This is especially true of research relating to clinical networks, which is often classified by clinical discipline. There is a lack of consistent terminology used to describe clinical networks, which was particularly evident in the earlier studies. To facilitate accurate identification of eligible studies, the researchers worked closely with a librarian to develop an iterative inclusive search strategy. It should be noted that 29 potentially relevant full-text articles were not available and, therefore, not screened for inclusion. This could have resulted in exclusion of potentially eligible articles. Furthermore, it is possible that other relevant articles have been published since the date of the last search.

Clinical networks have many forms, are hard to define and operate in different contexts. Further, the reasons for setting up networks vary, as do their goals. This is reflected in the diverse aims of the studies included in this

review, which made it challenging to draw together the lessons to be learned. We have strengthened the utility of this review by supplementing the relatively few quantitative empirical papers with qualitative research so as to be able to draw conclusions about the features necessary to enable clinical networks to be effectively used as implementation vehicles. To the best of our knowledge, this is the first time quantitative and qualitative results have been synthesised to evaluate clinical networks as an innovative way to organise healthcare delivery and what makes them successful.

Future research questions and methods

This review highlights the gaps in the literature relating to the effectiveness of clinical networks in improving quality of care and patient outcomes, particularly a lack of empirical studies with rigorous study designs. The absence of randomised controlled trials and the few observational studies limits the ability to draw robust conclusions about whether clinical networks are more effective at improving health service delivery and patient outcomes than other approaches.

While results so far have been mostly positive, more studies are necessary to determine whether improvements in service delivery are translating into improved patient outcomes. Of note, only two studies were identified that explicitly measured change in patient outcome indicators. There is a need to strengthen the existing body of knowledge through higher level evidence from rigorously designed randomised controlled trials to test the impact of clinical network-led initiatives on both quality of care and patient outcome indicators. Where it is not possible to conduct internally and externally valid experimental studies within a real-world setting, observational studies with stronger methodological designs, like controlled before-and-after or interrupted time series studies, would improve upon the learning from the descriptive studies that are currently most prevalent in the literature.

Empirical studies are also needed to quantify what makes a network more or less successful and determine the features necessary to strengthen existing and effectively implement new clinical networks. While the qualitative articles provided significant narrative on what was perceived to make a network effective, this was rarely quantified or examined in any depth in the quantitative studies. Furthermore, data on whether clinical networks are cost-effective vehicles to bring about change in a complex system is lacking. Only one study reported on the economic impact of the implementation of a clinical network [4] and found no difference in the average cost per patient. More comprehensive economic analyses are required to evaluate whether clinical networks are a cost-effective way to improve quality and outcomes through coordinated integration of services and better flow of knowledge about best practice.

2.9 Conclusions

There is some evidence that clinical networks may be vehicles to implement quality improvement initiatives. Given that clinical networks are being widely established, particularly in the UK and Australia, it is important to develop rigorous evidence to underpin future developments. Unfortunately, the generally low quality of quantitative effectiveness studies limits the ability to draw conclusions as to whether clinical networks can effectively improve the provision of healthcare and patient outcomes and whether these improvements can be maintained. Put simply, the research needs to 'catch up' with the operational developments in clinical networks. Our findings can, however, provide policymakers with some insight into the planning and implementation of a clinical network, specifically in regards to organisational structure, resourcing and interpersonal relationships, in order to increase the likelihood of success. Policymakers, clinicians and researchers need to work together in the implementation of clinical networks and their initiatives to design rigorous evaluations from the outset.

2.10 Authors' contributions

BB, in collaboration with MH, EM, NM and JY, conceptualised the idea of this systematic review. BB, MH and CP conducted the literature search. BB and CP completed the initial synthesis of results and drafted the manuscript. MH, EM, NM and JY contributed to interpretation of findings. All authors revised drafts of the manuscript for important intellectual content, and approved the final version of the manuscript.

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2.11 Research reporting checklist

The PRISMA Checklist for systematic reviews was used. A copy of the checklist is included in Appendix III.

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Chapter 3: Knowledge, attitudes and beliefs towards management of men with locally advanced prostate cancer following radical prostatectomy: an Australian survey of urologists

Publication arising from this chapter

Brown B, Young J, Kneebone AB, Brooks AJ, Dominello A & Haines M. Knowledge, Attitudes and Beliefs Towards Management of Men with Locally Advanced Prostate Cancer Following Radical Prostatectomy: An Australian Survey of Urologists. *BJU Int.* 2016; 117 (Supp 4): 35-44. doi: 10.1111/bju.13037.

3.1 Abstract

Objective: To investigate Australian urologists' knowledge, attitudes and beliefs, and the association of these with treatment preferences relating to guideline-recommended adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy.

Subjects and methods: A nationwide mailed and web-based survey of Australian urologist members of the Urological Society of Australia and New Zealand (USANZ).

Results: 157 surveys were included in the analysis (45% response rate). Just over half of respondents (54%) were aware of national clinical practice guidelines for the management of prostate cancer. Urologists' attitudes and beliefs towards the specific recommendation for post-operative adjuvant radiotherapy for men with locally advanced prostate cancer were mixed. Just over half agreed the recommendation is based on a valid interpretation of the underpinning evidence (54.1%, 95% CI [46%, 62.2%]) but less than one third agreed adjuvant radiotherapy will lead to improved patient outcomes (30.2%,

95% CI [22.8%, 37.6%]). Treatment preferences were varied, demonstrating clinical equipoise. A positive attitude towards the clinical practice recommendation was significantly associated with treatment preference for adjuvant radiotherapy (rho =0.520, p<0.0001). There was stronger preference for adjuvant radiotherapy in more recently trained urologists (registrars) while preference for watchful waiting was greater in more experienced urologists (consultants) (b=0.156, p=0.034; 95% CI [.048, 1.24]). Urologists' attitudes towards clinical practice guidelines in general were positive.

Conclusion: There remains clinical equipoise among Australian urologists in relation to adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy.

3.2 Introduction

As in other industrialised countries, prostate cancer is the most commonly registered cancer in Australia and the second most prevalent cause of cancer death in men.(1) Radical prostatectomy is the standard treatment for localised prostate cancer. Following surgery, however, it is estimated that between 20% and 50% of men are at "high risk" of experiencing progression or recurrence.(2) Rates of recurrence are 40-60% higher among patients with adverse pathological risk factors.(3) Three prospective randomized trials (RCTs) have shown the use of adjuvant therapy within 4 months of resection improves biochemical progression-free survival compared with surgery alone among patients with adverse pathological risk factors.(4-6) Furthermore, overall survival was improved after longer-term follow-up of patients in one trial.(7) On the basis of this evidence, Australian Cancer Network, (8) American Urological Association, (9) European Society for Medical Oncology, (10) and Canadian (11, 12) clinical practice guidelines recommend that men with extracapsular extension, seminal vesicle invasion or positive surgical margins should be offered adjuvant radiotherapy after radical prostatectomy.

However, a statewide patterns of care study found that in New South Wales (NSW), Australia's most populous state with 7.4 million inhabitants, less than 10% of men with locally advanced prostate cancer receive adjuvant radiotherapy within the recommended timeframe.(13) These figures are consistent with data from other regions of Australia (14, 15) and the United States where recent analyses indicate only 10 - 20% of qualifying patients receive adjuvant radiotherapy.(16-19)

The discrepancy between recommended care and clinical practice is indicative of the controversy surrounding adjuvant radiotherapy. In a recent American survey, urologists were less confident in the benefit of adjuvant radiotherapy in terms of overall survival or durable biochemical control and predicted higher rates of erectile dysfunction due to radiotherapy than radiation oncologists.(20) Furthermore, lack of access to radiotherapy services, concerns about overtreatment and toxicities, patient preferences and co-morbidities may all impact on referral patterns.

In more general terms, low rates of compliance with clinical practice guideline recommendations may be due to a number of factors, including lack of knowledge, negative attitudes, concerns about risks and benefits and underpinning evidence, or clinical inertia.(21, 22) Furthermore, when there is dissonance between clinical experience and clinical practice guideline recommendations, compliance is variable.(23) Thus it is has been demonstrated that less experienced physicians are more likely to follow new guideline recommendations.(24)

We do not know which of this multitude of potential barriers are the most important in the current context. To evaluate Australian urologists' knowledge, attitudes and beliefs and their association with treatment preferences relating to adjuvant radiotherapy for men with locally advanced

prostate cancer following radical prostatectomy we conducted a national survey of urologists. We hypothesised that:

1. A negative attitude towards the recommendation that '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery'* will be associated with a preference to not refer for adjuvant radiotherapy but rather 'watch and wait' and refer for salvage radiotherapy if the Prostate Specific Antigen (PSA) level rises.

2. In clinical scenarios where there is equipoise, guideline concordant practice i.e. preference for adjuvant radiotherapy will be more common in more recently trained urologists (registrars) and those working in teaching hospitals where there is a multidisciplinary approach to care.

The survey provided baseline data to inform the development of the "Clinician-Led Improvement in Cancer Care (CLICC)" study (NHMRC Partnership Grant APP1011474).(25) CLICC is an implementation trial working with urologists to test strategies to support change in practice to increase fully informed decision making in patients with locally advanced prostate cancer following radical prostatectomy.

3.3 Subjects and Methods

Study sample

Australian based urologists and trainees of the Urological Society of Australia and New Zealand (USANZ), identified through the USANZ member communications database.

Questionnaire development

Survey questions were developed following literature review in addition to

workshops with urologists, radiation oncologists and nurses. The survey comprised 6 sections (see Appendix IV for the full survey). Section 1 included three clinical scenarios (see Box 3.1) to investigate levels of clinical equipoise. Urologists were asked to indicate the strength of their preference for watchful waiting or adjuvant radiotherapy on a linear analog scale with one treatment option anchored at each end of the scale. The scale was centered on zero to represent ‘‘undecided’’ and marked from ‘‘1’’ to ‘‘5’’ toward each end to represent increasing certainty in the treatment approach.(26) Additional questions explored clinical uncertainty. Section 2 asked questions about the use of, and attitudes towards, clinical practice guidelines. This section also asked questions about acceptable levels of evidence, survival effects and side effects, in addition to providing an open response option to provide comments about adjuvant radiotherapy following radical prostatectomy. Section 3 asked questions relating to innovation and current clinical practice. Section 4 included questions relating to other barriers to adherence to the clinical practice recommendation including patient preferences, financial disincentives and administrative constraints. Section 5 assessed perceptions of organisational readiness for change. Section 6 collected demographic information. Where appropriate, questions were derived from previously validated (21, 27, 28) and non-validated tools (29-36) used to assess attitudes and barriers to the implementation of clinical practice guidelines (CPGs). The survey used a five-point Likert scale (“strongly disagree” to “strongly agree” with an additional “don’t know” option) and was formatted in both web-based and hard copy versions.

Pilot testing

The survey was pilot-tested on a purposive sample of senior urologists who are the clinical leaders at the hospitals involved in the CLICC implementation trial.(25)

Box 3.1: Clinical Case Scenarios

Case 1 – A 64 year old man, previously well, presented with a screening PSA 12.2. Patient had radical prostatectomy 10 weeks ago. Pathology results show a Gleason 3+4=7 carcinoma with extracapsular extension and positive margins near apex over a 2mm front. Seminal vesicle and lymph nodes were clear. Post radical prostatectomy he has good urinary control. Post-op PSA 0.01. No return of erections.

Case 2 – A 58 year old man had a nerve sparing radical prostatectomy 3 months ago for a low volume Gleason 3+4=7 carcinoma (20% high grade) with 0.2mm extracapsular extension in left peripheral zone but clear surgical margin. No perineural or lymphovascular invasion. Seminal vesicles clear. 0/12 nodes involved. Post op PSA <0.01. Some dribbling on straining but pad free. Partial erections but inadequate for intercourse.

Case 3 - A 62 year old man had a non nerve sparing prostatectomy for a clinical T3 prostate cancer with pre-op PSA of 14. Histopathology demonstrates a widespread Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension and involvement of base of right seminal vesicle. Multiple sites of positive surgical margins. Post op PSA 0.04. No lymph node involvement. Good urinary function and no erections.

Survey administration

An initial letter of invitation was mailed together with a hard copy of the survey. This written invitation was followed by an email invitation with a link to the web-based version. Two reminder emails and a final mailed postcard reminder with a further hard copy of the survey followed up initial contact. All correspondence was initiated centrally by USANZ Communications to maintain integrity of their member list. Respondents who completed the survey were eligible to enter a competition to win an iPad.

Statistical analyses

Data were analysed using IBM SPSS Statistics Version 22.0. Only surveys that provided responses beyond the three clinical scenarios were included in the analyses.

Likert scale response categories were collated for analysis such that strongly disagree/disagree are reported as a single disagree category and agree/strongly agree are reported as agree.

A summary score was calculated from respondents' total scores on questions within each domain by summing the values for all non-missing items and dividing by the total number of items completed to assess overall attitudes and beliefs relating to clinical practice guidelines. These summary scores were used in subsequent analyses.

Spearman correlation coefficients were used to examine associations between attitudes and beliefs, and treatment preference. T-tests were used to explore relationships between knowledge and treatment preference. Multiple regression modeling was conducted to identify independent predictors of CPG concordant treatment preference. Statistical significance was defined as $p<0.05$.

Qualitative textual data were explored inductively using content analysis to identify barriers to the implementation of the clinical practice recommendation that '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery*'.

Clinical Equipoise

Three clinical scenarios were given to urologists as outlined in Box 3.1. Each reflected a different risk of recurrence but all fell under the "high-risk" category as outlined in the Australian Cancer Network Guidelines.(8) Cases 1, 2 and 3 had a 19%, 10% and 89% 10-year risk of biochemical relapse respectively according to Memorial Sloan Kettering Cancer Center nomograms (37) highlighting the heterogeneity of patients in the "high-risk" cohort. Responses to clinical scenarios were transposed to a continuous 0 to 10 point

scale for analysis. Treatment preferences were categorised as follows: 0 – 3 = watchful waiting is preferable; 4 – 6 = undecided; 7 – 10 = adjuvant radiotherapy is preferable.

Clinical equipoise is defined as "genuine uncertainty within the expert medical community" about which treatment would be most beneficial for patients.(38) A recent US survey of Institutional Review Board committee expert members found that conduct of a clinical trial enrolling humans was perceived as unethical when the equipoise level was beyond 80% (80:20 distribution of uncertainty).(39) In line with this finding, and previous equipoise studies,(26) we define clinical equipoise as a situation in which less than 80% of clinicians are in agreement about the most appropriate treatment for a given scenario.

3.4 Results

Response Rate

Of 370 urologists invited to participate, 20 were considered ineligible for this study (Paediatrics n=1, Retired n=15, Deceased n=1, Insufficient address n=3) resulting in a final sample of 350. Surveys were included if they were completed up to the end of Clinical Scenario 3. All 157 returned surveys (79 hard copy, 78 online) were included in the final sample (45% response rate). Respondent characteristics are summarized in Table 3.1.

Knowledge – awareness of the Australia Cancer Network Clinical Practice Guidelines

54% of respondents reported that they were aware of the Guidelines. Of these, 45% found out about it from USANZ, the peak professional body for urological surgeons in Australia and New Zealand. A colleague referred 22% to the Guidelines.

Post-operative treatment decisions

Following radical prostatectomy 57% of urologists believed the multidisciplinary team is best placed to decide upon the most appropriate treatment option. 28% believed the urological surgeon is best placed to decide, 13% the patient, 1% the medical oncologist, and 1% the radiation oncologist.

Attitudes and beliefs related to the recommendation for adjuvant radiotherapy for locally advanced disease

There was variability in urologists' attitudes and beliefs towards this clinical practice recommendation. 54.1%; 95% CI [46%, 62.2%] agreed it is based on a valid interpretation of underpinning evidence. Less than one third agreed that following the recommendation would lead to improved patient outcomes (30.2%; 95% CI [22.8%, 37.6%]). Two thirds agreed that patients may experience unnecessary discomfort if they follow this recommendation (65.7%; 95% CI [58%, 73.4%]. 91.8%; 95% CI [87.3%, 96.3%] agreed this recommendation should only be followed within fully informed decision making by the patient. See Table 3.2 for full details.

Evidence from randomised controlled trials

More than half of urologists (54.8%) considered two to three randomised controlled trials provide an acceptable level of evidence to support a recommendation in favour of adjuvant radiotherapy. The majority of urologists (70%) considered that nine to 10 years or more follow up are necessary to convince them of the benefits of adjuvant radiotherapy.

Table 3.1: Baseline Characteristics of Respondents (n=157)

Demographic	n (%)
Sex	
Female	14 (8.9)
Male	126 (80.3)
Missing	17 (10.8)
Age Group	
20-30	1 (0.6)
31-40	38 (24.2)
41-50	48 (30.6)
51-60	27 (17.2)
>60	26 (16.6)
Missing	17 (10.8)
Level of experience	
Consultant	117 (74.5)
Salaried University Academic	5 (3.2)
Staff Specialist	11 (7.0)
Registrar	5 (3.2)
Other	2 (1.3)
Missing	17 (10.8)
Number of years in practice	
0-5	28 (24.2)
6-10	24 (15.3)
11-15	19 (12.1)
16-20	17 (10.8)
21-25	15 (9.6)
26-30	12 (7.6)
>30	15 (9.6)
Missing	17 (10.8)
Performs Radical Prostatectomy	
Yes	113 (72.0)
No	26 (16.6)
Missing	18 (11.4)
Location of Practice	
Capital City	91 (58.0)
Other major urban area	27 (17.2)
Rural	19 (12.1)
Remote	1 (0.6)
Other	1 (0.6)
Missing	18 (11.5)
Clinical setting in which MAJORITY of prostate cancer patients are treated	
Teaching hospital	51 (32.5)
Public non-teaching hospital	8 (5.1)
Private hospital	78 (49.7)
Missing	20 (12.7)

Attitudes and beliefs related to clinical practice guidelines in general

Overall, attitudes towards CPGs in general were positive with 78.4%; 95% CI [71.8%, 85%] of urologists reporting they use CPGs in their practice. Urologists agreed that CPGs are: good educational tools (89.3%; 95% CI [84.3%, 94.3%]); a convenient source of advice (89.2%; 95% CI [84.2%, 94.2%]); and intended to improve quality by standardising care (88.6%; 95% CI [83.5%, 93.7%]). There was less agreement that CPGs improve patient outcomes (52.4%; 95% CI [44.4%, 60.4%]. See Table 3.3 for full details.

Univariate analysis revealed a significant correlation between summary scores for attitudes towards CPGs in general and attitudes towards the clinical practice recommendation for adjuvant radiotherapy for locally advanced disease (rho=0.226; $p<0.01$).

Barriers to implementation

Thematic analysis of open text responses indicated that barriers to the implementation of the Australian Cancer Network Guidelines recommendation for adjuvant radiotherapy for locally advanced disease fall into three main categories:

1. *Need for individualised care* - 40% (32/80) of respondents expressed concerns about lack of applicability for some patients resulting in a preference to watch and wait. Particular concerns related to patients with incontinence *"return of continence without bladder neck stenosis is my major decision maker"* and those with concerns about impotence "*Those men who wish to maximize erectile function with PSA <.01 I am happy to keep under surveillance after fully informed discussion".*

2. *Perceived lack of evidence / lack of confidence in trial data* – 30% (24/80) of respondents reported concerns about the evidence base underlying the recommendation. "*My impression is the controversy lies*

with adjuvant versus salvage XRT when PSA becomes detectable. I understand there is no evidence to favour adjuvant yet".

3. *Concerns about side effects / overtreatment* – 25% (20/80) of respondents noted that toxicities related to radiotherapy and potential unnecessary treatment are a barrier to the implementation of this recommendation. *"Significant under-representing of urinary toxicity - incontinence & intractable strictures caused by RT [radiotherapy] post prostatectomy, therefore why expose 50% of men unnecessarily to potentially harmful treatment when with ultrasensitive PSA we can wait & select those men who really will benefit from it?"*

Treatment preference

Treatment preferences for the three clinical scenarios are detailed in Figure 3.1 and Table 3.4.

Figure 3.1: Current level of certainty about which treatment option is better

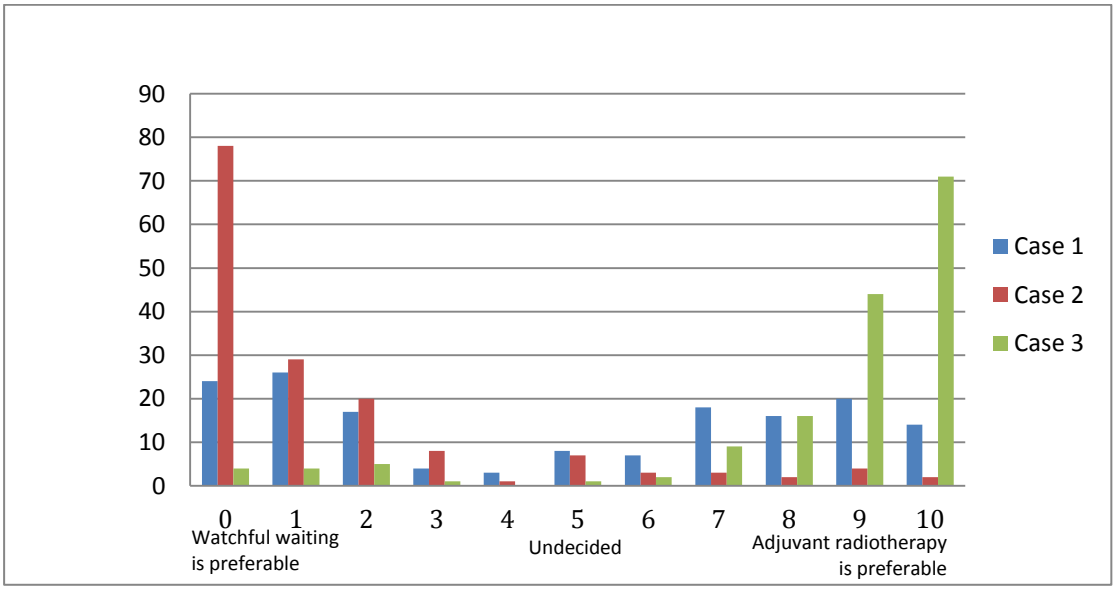

Table 3.2: Attitudes towards the Australia Cancer Network Guidelines recommendation that 'patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery'

	Disagree		Neither agree nor disagree		Agree		Don't know	
	n	%	n	%	n	%	n	%
This recommendation should only be followed within fully informed decision making by the patient	1	**0.6**	9	**6.2**	134	**91.8**	2	**1.4**
If I follow this recommendation my patients may experience unnecessary discomfort	21	**14.4**	28	**19.2**	96	**65.7**	1	**0.7**
The recommendation is based on a valid interpretation of the underpinning evidence	30	**20.6**	30	**20.5**	79	**54.1**	7	**4.8**
This recommendation is consistent with the opinions of my respected clinical colleagues	36	**24.7**	44	**30.1**	64	**43.8**	2	**1.4**
There are other recommendations for the appropriate management of this patient population that conflict with this one	26	**17.8**	51	**34.9**	63	**43.1**	6	**4.1**
This recommendation is consistent with my clinical experience with this patient group	42	**28.8**	42	**28.8**	62	**42.4**	-	**-**
I support post-operative external beam radiation therapy for patients but not within four months of surgery	44	**30.2**	48	**32.9**	52	**35.6**	2	**1.3**
Following this recommendation will lead to improved patient outcomes	24	**16.5**	64	**43.8**	44	**30.1**	14	**9.6**
This recommendation does not reflect evidence that is emerging on this topic	53	**39**	46	**33.8**	30	**22.1**	7	**5.1**
The side-effects of adjuvant radiotherapy for patients with locally advanced cancer outweigh the benefits	68	**46.5**	48	**32.9**	29	**19.9**	1	**0.7**
If I don't follow this recommendation I may be liable for malpractice	103	**70.5**	25	**17.1**	9	**6.2**	9	**6.2**

Table 3.3: Attitudes towards clinical practice guidelines in general

	Disagree		Neither agree nor disagree		Agree		Don't know	
In general, clinical guidelines:	n	**%**	n	%	n	%	n	**%**
Are good educational tools	4	**2.7**	12	**8.1**	133	**89.3**	-	**-**
Are a convenient source of advice	4	**2.7**	12	**8.1**	132	**89.2**	-	**-**
Are intended to improve quality by standardising care	3	**2.0**	14	**9.4**	132	**88.6**	-	**-**
Improve patient outcomes	4	**2.7**	60	**40.3**	78	**52.3**	7	**4.7**
Are based on an unbiased synthesis of robust scientific evidence	32	**21.5**	39	**26.2**	72	**48.3**	6	**4.0**
Are too rigid to apply and adapt to individual patients	68	**45.9**	33	**22.3**	46	**31.1**	1	**0.7**
Are oversimplified cookbook medicine	67	**45.3**	39	**26.3**	41	**27.7**	1	**0.7**
Are not readily accessible when I want to refer to them	69	**46.6**	46	**31.1**	32	**21.6**	1	**0.7**
Limit my ability to apply clinical judgment	98	**66.2**	24	**16.2**	26	**17.6**	-	**-**
Provide contradictory advice	74	**49.7**	47	**31.5**	24	**16.1**	4	**2.7**
Interfere with my professional autonomy	84	**56.8**	42	**28.4**	22	**14.8**	-	**-**
Are intended to cut costs	59	**39.6**	60	**40.3**	18	**12**	12	**8.1**

There was clinical equipoise for Case 1: 45% indicated that watchful waiting is preferable; 12% were undecided; 43% indicated that adjuvant radiotherapy is preferable. The preferred treatment option for Case 2 was watchful waiting in 86% of urologists. For Case 3 adjuvant radiotherapy was considered preferable by 89%.

There was no significant difference in treatment preferences between those who were aware of the Guidelines (M=5.28, SD=3.63) and those who were not (M=6.03, SD=3.66); t(147)=-1.244, p=0.215.

Univariate analysis revealed a significant positive correlation between attitude towards the clinical practice recommendation and concordant treatment preference (rho=0.520, p<0.0001).

Table 3.4: Current level of certainty about which treatment option is better

	Watchful waiting is preferable			**Undecided**			**Adjuvant radiotherapy is preferable**		
	N	**%**	**95% CI (%)**	**N**	**%**	**95% CI (%)**	**N**	**%**	**95% CI (%)**
Case 1	71	**45**	37.22, 52.78	18	**12**	6.92, 17.08	68	**43**	35.26, 50.74
Case 2	135	**86**	80.57, 91.43	11	**7**	3.01, 10.99	11	**7**	3.01, 10.99
Case 3	14	**9**	4.52, 13.48	3	**2**	0, 4.19	140	**89**	84.11, 93.89

Adjusted multivariable analysis demonstrated that a positive attitude towards the recommendation for adjuvant radiotherapy was the most significant predictor of concordant treatment preference (b=0.527, p<0.0001; 95% CI [.273, .473]). Preference for adjuvant radiotherapy decreased by urologist age group (b=-0.165, p=0.025; 95% CI [-1.055, -0.071]). Preference for adjuvant radiotherapy was greater in more recently trained urologists (registrars) while preference for watchful waiting was more common in experienced urologists (consultants) (b=0.156, p=0.034; 95% CI [0.048, 1.24]). There were no other significant associations with demographic or practice characteristics of respondents.

Other factors

Less than one fifth agreed (17.8%; 95% CI [11.46%, 24.17%]) that the Australian Cancer Network Guidelines recommendation takes into account patient needs and preferences. More than 60% (61.4%; 95% CI [53.34%, 69.46%]) believe routinely referring patients to radiation oncology will increase costs.

Innovation and readiness for change

There was some variation in regard to urologists' willingness to try new procedures in their practice; however, no urologists reported that they only try new procedures when regulations require them.

Urologists generally believed there is organisational readiness for change in their organisation. See table 3.5 for further details.

Table 3.5: Innovation and organisational readiness for change

	N	%	95% CI (%)
Innovation			
I experiment with new procedures	20	**14.2**	8.42, 19.98
I prefer to wait until other have tried new procedures	43	**30.5**	22.87, 38.13
I prefer to wait until new procedures have been established for a while	78	**55.3**	47.06, 63.54
I only try new procedures when regulations require them	0	**0**	N/A
Organisational readiness for change			
Urology leaders in my organisation believe current practice patterns can be improved	113	**81**	74.5, 87.5
Urology leaders in my organisation encourage and support changes in practice to improve care	130	**93**	91.39, 98.61
Urology leaders in my organisation are willing to try new protocols	114	**83**	76.78, 89.22
Urology leaders in my organisation work cooperatively with senior leadership/management to make appropriate changes	118	**84**	77.93, 90.07

3.5 Discussion

We conducted a survey of urologists throughout Australia. Just over half were aware of the Australia Cancer Network Clinical Practice Guidelines for the Management of Men with Locally Advanced and Metastatic Prostate Cancer (8) suggesting dissemination strategies could be improved.

Urologists varied in their attitudes and beliefs regarding adjuvant radiotherapy after radical prostatectomy for men with adverse pathologic features. Less than one third agreed following the recommendation for adjuvant radiotherapy would lead to improved patients outcomes. The lack of confidence in the efficacy of adjuvant radiotherapy is evident in the level of clinical uncertainty for a clinical scenario describing a patient with adverse pathologic features that would indicate its use. This may be a reflection of the

lack of confidence in the randomised controlled trials that form the evidence base for this recommendation.(4-7) These trials have been criticised for the absence of a well-defined salvage radiotherapy arm; many patients in the surgery alone control arm never received salvage radiotherapy and, when given, treatment was often delivered with PSA values >1.2ng/ml rather than at low PSA recurrence such as 0.2ng/ml which is the current trigger for salvage radiotherapy. The result is a perceived lack of evidence to support the benefit of adjuvant radiotherapy over selective early salvage radiotherapy. This direct comparison is the focus of two ongoing clinical trials (RAVES (40) and RADICALs (41)). Urologists also expressed concern about possible overtreatment for a significant proportion of patients whose cancer may never recur.(42) Clinical practice guidelines define “high-risk” as patients with positive surgical margins, seminal vesicle involvement or extra-capsular extension.(8-12) However, established post-prostatectomy nomograms indicate that not all adverse pathologic features are equal in terms of risk of relapse.(37) For example, a patient with a pre-operative PSA of 5, Gleason 7 disease with some extracapsular extension and clear margins has a less than 10% risk of relapse (our case 2 clinical scenario). We can see that urologists are using information other than the presence of adverse pathologic features in clinical decision-making through their reluctance to recommend adjuvant radiotherapy for this case.

There was also concern about the potential side effects and toxicities associated with radiotherapy treatment. These concerns may be abated by longer term follow up data from randomised controlled trials given that 70% considered 9 to 10 years or more follow up are necessary to convince them of the benefits of adjuvant radiotherapy. Longer-term follow-up for the Southwest Oncology Group (SWOG) trial reported improvements in biochemical and clinical progression-free survival and local control at 10 years

and increased overall survival at 12 years.(7) Results at median follow-up of 10.6 years for the European Organisation for Research and Treatment of Cancer (EORTC) trial (43) support results at 5 year follow up for improved biochemical progression-free survival and local control. While improvements in clinical progression-free survival were not maintained, exploratory analyses suggest that adjuvant radiotherapy may improve clinical progression-free survival in patients with positive surgical margins. A recent Australian study that sought to establish predictors of biochemical recurrence by analysing the pathological characteristics of positive surgical margins, found that the presence of Gleason grade 4 or 5 at the margin was significantly associated with biochemical recurrence.(44) These results concur with the updated report of the SWOG trial (7) which indicates patients with higher Gleason score tumours may receive a larger metastasis-free survival benefit from adjuvant radiotherapy than those with lower Gleason scores so the former group may be the most appropriate for referral to radiation oncology.

There was a perception that the clinical practice recommendation is not applicable, or does not take into account treatment preference, for some patients, especially those with ongoing incontinence or who wish to maximize erectile function. Overwhelmingly, urologists agreed that the recommendation for adjuvant radiotherapy should only be followed within fully informed patient decision-making, suggesting a propensity for shared-decision making.

It is of note that attitudes towards clinical practice guidelines in general were positive with the majority of urologists reporting that they routinely use them in practice, implying that the conflicting opinions around this particular clinical practice recommendation are due to some underlying factor rather than more general reticence.

Following radical prostatectomy, just over half of urologists believed the multidisciplinary team is best placed to decide upon the most appropriate treatment option. However, nearly one third believed the urological surgeon is best placed suggesting there may be some inconsistency in engagement with a multidisciplinary approach to cancer care despite evidence that it leads to improved survival, adherence to guidelines (45), reduced time to diagnosis and treatment and increased enrolment in clinical trials, in addition to improved patient satisfaction.(46) A recent single-centre Australian study (47) found that discussion of patients at a uro-oncology multidisciplinary meeting resulted in substantial changes to the clinician's original treatment plan in more that one quarter of cases presented. That study additionally reported that where there was no original plan, multidisciplinary discussion increased cross-referral between clinical disciplines, a significant finding given that only one per cent of urologists in our survey sample agreed a radiation oncologist is best placed to decide upon the most appropriate post-operative treatment. This reluctance to refer patients for a radiation oncology opinion (8, 9) could potentially explain the low uptake of adjuvant radiotherapy.(13-18) It could additionally signify a more general need to promote multimodality as the standard of care for high-risk disease.(48) Wider adoption of a collaborative multidisciplinary approach to treatment planning would enhance cross-discipline communication and understanding of the relative risks and benefits associated with multimodal and adjuvant treatment strategies.

Concordant treatment preference was not associated with awareness of the Guidelines suggesting that knowledge may be necessary but insufficient to bring about change in practice. However, a positive attitude toward the clinical practice recommendation for adjuvant radiotherapy was significantly associated with concordant treatment preference. This implies that change efforts seeking to increase guideline adherence would be better focused on

changing clinician attitudes and beliefs rather than seeking to simply increase knowledge. Guidelines concordant treatment preference was greater in registrars suggesting that continuing medical education or professional development maybe a successful vehicle to improve attitudes towards clinical practice guidelines and promulgate new research evidence. Targeting clinicians to embed a culture of evidence-based practice at an early stage in their career may also increase the likelihood of life long practice improvement and more timely adoption of new innovations in care.

The design of the CLICC study (25) was informed by the results of this survey, which highlight the need to increase engagement with a multidisciplinary approach to care. Specifically, CLICC elements include: 1. National and local urological clinical leaders to promote key messages including the potential need for multimodal care and referral to radiation oncology for discussion of adjuvant radiotherapy if adverse pathological features are present post-prostatectomy. 2. A quick reference guide to supporting evidence, information on current radiotherapy techniques, potential side effects and toxicity, together with key points to aid discussion with patients before and after surgery to support fully informed decision-making. 3. Regular audit and feedback reports detailing the number of patients referred to radiation oncology and information on the number of patients at high risk who are discussed at multidisciplinary team meetings. 4. Automatic case flagging whereby all patients of participating urologists who have had a histopathological examination of a radical prostatectomy specimen and who have extracapsular extension, positive surgical margins or seminal vesicle invasion are submitted automatically through the pathology provider to the hospital urology multidisciplinary team meeting for discussion. Full details of CLICC elements are detailed in the study protocol.(25)

The response rate (45%) is higher than the average response rate for online

surveys reported at 33% (49) and that of a similar US survey of urologists and radiation oncologists (20% overall).(20) This study is, limited by the reliance on self-reported physician treatment preferences, which may not directly reflect real-world utilisation of adjuvant radiotherapy. However, the results are in line with Australian and US analyses that report low levels of post-surgery radiotherapy treatment for high-risk prostate cancer (13-18) and the self reported practice of American urologists.(20) The CLICC implementation trial (25) will provide further data on current referral patterns in participating NSW hospitals.

3.6 Conclusion

This national survey of urologists highlights remaining clinical equipoise among Australian urologists in relation to adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy.

3.7 Authors' contributions

BB, in collaboration with all other authors, conceptualised the survey, analysed and interpreted the results presented in this paper. All authors provided input into various aspects of the study, provided ongoing critique, and approved the final version of the manuscript.

3.8 Ethics Approval

Ethical approval for this study was obtained from the University of Sydney Human Research Ethics Committee, September 2012 (Protocol No: 15222).

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Chapter 4: The CLICC conceptual program logic model and intervention mapping

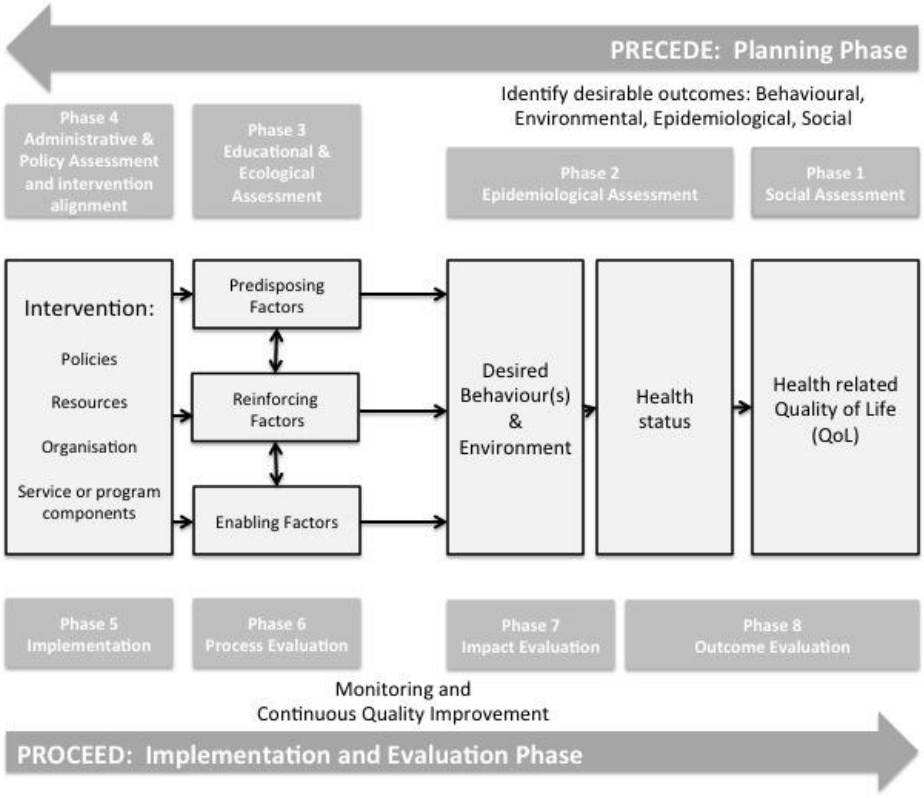
4.1 Overview of the PRECEDE-PROCEED model of behaviour change

The PRECEDE-PROCEED model (Figure 4.1) (1-3) was originally developed in the 1970s by Lawrence Green and colleagues from a number of US academic institutions and public and private health service providers as a model for preventive public health. The model has been updated and refined over the subsequent four decades to allow more intrinsic strategic mapping of interventions to contextual educational and environmental needs, and is a widely utilised tool for designing, implementing and evaluating health behaviour change programs. A fundamental premise behind the model is that any change process should focus initially on the desired outcome rather than the activities that may give rise to that outcome. The four formative phases of PRECEDE, therefore, move logically backward from: social (Phase 1) and epidemiological (Phase 2) assessment of the desired outcome; to where and how one might intervene to bring about that outcome through educational and environmental assessment (Phase 3); to administrative and policy assessment and intervention alignment (Phase 4). The subsequent four phases of PROCEED cover the actual implementation of the intervention (Phase 5); process evaluation (Phase 6) to determine whether the intervention is being delivered as intended; impact evaluation (Phase 7) to determine if the program is having the intended impact on the target population and if there are any unintended consequences be they positive or negative; and outcome evaluation (Phase 8) to assess whether the intervention is resulting in the desired outcome that was envisioned in Phase 1.

The PRECEDE-PROCEED model stresses that since health-related behaviours are caused by multiple factors, efforts to effect change should also be

multidimensional. Further, given that most health-related behaviours are voluntary, including those of treating clinicians, change interventions should be participatory and, from the outset, involve all stakeholders whose behaviour needs to change.

Figure 4.1: Phases of the PRECEDE-PROCEED model



Adapted from Green L. http://www.lgreen.net/precede.htm *[accessed October 2015]*

4.2 Phases of the PRECEDE-PROCEED model in relation to this thesis

In the context of this thesis, Phase 1 was predetermined by an Australian national strategy to improve prostate cancer services and thereby improve patients' quality of life and survival, which identified the provision of evidence-based care for these men as a high priority (4) (Phase 1: social assessment). Evidence from a number of randomised controlled trials (5-9) indicates that the desired outcome of improved quality of life and survival can be achieved by altering clinical practice to increase referral to radiation

oncology for consideration of adjuvant radiotherapy for men with adverse disease features following surgery, in line with the clinical practice recommendation in published guidelines (10-14) (Phase 2: epidemiological assessment). The remainder of this chapter outlines how educational and ecological assessment (Phase 3) and administrative and policy assessment (Phase 4) were used to conceptualise the design of the CLICC implementation trial, which aimed to increase the uptake of this clinical practice recommendation. The planned implementation (Phase 5) of the CLICC intervention is outlined in the published study protocol (Chapter 5). The process evaluation (Phase 6) is presented in Chapter 6. The impact evaluation (Phase 7) and outcome evaluation (Phase 8) are presented in Chapters 7 and 8.

4.3 Needs and barriers analysis to inform the development of the CLICC implementation trial

In keeping with the participatory emphasis of the PRECEDE-PROCEED model, a needs and barriers analysis (Figure 4.2) was conducted by the author, as outlined under Phase 3: Educational and ecological assessment and Phase 4: Administrative and policy assessment below. The needs and barriers analysis involved consultation with multiple clinical stakeholders, consumers and representatives of cancer policy agencies through workshops, interviews and surveys to maximise engagement and ensure that intervention elements were aligned with the local context. Barriers were considered at three levels: (i) individual clinician; (ii) patient; and (iii) hospital systems and processes, including the urological multidisciplinary team. A summary of identified barriers at each level is provided in Figure 4.3.

Phase 3: Educational and ecological assessment

Iterative workshops

A convenience sample of twenty-five Urology Network members participated in two workshops. Prior to submission of a research grant funding application, an initial workshop was undertaken during a routinely scheduled Network meeting attended by the Network Co-Chairs, Network Manager, urologist members and consumer representatives. This workshop aimed to determine whether the scope of the proposed study was viable within the Network context. Following award of funding, interviews were conducted with a purposive sample of nursing and radiation oncology staff, from three hospitals within the Network to identify perceived barriers to the implementation of the clinical practice recommendation at the local level. Barriers identified through these interviews were fed back during a second workshop, conducted during a subsequent routinely scheduled Network meeting, to determine whether there was consensus and to assess the relative importance of each barrier from the perspective of Network members. In priority order barriers agreed by Network members were as follows:

Clinician level barriers

Perceived clinician level barriers predominantly related to divergent interpretation of the evidence to support the clinical practice recommendation.

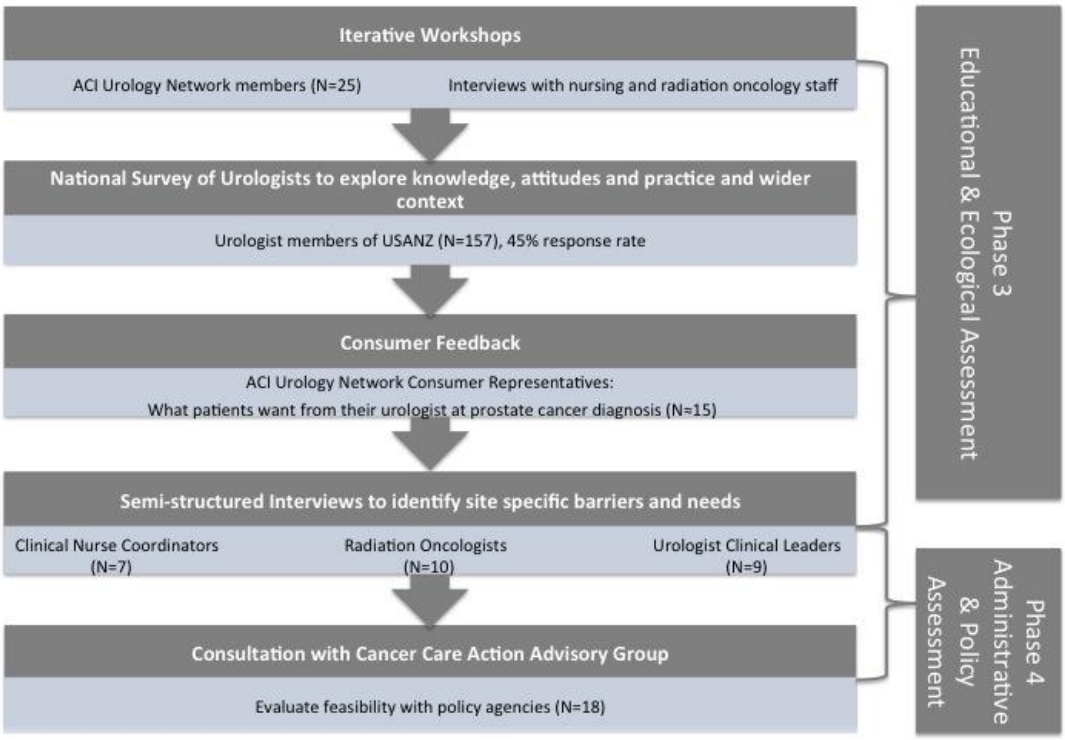
Patient level barriers

Treatment preference and cost of care were proposed as patient level barriers.

Systems and process level barriers

Waiting times for pathology results and post-surgical appointments with the consulting urologist and radiation oncologist were cited as the most likely hospital systems and process barriers.

Figure 4.2: Needs and barriers analysis to inform CLICC intervention design



National survey of urologists

To determine the extent to which barriers identified at the local level by Network members were representative of those evident in the wider urological population, a survey was administered to all urologist members of the Urological Society of Australia and New Zealand. Completed by more than half of all practicing urologists in Australia (n=157), and detailed fully in Chapter 3 previously, this survey identified a poor level of awareness of the Australian version of this clinical practice guideline. Other barriers were identified through the survey as follows:

Clinician level barriers

In addition to some lack of knowledge, other clinician level barriers related to concerns about the quality of evidence from the randomised controlled trials that underpin the clinical practice recommendation. This was coupled with concerns about the potential for overtreatment in some patients whose cancer may not recur and subsequent unnecessary discomfort and/or radiotherapy associated toxicity or side effects such as impotence, urinary or fecal incontinence and urethral stricture.

Patient level barriers

Perceived patient level barriers were similar to those cited by Network members, these being individual treatment preferences and financial cost.

Systems and process level barriers

Survey participants indicated no hospital system or process barriers.

Consumer feedback

During the development phase of the CLICC study, the Urology Network conducted a focus group with 15 consumer representatives to develop a guide for clinicians on the patient experience of prostate cancer.(15) The results of this consultation demonstrated that the majority of patients want to be fully informed about all potential treatment options, and their associated outcomes and side effects. Of significance to Phase 3: Educational and ecological needs assessment, patients indicated that their preference was for the urologist to initiate discussion and provide sufficient information to support fully informed patient decision-making. Key information priorities, in addition to considerations for psychosocial support, were:

- Curative treatment versus active surveillance and the likely associated outcomes
- Available treatment options, including surgery and/or radiation therapy and the types of each

- Treatment side effects including short- and long-term risks of incontinence and impotence and options for rectification if these occur
- Risk of short- or long-term recurrence after initial treatment and management should this occurs
- Experience in treating prostate cancer including patient outcomes
- Recommended treatment for the individual patient and the reasoning for this recommendation
- Other health professionals that may be involved in treatment such as radiation oncologists, physiotherapists and continence nurses
- An estimate of treatment timings and costs and explanation of issues around public versus private treatment

Semi-structured interviews

To further elucidate local educational and ecological needs, and to inform the design of intervention components to address these context specific needs, semi-structured telephone interviews were undertaken with a purposive sample of urologists (n=9), clinical nurse consultants (n=7) and radiation oncologists (n=10) at the nine participating CLICC study sites (see Chapter 5 for further details of hospital eligibility and urologist inclusion/exclusion criteria). Interviews asked questions about the membership and structure of the urological multidisciplinary team, perceived current practice in relation to post-radical prostatectomy referrals to radiation oncology, and barriers to the implementation of the clinical practice recommendation. Interviews were transcribed verbatim and textual data were analysed against the three barrier levels identified previously, namely: (i) individual clinician; (ii) patient; and (iii) hospital systems and processes, including the urological multidisciplinary team. Barriers identified by urologists were consistent with those highlighted in the workshops and survey.

Clinician level barriers

Clinician level barriers related to concerns about evidence, potential overtreatment and radiotherapy associated toxicity/side effects. In addition, two ongoing clinical trials (RAVES (16) and RADICALS (17)) comparing the efficacy of adjuvant radiotherapy with early salvage radiotherapy at the time of a confirmed PSA recurrence, the former being conducted within Australia, also raised doubt about routine referral for adjuvant radiotherapy.

Patient level barriers

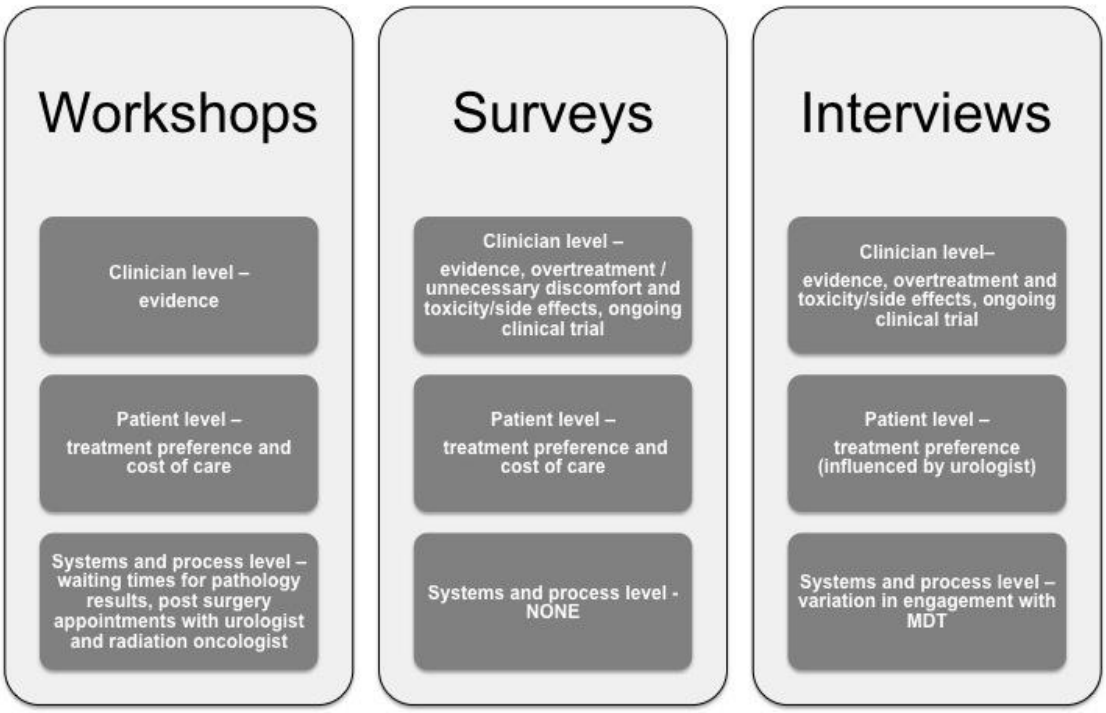
Treatment cost was not considered to be a barrier within CLICC study hospitals as radiotherapy services tend to sit within the public system and are therefore not billed to patients. Clinical nurse consultants and radiation oncologists perceived that patient treatment preferences were highly influenced by the opinion of the urological surgeon and this was frequently cited as a barrier to attending a radiation oncology consultation. Radiation oncologists further noted that urologists did not have sufficient specialist knowledge to enable fully informed discussion with patients about radiotherapy treatment options, their associated outcomes and potential side effects or toxicity.

Systems and process level barriers

Waiting times for pathology results or post-surgical appointments and timely access to radiotherapy services were not considered to affect capacity to change clinical practice in CLICC study sites. Reportedly there was, however, considerable cultural variation in engagement with the urological multidisciplinary team (MDT) both between urologists within CLICC study hospitals and across CLICC study hospitals more generally. This was exemplified by variable attendance at MDT meetings and selective presentation of patients for discussion. Variable engagement with the MDT in CLICC hospitals was suggested to be indicative of urologists' reticence towards

collaborative multidisciplinary treatment planning. This view is supported somewhat by the results of the national urologist survey (Chapter 3) in which just over half (57%) believed the multidisciplinary team is best placed to decide upon the most appropriate post-operative treatment option. Further, data for the period 2008 – 2011 from the Cancer Institute NSW demonstrate that while there was an increase in the proportion of new patients diagnosed with many cancers discussed at MDT meetings, the proportion decreased in urological MDTs.(18) The reduction in numbers of patients with urological cancers presented for discussion at MDT meetings is possibly due to selective presentation of cases, as noted in CLICC semi-structured interviews. Across all CLICC hospital study sites, presentation of cases to the MDT is at the discretion of the consulting urologist. There is no requirement for all cancer patients to be discussed by the MDT and no formal process to identify sub-groups of patients with higher risk cancers that may benefit from multidisciplinary input or multimodal care.

Figure 4.3: Summary of barriers to implementation



Phase 4: Administrative and policy assessment and intervention alignment

Consultation with the Cancer Care Action Advisory Group

As part of the CLICC study, a Cancer Care Action Advisory Group was established to provide advice about the policy positioning of the study, opportunities and barriers to impact cancer care, and how best to disseminate results into policy and practice. The group includes representatives from a number of Australian cancer policy agencies, professional societies including those representing urologists and radiation oncologists, urological clinical trials groups and consumer advocacy groups.

Eighteen members of the Cancer Care Action Advisory Group attended a two-hour meeting to evaluate the barriers identified in Phase 3 and the proposed intervention elements to address these barriers to ensure they were feasible, scalable and potentially translatable to other cancers. The group considered that the proposed intervention elements were feasible and that they had face validity.

4.4 The CLICC conceptual program logic framework

Intervention alignment

Intervention elements were mapped to barriers identified in Phase 3 using the CLICC conceptual program logic framework (Chapter 5, Figure 5.2). Through this framework, clinician level barriers (*knowledge, attitudes, perceptions,* and *norms*) were mapped to physician-focused components (*predisposing* and *reinforcing* factors). Hospital level barriers (*systems and processes,* and *culture*) were mapped to context-focused components (*enabling* factors). Intervention elements were developed in consultation with members of the Urology Network to ensure they had face validity.

Briefly, *physician-focused* intervention components included:

- Non-didactic, interactive provider education (*predisposing* factor)
- Dissemination of printed materials (*predisposing* factor)
- Opinion leaders (*reinforcing* factor)
- Audit and feedback (*reinforcing* factor)

The *context-focused* component comprised:

- Implementation of a new system for automatic flagging of eligible cases for discussion at MDT meetings (*enabling* factor)

A full description of intervention elements and how these relate to the PRECEDE-PROCEED model is provided in the study protocol (Chapter 5).

It should be noted that the CLICC study was primarily conceptualised a physician-focused intervention with the specific aim of changing provider referral behaviour. Consequently, research governance and ethical approvals did not permit direct patient interaction. Patient level barriers (treatment preferences) were, therefore, outside the scope of the study. However, to the extent that the consulting urologist influences patient treatment preferences, CLICC attempted to address these barriers through provider education and printed materials. Health system and wider contextual barriers were also excluded. Policy and resource implications will be considered by the Cancer Care Action Advisory Group and the Urology Network at the conclusion of the study when results are determined, if it is deemed appropriate that any or all of the CLICC intervention elements should be scaled-up and spread beyond the participating study sites.

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Chapter 5: Clinician-led improvement in cancer care (CLICC) - testing a multifaceted implementation strategy to increase evidence-based prostate cancer care: phased randomised controlled trial - study protocol

Publication arising from this chapter

Brown B, Young J, Smith D, Kneebone A, Brooks A, Xhilaga M, Dominello A, O'Connell D & Haines M. Clinician-Led Improvement in Cancer Care (CLICC) - testing a multifaceted intervention to increase evidence-based prostate cancer care: phased randomised controlled trial - study protocol. Implementation Science 2014;9:64

5.1 Abstract

Background: Clinical practice guidelines have been widely developed and disseminated with the aim of improving healthcare processes and patient outcomes but the uptake of evidence-based practice remains haphazard. There is a need to develop effective implementation methods to achieve large-scale adoption of proven innovations and recommended care. Clinical networks are increasingly being viewed as a vehicle through which evidence-based care can be embedded into healthcare systems using a collegial approach to agree on and implement a range of strategies within hospitals. In Australia, the provision of evidence-based care for men with prostate cancer has been identified as a high priority. Clinical audits have shown that fewer than 10% of patients in New South Wales (NSW) Australia at high risk of recurrence after radical prostatectomy receive guideline recommended radiation treatment following surgery. This trial will test a clinical network-based intervention to improve uptake of guideline recommended care for men with high-risk prostate cancer.

Methods/Design: In Phase I, a phased randomised cluster trial will test a multifaceted intervention that harnesses the NSW Agency for Clinical Innovation (ACI) Urology Clinical Network to increase evidence-based care for men with high-risk prostate cancer following surgery. The intervention will be introduced in nine NSW hospitals over 10 months using a stepped wedge design. Outcome data (referral to radiation oncology for discussion of adjuvant radiotherapy in line with guideline recommended care or referral to a clinical trial of adjuvant versus salvage radiotherapy) will be collected through review of patient medical records. In Phase II, mixed methods will be used to identify mechanisms of provider and organisational change. Clinicians' knowledge and attitudes will be assessed through surveys. Process outcome measures will be assessed through document review. Semi-structured interviews will be conducted to elucidate mechanisms of change.
Discussion: The study will be one of the first randomised controlled trials to test the effectiveness of clinical networks to lead changes in clinical practice in hospitals treating patients with high-risk cancer. It will additionally provide direction regarding implementation strategies that can be effectively employed to encourage widespread adoption of clinical practice guidelines.
Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR): ACTRN12611001251910.

5.2 Background

The evidence-practice gap

The discrepancy between research evidence and clinical practice is well documented (1), and remains one of the most persistent problems in providing high-quality healthcare.(2) Clinical practice guidelines have been extensively developed as a means to disseminate best practice and ensure clinical decision-making is informed by recent, credible research evidence, thereby improving healthcare processes and outcomes. However, timely and

effective implementation of guidelines into clinical practice is inconsistent (3), and it remains surprisingly difficult to make changes across the health system even when there is compelling evidence.(4)

The difficulty in achieving large scale adoption of proven innovations and recommended care (as well as discontinuing ineffective or harmful practices) has been characterised as a 'translation block'.(5-8)

Effective implementation

Previous research indicates that successful implementation of evidence-based care depends critically on the extent to which strategies address prospectively identified barriers, through theoretical frameworks of behaviour change (9, 10), and promote provider acceptance.(3) Recommendations from clinical guidelines are more likely to become embedded within practice when they: are initiated and led by local clinical leaders; are tailored to the local context; and engage clinicians in the design of the implementation strategy.(1,3, 11-13) Grol (14) argues that to effectively implement evidence-based practice, research urgently has to change so that it develops through collaborations between clinicians, researchers, patients, policy makers, and quality improvement experts.

Specifically, the growing body of evidence suggests several core implementation strategies are effective in bringing about system-wide and sustained change (1, 11, 15, 16):

1. Clinical champions/leaders supporting change within their practices and settings;
2. System, structural, and organisational support for system-wide changes to enable implementation strategies to be rolled out and scaled up (*e.g.*, legislation, resources, mechanisms for communication and collaboration between health sectors);

3. Ongoing monitoring, evaluation, and feedback of changes as they are implemented.

Clinical networks—a medium for implementation

In New South Wales (NSW), Australia, a coordinated program of 30 clinical networks, institutes and taskforces has been established by the NSW Agency for Clinical Innovation (ACI), a board-governed statutory organisation funded by the NSW Ministry of Health.

These clinical networks of volunteer health professionals provide a framework for doctors, nurses, allied health professionals, managers, and consumers to collaborate across regional and service boundaries to drive improvements in service delivery and care outcomes through innovation in clinical practice.

This type of non-mandatory clinical network is increasingly being viewed as a vehicle through which evidence-based care can be embedded into healthcare systems using a collegial approach to agree on and implement a range of strategies within hospitals. They provide 'bottom up' views on the best ways of tackling complex healthcare problems coupled with the strategic and operational 'top down' support necessary to facilitate and champion changes in practice at the clinical interface.(17, 18) There is evidence from 'before and after' controlled studies that when clinical practice guidelines are implemented through clinical networks there are improvements in compliance with guideline recommendations and the quality of care.(19, 20)

Clinical networks embody, or have the potential to enable, the core features of successful implementation strategies and therefore are a mechanism for health system change and increasing the uptake of evidence-based care for three reasons:

1. Clinical networks contain clinical leaders who can design and champion change to improve care within their practices and influence wider culture

change within their healthcare settings.

2. Clinical networks are a 'ready-made' organisational structure through which innovations may be promulgated and accelerated by clinicians.

3. Clinical networks provide a structure to monitor and evaluate changes as they are implemented to answer questions about effectiveness and the success of implementation strategies.

Prostate cancer clinical practice guidelines—an opportunity to translate research into effective healthcare practice

Prostate cancer is the most common cancer registered in Australia and is the second highest cause of cancer death in males.(21) Radical prostatectomy is the most frequent procedure for localised prostate cancer, however following surgery it is estimated that 20% to 50% of men are at 'high risk' of experiencing progression or recurrence.(22-25) A national strategy to improve prostate cancer services and thereby improve patients' quality of life and survival identified the provision of evidence-based care for these men as a high priority.(26) Persuasive evidence from randomised controlled trials indicates the need to alter current practice by offering radiotherapy to men with adverse disease features following surgery as radiotherapy treatment halves the risk of recurrence [27-29] and improves biochemical disease-free survival.(30) A Grade B recommendation (denoting that the Clinical Practice Guideline expert working group considered that the body of evidence can be trusted to guide practice in most situations) in the *Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer* produced by the Australian Cancer Network (31) recommends that 'patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery.' This recommendation is echoed in the more recently published American Urological Association Guideline, *Adjuvant and Salvage*

Radiotherapy after Prostatectomy, which states 'Physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy (Standard; Evidence Strength: Grade A)'.(32) The most recently available data indicate less than 10% of patients with locally advanced prostate cancer in NSW Australia receive guideline recommended care.(33) Patterns of care for prostate cancer in NSW generally reflect practice in other Australian jurisdictions.(34, 35) These data are consistent with that from the United States where less than 20% of eligible patients receive adjuvant radiotherapy, indicating substantial room for improvement.(36) Current evidence about strategies to encourage the adoption of clinical practice guidelines is limited (1-3, 9, 37) and provides little clear direction about approaches that can be effectively employed in specific settings.

5.3 Aims

The aim of this study is to develop and trial a locally tailored, multifaceted implementation strategy that harnesses the NSW Agency for Clinical Innovation (ACI) Urology Clinical Network to increase evidence-based care for men with high-risk prostate cancer following prostatectomy in selected NSW hospitals.(31) Specifically, the aim is to increase referral to radiation oncology for a discussion about radiotherapy, and the associated risks and benefits of treatment, to support fully informed decision making.

An additional aim is to identify reasons why changes in behaviour and outcomes occurred or did not occur in study hospitals and why the implementation strategy did or did not result in increased compliance with guideline recommended care.

If the intervention is successful we will also assess the sustainability of increases in referral patterns within the hospitals through interviews with key stakeholders.

5.4 Approach to intervention design

Any reason for resisting new practice is a barrier to change and the potential importance of such barriers and their influence on quality improvement activities has been highlighted in numerous studies(38-41) A recent systematic review indicates that tailored interventions are more effective when they are designed to address prospectively identified local barriers to change.(10) A key component of our method is to tailor our intervention so that it incorporates features that will facilitate changes in provider behaviour by addressing local level obstacles.

Intervention elements have been informed by reviews of the clinical practice change literature (9, 11, 37, 38, 42-61), and refined and tailored to take account of the organisational context in which providers practice through a multi-component needs and barriers analysis, including: iterative workshops with members of the ACI Urology Clinical Network; a national baseline survey (offered in web-based and paper form) of all urologist members of the Urological Society of Australia and New Zealand, the peak professional body, to explore current knowledge, attitudes and practice in the wider context (results published elsewhere); semi-structured interviews with urology, radiation oncology, and nursing staff at target hospitals to explore site specific practice and barriers; consumer feedback on what information patients want from their urologist; and consultation with a cancer policy advisory group to ensure intervention elements are feasible, scalable and potentially translatable to other cancers (see Figure 5.1 for summary).

Figure 5.1: Approach to intervention design

Results from these activities indicate that, in priority order, barriers can be grouped into three main clusters:

1. Clinician: attitudes and beliefs held by individual clinicians about the validity of the evidence base supporting the guideline recommendation (54% of urologists surveyed agreed that the recommendation is based on a valid interpretation of the underlying evidence) - notably due to ongoing clinical trials, which raise doubts as to the treatment benefit of adjuvant radiotherapy versus early salvage radiotherapy; concerns about overtreatment and toxicity/side effects associated with radiotherapy and lack of familiarity with current radiotherapy techniques (two thirds of urologists surveyed agreed that patients may experience unnecessary discomfort if they follow the recommendation).

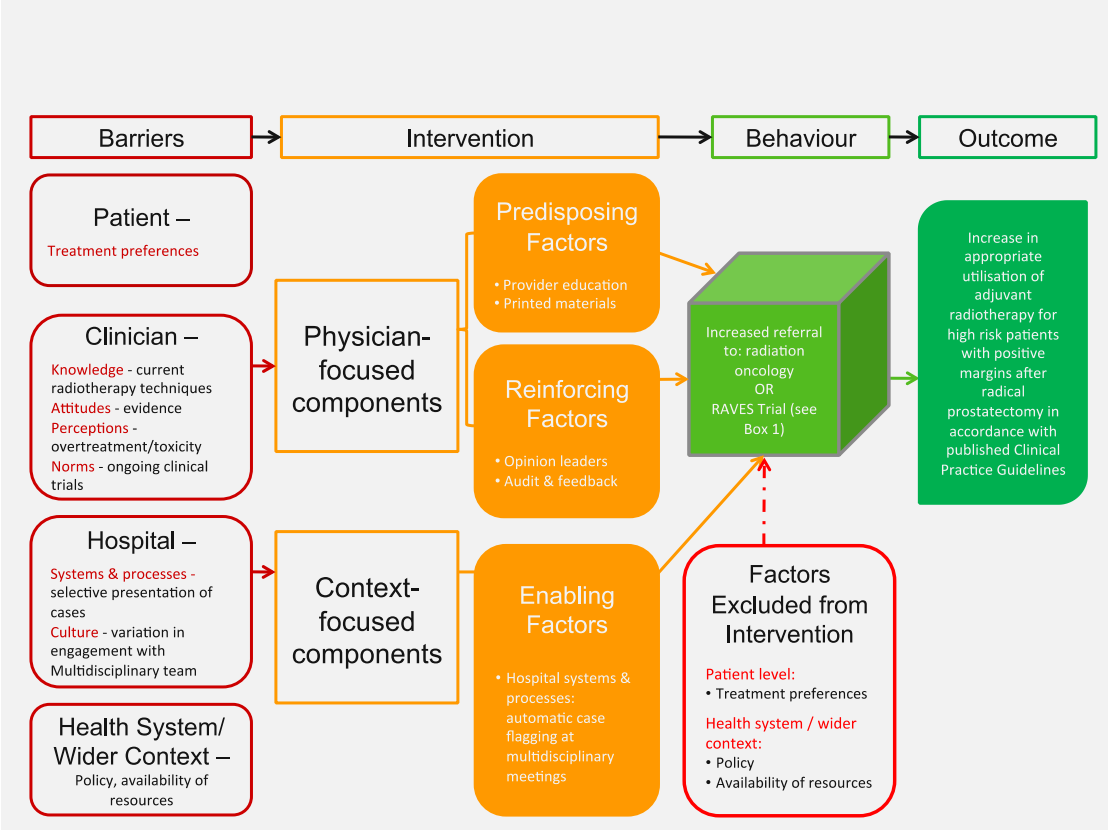
2. Patient: treatment preferences (perceived to be influenced by interaction with urologists).

3. Hospital system and processes: variation in urologists' engagement with the multidisciplinary team (MDT) of specialist surgeons, medical oncologists, radiation oncologists, nurses and other allied health professionals providing specialist cancer care; and selective presentation of high-risk prostate cancer cases to the MDT resulting in inconsistent multidisciplinary discussion of all available treatment options and pathways.

5.5 Conceptual model

Intervention components are underpinned by the PRECEDE-PROCEED theory of behaviour change (62, 63) that relates interpersonal factors and system characteristics into one model to inform change in practice. This theory enables the integration of barriers identified through our mixed methods needs and barriers analysis into 'predisposing factors' (*e.g.*, knowledge and attitudes of the target group); 'reinforcing factors' (*e.g.*, opinions and behaviour of peers); and 'enabling factors' (*e.g.*, capacity of the system and hospital processes). This is one of the most widely used theories to support rigorous trials of the implementation of guidelines (16) and systematic reviews have shown that trials that intervene to alter these three factors are the most successful.(13) Figure 5.2 illustrates how the identified barriers to change in prostate cancer care have been grouped into the factors of the PRECEDE-PROCEED theory. Additionally, Figure 5.2 illustrates the intervention components that have been designed to target each barrier.

Figure 5.2: Conceptual Model: adaptation of PRECEDE-PROCEED model of behaviour change



5.6 Intervention components

Physician-focused components

1. Provider education (predisposing factor): The Urologist Clinical Leader at each hospital will be supported to facilitate an interactive education session at a routinely scheduled multidisciplinary team (MDT) meeting. This session will be moderated by members of the research team to ensure fidelity and will last approximately 10 to 15 minutes. Participants will be presented with an introduction to the study, including a summary of the evidence underlying the guideline recommendation through a video presentation to control for inconsistency across sites. The video includes the Co-Chair of the ACI Urology Clinical Network, a peer-identified national urologist opinion leader, and a consumer who introduce key messages through discussion of their practice and experience.

2. Dissemination of printed materials (predisposing factor): In the active implementation phase all urologists will be given a full copy of the *Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer* and a summary card that allows quick reference to the evidence supporting the specific recommendation that is the focus of the study, together with information on potential side effects and toxicity. The reverse of this summary card provides information on current radiotherapy techniques and key points to guide impartial discussion with patients before and after surgery to support fully informed decision-making. This includes the potential need for multidisciplinary care and consultation with a radiation oncologist to obtain information about what radiotherapy would involve and the likely benefits and risks of treatment if high-risk features are found upon histopathological examination of the prostate specimen.

3. Opinion leaders (reinforcing factor): A key aspect of the intervention will be the use of Urologist Clinical Leaders in each hospital, identified by peers as being educationally influential, to engage the target group. Clinical Leaders will reinforce key messages, persuade peers to participate in the study and will model targeted referral behaviours and promote practice change.(64) Following the education session, Clinical Leaders will provide ongoing peer support and engage in discussions with colleagues to seek and provide feedback on practice and any continuing barriers to change. The Clinical Leaders are members of the ACI Urology Clinical Network and were recruited by the Network Co-Chair, an expert opinion leader who is influential due to his authority and status amongst his peers.(65) The introduction of key messages by a national opinion leader in the video presented at the education session provides an additional level of peer-to-peer influence.

4. Audit and feedback (reinforcing factor): Following commencement of the intervention, urologists will be provided with ongoing feedback reports detailing the number of patients referred to radiation oncology, at the individual, hospital and study level, obtained through data extraction from medical records. The feedback report will also include information on the number of patients at high risk who are discussed at MDT meetings. The initial feedback report will include baseline data. Feedback will be provided via email or SMS depending on the preferred method of communication of each participant. Aggregated quarterly feedback reports will additionally be presented verbally by the Clinical Leader at MDT meetings.

Context-focused components

Guideline dissemination and educational components will address gaps in provider knowledge. However, a number of reviews indicate that increased knowledge is necessary but insufficient to change individual or organisational behaviour.(41) It is also necessary to enable change by increasing means or reducing barriers.(66) Therefore, in conjunction with physician-focused components, utilising the leverage of the ACI Urology Clinical Network to address the systems barriers identified through the mixed methods needs and barriers analysis, context-focused components will include a new system for automatic case flagging at MDT meetings (enabling factor). Urologists practising at the nine target hospitals will be requested to provide consent for the names of all patients who have had a histopathological examination of a radical prostatectomy specimen and who have extracapsular extension, positive surgical margins or seminal vesicle involvement to be submitted automatically to the hospital urology MDT meeting for discussion. Pathology providers will provide a list of all eligible patients to the MDT coordinator. This will reduce variation in practice and selective presentation of cases to the MDT meeting with the intent to promote more collaborative decision-making and increased referral to radiation oncology for high-risk patients.

5.6 Methods

Phase I: intervention rollout and implementation trial

Hypotheses

Compared with pre-intervention, a larger proportion of post-operative radical prostatectomy patients who are at high risk of recurrence (have extracapsular extension, seminal vesicle involvement or positive surgical margins) treated in hospitals after implementation of the intervention will receive a referral to radiation oncology for consideration of adjuvant radiotherapy or referral to the RAVES trial [Radiotherapy Adjuvant Vs Early Salvage (Protocol Number: TROG.08.03); see the "RAVES Trial" subsection for details].

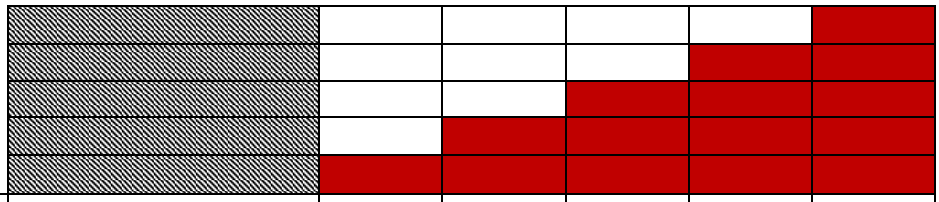
Design

This will be a phased randomised cluster trial with phased introduction of a clinical network led organisational intervention in nine hospitals over 10 months. The order in which hospitals will receive the intervention will be determined randomly using a stepped wedge study design (see Figure 3). This design, originally developed for community studies, has more recently been applied to health service interventions in hospitals (67) and has the following advantages: provides a control comparison where geographic controls are not possible; allows all hospitals in the clinical network with multidisciplinary teams to take part in the intervention; enables the intervention to be tested within the parameters of real-world allocation of clinical network resources with a phased roll out of the hospital-based intervention; and complies with the Cochrane Effective Practice and Organisation of Care Group's consensus statement about study designs of sufficient quality to be included in systematic reviews. This study will be conducted and reported in accordance with the CONSORT statement for the reporting of pragmatic trials.(68, 69)

The intervention will be rolled out across the nine hospitals in five steps of two-month blocks from November 2013 to September 2014. Throughout the

study, hospitals will either be in the active implementation (intervention) or passive (control) phase (see Figure 5.3). Eligibility criteria for inclusion are public hospitals: with a urology multidisciplinary team (MDT) comprising specialists, nurses, and allied health professionals; and that are members of the ACI Urology Clinical Network and have a urologist who will act as the Clinical Leader for that site. All urologists who are members of the urology multidisciplinary team at intervention hospitals will be eligible for inclusion (n≈4 – 10 urologists per hospital).

Figure 5.3: Stepped Wedge Study Design: Staged rollout of intervention from December 2013 to September 2014



Period	Jan–Nov 2013*	Dec 2013	Feb/Mar 2014	Apr/May 2014	Jun/Jul 2014	Aug/Sep 2014
Hospitals Control Intervention	 9 0	 8 1	 6 3	 4 5	 2 7	 0 9

*The solid shaded blocks represent introduction of the intervention over 5 steps. The intervention will be rolled out across the nine hospitals in two-month blocks. Patient medical records will be reviewed for a period of 12 months following the interactive education session. Therefore data collection will not be completed until September 2015. *Control-only monitoring.*

Outcomes

Primary outcomes are patient referral to radiation oncology for discussion of adjuvant radiotherapy in line with guideline recommended care or referral to the RAVES trial (see the 'RAVES Trial' subsection for details). Secondary outcomes include: an initial patient consultation with a radiation oncologist; enrolment in the RAVES trial; and commencement of radiotherapy.

RAVES Trial – an opportunity to demonstrate shift in equipoise

RAVES [Radiotherapy Adjuvant Vs Early Salvage (Protocol Number: TROG.08.03)] is a multi-centre phase III clinical trial comparing survival and quality of life outcomes for patients at high-risk post prostatectomy who are randomised to have: i) radiotherapy deferred (salvage radiotherapy) until their prostate specific antigen (PSA) begins to rise (common current practice); OR ii) immediate radiotherapy (adjuvant radiotherapy) after surgery (regarded as evidence-based standard of care). This is seen as a very important local trial as, despite international evidence that adjuvant radiotherapy is effective, this practice has not been widely adopted due to Urologists' concerns about side effects and overtreatment. The aim of the RAVES trial is to determine whether salvage radiotherapy is as effective as adjuvant radiotherapy and results in improved quality of life.

Data collection—data extraction from patients' medical records

Outcome data to assess changes in healthcare practice will be collected through data extraction from urologists' and radiotherapy patients' medical records by independent, trained research assistants who are blind to the date that the intervention was commenced at the hospital. Baseline data will be collected retrospectively for patients undergoing a radical prostatectomy during January 2013 to November 2013. Pilot testing of the medical record review tools and processes will allow us to train the research assistants and establish and test data collection procedures.

Information from medical records

Treatment outcomes that will be collected through medical record review for cases with extracapsular extension, seminal vesicle involvement or positive surgical margins (confirmed by pathology reports) are: referral to radiotherapy, taken from the surgeon's notes (including dates of surgery and referral) or in the case where there was no referral that radiotherapy was

discussed and the reason(s) for not referring to radiotherapy; uptake of radiotherapy or enrolment into the RAVES trial from the radiation oncology database; and time between surgery and commencement of radiotherapy. Individual case records will be reviewed for a minimum of six months after initial radical prostatectomy.

Data will be abstracted from medical records at hospitals, cancer centres and urologists' private consulting rooms using previously established methods.(33)

Hospital level factors will be collected from centrally held records including specialist cancer centre and size. Patient level factors will be collected from the medical and hospital records including: month and year of birth, comorbidities, stage of cancer, Gleason score, PSA level at diagnosis, country of birth and private health insurance status. Remoteness of residence and socio-economic status (SES) of the cases will be assigned using their postcode of residence and the ARIA (70) and SEIFA (71), respectively.

Hormone therapy, comorbidities, pre-diagnostic PSA levels, Gleason score, country of birth, and health insurance status are potential barriers to referral for radiotherapy.

Study sample

The unit of study will be the participating multidisciplinary teams (MDT). Nine public hospital-based MDTs in NSW will participate. The hospitals are located in both metropolitan and regional areas. Approximately four to ten urologists will be included at each site.

Data analysis

The primary analysis will be conducted at the individual patient level using a generalised estimating equations (GEE) approach to account for repeated outcome observations within clusters (urologists and MDTs). The dependent variable for this analysis will be referral to a radiation oncology service for

adjuvant radiotherapy or enrolment into the RAVES trial (versus no referral) for each prostate cancer case. The exposure variable will be the intervention status (pre versus post) of the hospital at the time of the post-prostatectomy consultation. Other independent variables will be added to the model if they are shown to be independently associated with radiotherapy referral and/or their inclusion in the model changes the linear coefficient of the intervention effect by more than 20% in absolute value. Analysis to determine the extent to which changes in urologists' knowledge, attitudes and beliefs (Phase II) mediated any changes in referral patterns will be assessed by including clinicians' change scores in the GEEs.

Sample size and statistical power

Based on estimates from the NSW Central Cancer Registry and Medicare claims data we estimate that 3,517 NSW men will have a radical prostatectomy in 2013. Approximately 1,618 (46%) of these will be performed in the nine hospitals with urological MDTs participating in the ACI Urology Clinical Network according to linked cancer registry and hospital data for all NSW men diagnosed with prostate cancer. Assuming no major change has occurred in this distribution, there will be 1,348 radical prostatectomies over the 10 months of this trial. Of these, 20 to 50% or 270 to 671 men will be at 'high risk'.(72-75) The stepped wedge design is relatively insensitive to variations in the intracluster correlation (ICC) as a consequence of its efficient use of within-cluster and between-cluster information and has little impact on the study's power. However, based on the best available information, we estimate that the ICC for use of radiotherapy will be between 0.09 and 0.15.(76)

The most recently available data indicate 10% of high-risk men receive radiotherapy after surgery in NSW.(33) With the release of the Australian Cancer Network Clinical Practice Guidelines and the commencement of the

RAVES trial we estimate that at the commencement of our trial, administration of radiotherapy following surgery will have increased to 15% to 20% of high-risk patients. Our stepped wedge study design with nine clusters, six time intervals (including the pre-intervention control step) and ICCs of 0.09 to 0.15 will have at least 80% power to detect an increase in referral to a radiation oncologist from 15% to 35%, or 20% to 40% if a minimum of 30% of patients are at high risk, and from 20% to 35% if at least 50% of prostate cancer cases are at high risk.

Staff training and evaluation

Primary and secondary outcomes can be measured reliably through clinical data collection and this method has been used previously.(33, 77, 78) Research assistants conducting the medical record review will be trained and we will conduct a 10% blinded re-review to assess inter-rater reliability.

Phase II: identify mechanisms of provider and organisational change

Design

'Before and after' mixed methods study to measure knowledge, attitudes, process, and explanatory variables.

Urologists' knowledge and attitudinal outcomes

Hypotheses

Compared with pre-intervention measures, urologists post-intervention will have: increased knowledge about the evidence for appropriate adjuvant radiotherapy for high-risk prostate cancer patients after radical prostatectomy and the associated risks and benefits of treatment; and more positive attitudes towards the need for referral to radiation oncology as a means to support fully informed patient decision making.

Data Collection

A quantitative study of urologists will be conducted using a questionnaire to assess knowledge, beliefs, social influences, attitudes and motivation at three time points: baseline (pre-intervention); six months after the roll-out of the intervention; and at the end of the study (n ≈ 4 – 10 urologists per hospital). The survey is tailored to the intervention, uses previously identified domains (knowledge, beliefs, motivation, social influences), constructs, and generic questions to investigate the implementation of evidence-based practice (48), and is modelled on questions developed for other clinical conditions.(79) The measures using Likert scales have been developed through pilot testing and their feasibility and reliability will be assessed as part of the data collection in accordance with best practice.(80) Questions are consistent with those used in the baseline nationwide survey of urologists to enable comparison between groups. These surveys produce continuous scores for knowledge, beliefs, social influences, attitudes, and motivation at the clinician level that will be averaged for each hospital at each time point.

A follow up nationwide survey of urologist members of the Urological Society of Australia and New Zealand (USANZ) (n ≈ 370) will be conducted to determine whether urologists' attitudes shifted locally/nationally without intervention.

Process outcomes

Research question

Was the intervention implemented as intended?

Data collection

The date of commencement of the intervention will be noted as the day the Urologist Clinical Leader within each site facilitated the educational intervention session. Agendas and minutes of subsequent MDT meetings will

be reviewed using a method developed by members of the investigator team (81) to assess: numbers attending the meeting; frequency of mentioning the study; discussion of cases flagged by pathology; presentation of medical record review feedback; and changes in hospital practice as indicators of sustained interest in the intervention and organisational process changes.

Research Questions

1. Why did or did not the intervention result in evidence-based care?
2. Why was or was not the intervention implemented or sustained in hospitals?

Data Collection

1. Qualitative semi-structured interviews with Clinical Leaders at the end of the study to feedback study results and explore the reasons for them (n=9).
2. Qualitative semi-structured telephone interviews, informed by feedback from Clinical Leaders, with urologists in the nine intervention hospitals at the end of the study to feedback study results and further explore the reasons for them (n≈4 – 10 urologists per hospital).

Data analysis

Survey data will be analysed using bivariable methods (means, t-tests and ANOVA for normally distributed continuous data; medians and non-parametric tests for non-normally distributed continuous data; and proportions and chi-squared tests for categorical data).

Semi-structured interview data will be analysed thematically using a matrix-based framework to organise data according to the theoretical framework used for the intervention design to identify why changes did or did not happen in the hospitals and why the intervention did or did not result in improved care.

5.7 Research governance

The study has been approved by Royal Prince Alfred Research Ethics Committee (ID: X12-0388 & HREC/12/RPAH/584). Site-specific approval (SSAs) from the research governance office at each of the nine participating hospitals has been obtained. Site-specific approval from Cancer Council NSW ethics committee has been granted to cover data collection, storage and analysis at Cancer Council NSW.

5.8 Trial status

The intervention and data collection phase of the study commenced in November 2013.

5.9 Discussion

Clinical networks such as those established by the NSW Agency for Clinical Innovation are increasingly being viewed as an important strategy for increasing evidence-based practice in Australia and other countries. This interest in clinical networks is accompanied by significant investment in them but few studies have directly tested their effectiveness in driving implementation initiatives. To the authors' knowledge, this study will be one of the first randomised controlled trials to test the effectiveness of clinical networks to lead changes in clinical practice in hospitals treating patients with high-risk cancer and improve evidence-based care.

5.10 Limitations

The aim of this study is to target referral patterns of practising clinicians using the leverage of a clinical network. Intervention components therefore focus on the attitudinal and systems barriers at the urologist and hospital level. While we have sought consumer input into the design of provider-focused materials to provide guidance on what information patients want from

consultation with their physician, ethics approval for the current study does not permit direct interaction with patients being treated by urologists in the study. The research team is developing a proposal for a sub-study focused on how patients can influence the treatment they receive, to be conducted at the end of Phase I.

5.12 Authors' contributions

The authors are the investigators of the research grant funding this research activity. BB, in collaboration with all other authors, conceptualised the research project and developed the protocol presented in this paper. All authors provided input into various aspects of the study, provided ongoing critique, and approved the final version of the manuscript.

5.13 Ethics approval

Ethical approval to conduct the study has been obtained from Royal Prince Albert Hospital Human Research Ethics Committee, January 2013 (ID: X12-0388 & HREC/12/RPAH/584).

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Chapter 6: Process evaluation

6.1 Background

In order to increase the utility of implementation research and aid interpretation of outcomes, it is necessary to conduct high quality process evaluation in parallel with trials of complex interventions.(1, 2) This is especially true for interventions that seek to change health care provider behaviours in complex settings, where there may not be a clear causal pathway.(3) Process evaluation can help understand issues of program implementation, explain discrepancies between expected and observed outcomes in relation to context, and provide insights into possible causal mechanisms and effect modifiers to aid subsequent translation from research into practice.(4)

Process evaluations most commonly use qualitative methods to explore participants' perceptions of acceptability of interventions and whether they were implemented as planned, with fidelity. This type of evaluation provides context-specific insights that can help interpret the results of an individual trial, but is arguably less helpful in predicting the likely generalisability of findings.(3) Given that complex interventions may act at multiple levels including systems, organisations, professions or individuals, a theory-oriented approach to process evaluation, underpinned by behavioural constructs hypothesised a priori, may be more useful for exploring how interventions function across different settings and to identify causal mechanisms, and barriers and enablers to translation into routine clinical practice.

6.2 Aims and objectives

The primary aim of the CLICC process evaluation was to identify mechanisms of provider and organisational change (5), which were assessed using three domains adapted from the process evaluation of a complex intervention aiming to increase the use of research in health policy and programs(6): (i) whether the intervention

was implemented as intended (*implementation*); (ii) why the intervention did or did not result in more evidence-based care (*participation and response*); and (iii) why was or was not the intervention implemented or sustained across implementation sites (*context*). Specifically domains were assessed as follows:

Participation

Participation was considered in terms of recruitment and reach, specifically: the proportion of the target population that actually received the intervention, and their representativeness.

Implementation

Implementation was considered as the extent to which the intervention was implemented as planned with fidelity, the degree to which essential elements were delivered, the level of exposure, and local adaptation.

Response

Response was considered as the extent to which multidisciplinary teams integrated and adopted new knowledge, systems and processes into their routine practice. Unintended consequences and outcomes in response to the intervention were also evaluated.

Context

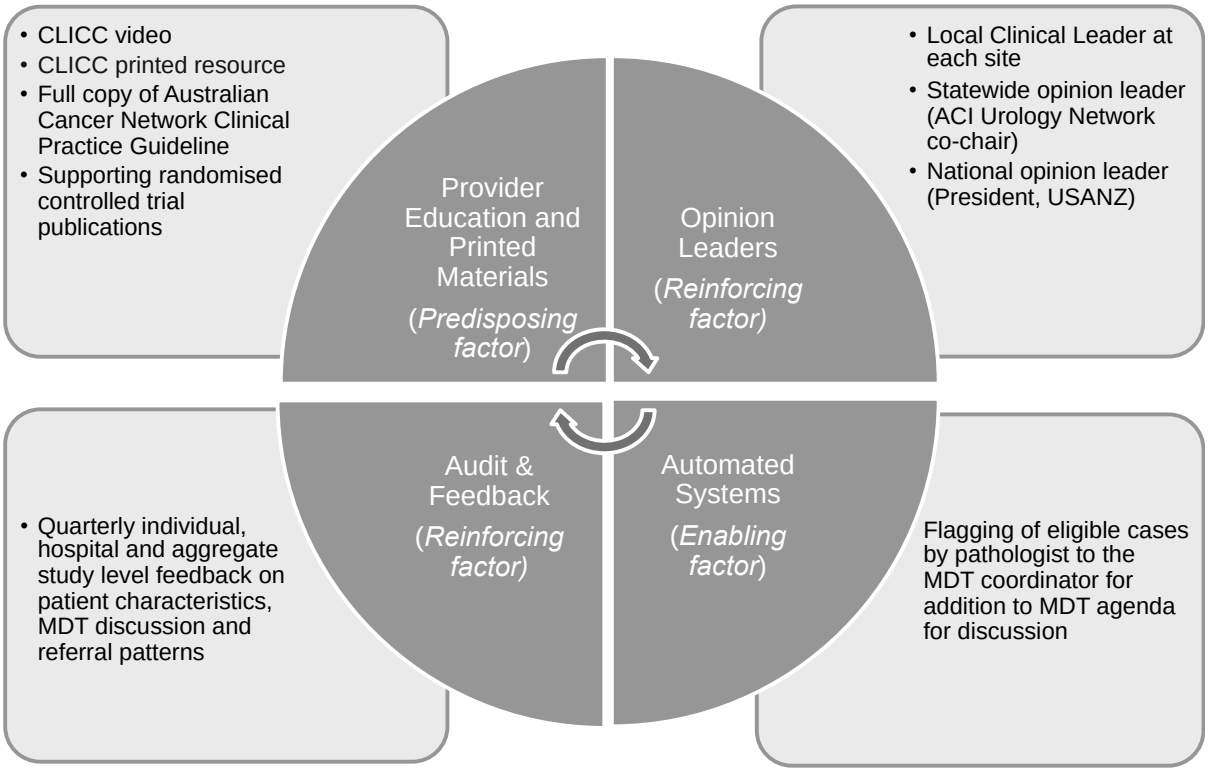
Context was documented to enable consideration of any setting characteristics that may have influenced the delivery of the intervention or impacted on its effectiveness or maintenance/sustainability across study sites. Contextual evaluation will facilitate interpretation of the outcomes of the CLICC trial and maximise the potential for scale up and spread.

6.3 Methods

6.3.1 Evaluation framework

The CLICC conceptual program logic model (5) (Chapter Four) informed the design of the process evaluation to explore how well the theory underpinning the intervention was realised in the design and delivered in the real world context of the study.(6) CLICC elements are summarised in Figure 6.1. A mixed methods approach was used to gather quantitative measures of intervention elements to assess *implementation*, *participation* and *response*, and *context*, combined with qualitative exploration of participants experience of, and *response* to, the intervention (predisposing, enabling and reinforcing factors) and the *context*ual characteristics of the nine participating study sites.

Figure 6.1 CLICC intervention elements



6.3.2 Data collection

Quantitative data

Quantitative data were extracted into an intervention tracking data collection form (fidelity checklist) for each participant. This tracking form was completed by the study team, using the data sources outlined below, to record individual exposure to intervention elements including: opinion leaders; the CLICC introductory video; printed educational materials; audit feedback reports; and flagging of eligible patients by pathology for discussion at multidisciplinary team meetings, together with participation in evaluation activities.

Participation

Participant recruitment at each site was documented in a recruitment database, which included the overall number of urologist members of each of the nine participating multidisciplinary teams and the number who consented, declined, did not respond or withdrew from the study (including dates). The recruitment database was also used to track follow-up of non-attendees by Clinical Leaders and/or the research team to recruit them into the study according to predetermined protocols.

Implementation

The date of commencement of the intervention was recorded as the day the Urologist Clinical Leader at each site facilitated the educational intervention session during a routinely scheduled multidisciplinary team meeting. Attendance of urologists at the intervention session was recorded. The aggregate level of exposure to, and adaptation of, intervention elements at each site was also recorded in an intervention-tracking database.

Response

Where available, agendas and minutes of MDT meetings for the duration of the active intervention phase were reviewed to assess response to the intervention.

The extent to which participants integrated and adopted new knowledge was assessed through pre- and post-intervention surveys to measure knowledge, attitudes and beliefs. Results are presented in Chapter Eight.

The extent to which multidisciplinary teams integrated the MDT flagging process into routine practice was recorded in an MDT tracking database, which included the date the patient was flagged by pathology, whether the patient was added to an MDT agenda, date of discussion, and the MDT recommendation (where known). Data were extracted from MDT administrative records and supplemented with data from patient medical records (data collection methods for patient medical record review are detailed in Chapter Seven).

It was not possible to assess frequency of mentioning the study or changes in hospital practice through meeting minutes, as proposed in the published study protocol, due to inconsistencies in MDT recording keeping.(5)

Context

Setting characteristics such as frequency, organisation and record keeping of multidisciplinary team meetings were documented together with contact information for the MDT coordinator at each site, and for public and private pathology and radiation oncology service providers for each participating Clinical Leader and urologist. Patient volume, public/private case mix and other setting characteristics were collected through independent medical record review. Further analyses including potential effect modifiers are detailed in Chapter Seven.

Qualitative data

Qualitative semi-structured interviews were conducted with Clinical Leaders and urologist participants at the end of the active intervention phase of the study to explore participants' experience of, and response to intervention elements (*predisposing*, *reinforcing* and *enabling* factors), together with contextual factors which may have hindered or facilitated their implementation and sustainability.

Interview themes are detailed in Table 6.1. Full interview guides can be found in Appendices V and VI.

Analyses

Generalised linear regression models with a Poisson distribution and log link, and generalised estimating equation (GEE) adjustment for the clustering of patients within urologists were used to estimate the relative proportions (RR) of patients who, within 4 months after prostatectomy, were: (1) flagged by pathology for discussion at the MDT; and (2) discussed by the MDT among those flagged. The dichotomous dependent variable in each regression model was outcome (1) or (2). Independent variables were site (1 through 9) and insurance status (public versus private patient). The categories within each independent variable correspond to groups for which the outcomes are compared.

Interviews were transcribed verbatim to produce transcripts of narrative text for thematic analysis. The CLICC evaluation framework guided the initial categorisation of text, whereby each segment of interview text was conceptually linked to one of two qualitative evaluation domains: *response* to the intervention (predisposing, enabling and reinforcing factors); and the *context*ual characteristics of the nine participating study sites. The author conducted all interviews and analyses and two iterations of comparative coding were undertaken to ensure consistency. Negative cases are reported with supporting text where identified. The CLICC investigator team assessed applicability and face validity.

6.4 Results

6.4.1 Participation

Eligibility criteria

Eleven NSW hospitals met the CLICC implementation trial inclusion criteria of having: (i) a urological MDT; and (ii) a member(s) of the ACI Urology Network.

All urologist members of a participating urology MDT, who: (i) performed radical prostatectomy during the control or intervention phase; and (ii) reviewed their high-risk prostate cancer cases (post-radical prostatectomy) at the participating MDT at the time the intervention commenced at that site, were eligible for inclusion. The latter two eligibility criteria were included after publication of the study protocol [5] to enable exclusion of urologists who: (i) did not perform any radical prostatectomies during the study period and, therefore, would not contribute any clinical data; and (ii) are members of a participating MDT for the purposes of other urological conditions but present radical prostatectomy patients for review at a different non-participating MDT.

Participation

The urological MDTs at two eligible hospitals declined to participate. From the remaining nine eligible sites 55 urologists (inclusive of nine Clinical Leaders) were invited to participate in CLICC. Six were ineligible as they performed no radical prostatectomies during the specified study period, eight declined, and four withdrew consent, resulting in a total of 37 participants (nine Clinical Leaders and 28 participating urologists). The proportion of participating eligible urologists across sites is shown in Table 6.2. Overall participation was 76% with 100% of eligible urologists participating at five out of nine sites (Sites 1, 4, 5, 6 and 8). The response rate at Site 2 was anomalously low (18%) with only two out of 11 eligible urologists participating. Of note, four urologists at that site initially provided consent but withdrew when contacted by the medical record review team to arrange access patient medical records. Sites 3, 7 and 9 each had one eligible urologist who declined to participate. A participant flow diagram is provided in Chapter Seven (Figure 7.2).

Table 6.1: Process evaluation interview themes

Interviewee	Process evaluation domain	Interview theme
Clinical Leader	*Participation and response*	- Understanding of role and work undertaken as Clinical Leader
	Context	- Factors that hindered or facilitated role as Clinical Leader
		- Interaction with colleagues
		- Contextual factors that hindered or facilitated the implementation of the project
	Sustainability	- Continuation of CLICC elements
Clinical Leader **Participating urologist**	*Participation and response*	- Adequacy of information about what the study was hoping to achieve
		- Perceptions of study success
		- Most helpful intervention components
		- Effect(s) of the intervention on MDT decision-making
		- Effect(s) of the intervention on relationships with colleagues
		- Any concerns regarding the implementation of the intervention or unintended outcomes
		- Perceptions of the extent to which the intervention resulted in change in practice and any wider changes in patterns of care
		- Contributions of the project to patient care
		- Benefits of the project for participants
	Context	- Conditions critical to the project's success/lack of success
Participating urologist	*Context*	- Perception of the supportiveness of, and interaction with, the Clinical Leader

Table 6.2: Proportion of participating eligible urologists by site (ranked)

	Total number of eligible* urologists	Number of participating urologists	Proportion participating in CLICC %
Site 6	5	5	**100**
Site 5	5	5	**100**
Site 4	4	4	**100**
Site 8	4	4	**100**
Site 1	4	4	**100**
Site 3	6	5	**83**
Site 7	5	4	**80**
Site 9	5	4	**80**
Site 2	11	2	**18**
Total	49	37	**76**

*Performed one or more radical prostatectomies during the baseline and/or study period and reviewed high-risk prostate cancer cases (post-radical prostatectomy) at the participating MDT at the time the intervention commenced at that site

6.4.2 Implementation

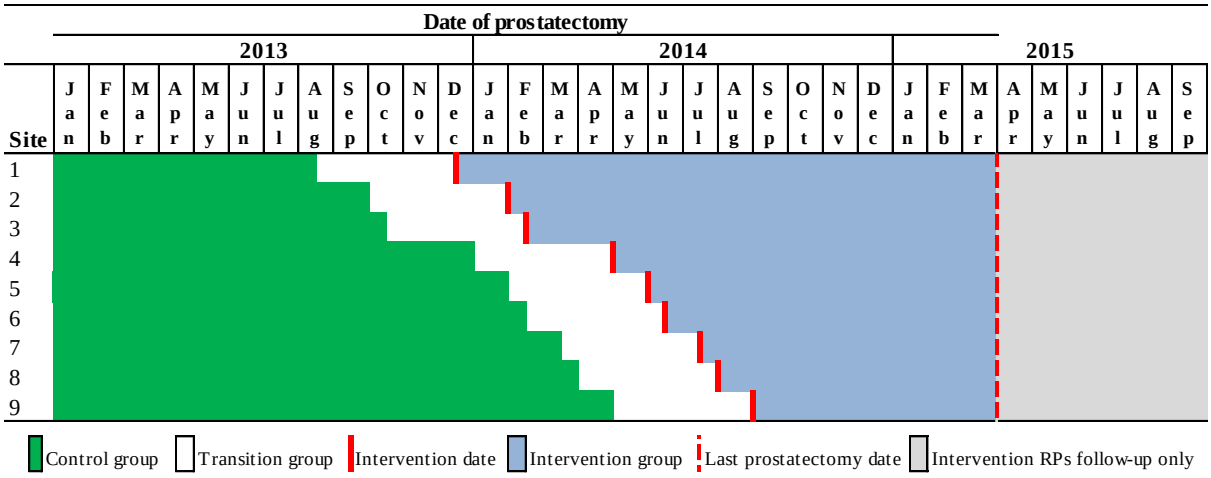
The CLICC intervention was rolled out across the nine participating sites as per the stepped wedge design in the study protocol (Figure 6.1). The trial commenced at the first site in December 2013 and the final site in August 2014.

The last RP recruited to the Intervention group occurred on 31 March 2015. The minimum period of exposure to CLICC intervention elements was 13 months (Site 9) and the maximum period of exposure was 21 months (Site 1).

Attendance at the introductory CLICC intervention session

Twenty-nine participating urologists attended the introductory CLICC intervention sessions across the nine sites. This included all nine Clinical Leaders and 20 of the 28 other participating urologists.

Figure 6.1: Stepped Wedge Study Design: Staged rollout of CLICC intervention from December 2013 to September 2014



Exposure to CLICC intervention elements

Aggregate site level exposure to CLICC intervention elements is summarised in Table 6.3.

Opinion leaders

The CLICC implementation trial incorporated three levels of opinion leader: (i) a local Clinical Leader for each site; (ii) a statewide opinion leader (Urology Network Co-Chair); and (iii) a national opinion leader (President of USANZ).

The Urology Network Co-Chair made the initial approach to the nine Clinical Leaders to recruit them to their role in the study. The Clinical Leader for each study site was briefed on the aims and elements of CLICC by the study team and was provided with a script to facilitate the introductory CLICC intervention session. All urologist participants attended at least one MDT meeting at which the Clinical Leader presented aggregate quarterly feedback reports for discussion, providing further exposure to the local opinion leader element. Thirty-two of the 37 participants (all nine clinical leaders and 23 participating urologists) (86%), were exposed to the Urology Network Chair and President of USANZ through the CLICC introductory video; 29 viewed the video at the introductory CLICC intervention sessions and three

viewed it subsequently as part of recruitment to the study. Four of the five participants who did not view the CLICC introductory video discussed the study directly with the Urology Network Chair. The Clinical Leader discussed the study with the remaining participating urologist.

All participants met the minimum requirement of watching the CLICC introductory video or having a discussion with the Clinical Leader for their site and/or Urology Network Co-Chair.

Provider education and printed materials

In addition to the educational elements in the CLICC introductory video, participants were provided with an information pack at the CLICC intervention session containing: a full copy of the Australian Cancer Network Clinical Practice Guideline for the Management of Locally Advanced and Metastatic Prostate Cancer; peer review journal publications reporting the results and long-term follow up of the EORTC (7, 8), SWOG (9-11) and ARO (12, 13) randomised controlled trials that form the evidence base for the clinical practice guideline recommendation; and the CLICC printed resource (Appendix VII) comprising a summary of the guideline recommendation and supporting evidence and a patient-urologist discussion guide. The information pack was emailed and mailed to participants who did not attend the CLICC intervention session.

All participants met the minimum requirement of receiving the CLICC printed resource.

Audit and feedback

Individual quarterly feedback reports, based on data from independent patient medical record and MDT record review, were sent to participants by mail and email (see Appendix VIII for feedback report templates). Individual reports were received on the day of a routinely scheduled MDT meeting at which the Clinical Leader presented site and aggregate study level reports for discussion. Participants received

a maximum of four and a minimum of two feedback reports, as outlined in Table 6.2, depending on date of commencement of the intervention at their site. A total of 110 individual feedback reports and 26 site and aggregate study level reports for presentation by the Clinical Leader to the MDT were distributed to participants.

All participants attended at least one MDT meeting at which the Clinical Leader presented site and aggregate study level feedback. Inconsistencies in MDT record keeping across sites meant that it was not possible to accurately determine which participants were in attendance at all MDT meetings where feedback was presented. Nor were we able to confirm whether all feedback was presented for discussion at the MDT meetings as scheduled at two sites (Sites 3 and 5).

All participants met the minimum requirement being mailed and emailed all scheduled individual feedback reports following consent to participate in the study.

Automated systems

Clinical Leaders and urologist participants provided consent for the names of all patients (public and private) who were subject to a histopathological examination of a radical prostatectomy specimen for prostate cancer and who had extracapsular extension, positive surgical margins or seminal vesicle invasion to be submitted to the urology MDT for discussion. Flagging commenced as soon as signed consent was forwarded to the pathology provider. There was an unanticipated gap in flagging from March 2014 to June 2014 for private patients serviced by one pathology provider, which affected Sites 1, 2 and 3.

Flagging of eligible patients involved six private pathology providers. The largest private pathology provider serviced more than three quarters (78%; 29 out of 37) of the participating urologists across eight of the nine sites. After an initial period of manual identification and flagging, this provider integrated software code into their database such that reports were generated every two weeks to capture eligible patients from the preceding fortnight. Email notifications were sent directly from the

pathologist to the nominated MDT coordinator (copying the Clinical Leader and participating urologist(s)) for each site with a list of patients to be added to the agenda for the subsequent MDT meeting. The remaining five private pathology providers and eight public pathology providers manually identified and flagged eligible patients as per locally agreed protocols. Calendar reminders were set up for the nominated contact at each pathology service to prompt notification prior to scheduled MDT meetings. The study team monitored pathology flagging and, where necessary, followed up with reminder telephone calls. One public pathology service provider (Site 7) declined to support patient flagging citing insufficient resources.

All participants met the minimum requirement providing consent for eligible patients to be flagged by pathology to the MDT coordinator for discussion by the MDT from the time of consent or for a minimum of six months.

The extent to which pathology providers within and across sites were able to implement the flagging process is detailed in Table 6.4. There was significant variation in the proportions of "all patients" flagged between sites ($p<0.001$) (p-value shown in Table 6.5, proportions shown in Table 6.4 and Table 6.5). Overall, 318 of 407 eligible patients were flagged by pathology for discussion at the MDT (78%). Flagging of private patients was consistent across the sites that used the largest private pathology provider. One hundred percent of private patients were flagged for discussion during the study period at two of the eight sites that used this provider, these being the last two sites to enter the trial when the process was fully established (Sites 8 and 9). As noted, Sites 1, 2 and 3, the first to enter the CLICC trial prior to the establishment of an optimally efficient process, were adversely affected by a gap in MDT flagging that occurred while this pathology provider integrated software code with 68%, 67% and 84% of eligible private patients flagged respectively. Across all private pathology service providers, 85% (280 of 329) of eligible private patients were flagged for discussion. The Clinical Leader and all participating urologists at Site 5 used alternate private pathology providers who combined flagged a little over a third (4 of 11; 36%) of eligible patients.

Table 6.3: Site level exposures to CLICC intervention elements

	Opinion Leaders			Provider Education and Printed Materials				Audit & Feedback^				Automated Systems	
	Clinical Leader	Urology Network Co-Chair*	President of USANZ*	CLICC Video	Full CPG**	RCT*** papers	CLICC printed resource	Report 1	Report 2	Report 3	Report 4	Public pathology MDT flagging	Private pathology MDT flagging
Site 1	X	X	X	X	X	X	X	X	X	X	X	X	X
Site 2	X	X	X	X	X	X	X	X	X	X	X	X	X
Site 3	X	X	X	X	X	X	X	X	X	X	X	X	X
Site 4	X	X	X	X	X	X	X	X	X	X		X	X
Site 5	X	X	X	X	X	X	X	X	X	X		X	X
Site 6	X	X	X	X	X	X	X	X	X			X	X
Site 7	X	X	X	X	X	X	X	X	X				X
Site 8	X	X	X	X	X	X	X	X	X			X	X
Site 9	X	X	X	X	X	X	X	X	X			X	X

* CLICC video

** CPG: Australian Cancer Network Clinical Practice Guideline for the Management of Locally Advanced and Metastatic Prostate Cancer(14)

*** Randomised controlled trial

^ Feedback report templates are included in Appendix VII

Feedback Report 1: individual, site level and aggregate study level pre-CLICC (baseline) outcome data (1 January 2013 – end of month prior to CLICC intervention commencement)

Feedback Report 2: site level and aggregate study level pre-CLICC (baseline) outcome data / individual and site level post-CLICC MDT discussion data

Feedback Report 3: individual, site level and aggregate study level pre-CLICC (baseline) and post-CLICC outcome data / individual and site level post-CLICC MDT discussion data

Feedback Report 4: individual, site level and aggregate study level post-CLICC MDT discussion data / aggregate study level pre-CLICC (baseline) outcome data

Public patients were significantly less likely to be flagged by pathology for discussion than private patients (Relative Risk 0.56; 95% CI [0.42, 0.75; p<0.001) (data shown in Table 6.5). Overall, 38 of 78 (49%) of eligible public patients were flagged. The public pathology provider at Site 7 declined to support flagging. While agreement was received from the other public pathology providers, no eligible public patients were flagged at Site 6 (0 of 1 eligible patients flagged; 0%) or Site 8 (0 of 4 eligible patients flagged; 0%). One public pathology provider (Site 9), with regular prompts from the study team, was able to achieve comparable results with the largest private pathology provider with 15 of 18 eligible patients flagged (83%).

Integration of the MDT flagging process into routine practice by multidisciplinary teams is detailed in Table 6.5.

Table 6.4: Proportion of eligible patients who were flagged by pathology (ranked by All patients)

	All patients			**Private patients**			**Public patients**		
	Number of high-risk cases	Number of cases flagged	**% flagged**	Number of high-risk cases	Number of cases flagged	**% flagged**	Number of high-risk cases	Number of cases flagged	**% flagged**
Site 6	36	34	**94%**	35	34	**97%**	1	0	**0%**
Site 8	52	48	**92%**	48	48	**100%**	4	0	**0%**
Site 9	32	29	**91%**	14	14	**100%**	18	15	**83%**
Site 3	120	96	**80%**	106	89	**84%**	14	7	**50%**
Site 4	54	40	**74%**	44	37	**84%**	10	3	**30%**
Site 7	34	25	**74%**	28	25	**89%**	6	0	**0%**
Site 1	48	32	**67%**	31	21	**68%**	17	11	**65%**
Site 2	12	8	**67%**	12	8	**67%**	0	0	**.**
Site 5	19	6	**32%**	11	4	**36%**	8	2	**25%**
Total	**407**	**318**	**78%**	**329**	**280**	**85%**	**78**	**38**	**49%**

6.4.3 Response

The proportion of flagged patients who were added to an agenda and discussed by the MDT within four months of surgery is presented in Table 6.5

as a measure of integration of the MDT flagging process into routine clinical practice. There was significant variation between sites in the proportion of patients discussed among those flagged ($p<0.001$). While, as noted previously, public patients were significantly less likely to be flagged for discussion than private patients, there was no significant difference in the proportion discussed among those flagged (Relative Risk 1.15; 95% CI [0.89, 1.49]; $p=0.282$). Two sites discussed 100% of flagged patients (Site 5: 6 of 6; Site 6: 34 of 34). Site 3, the site with the highest patient volume, discussed the lowest proportion flagged cases (30 of 96; 31%).

Three sites (Sites 2, 3 and 8) adapted the process for adding patients to the MDT agenda after receiving notification of eligible patients from pathology. At Site 2 the MDT coordinator did not list eligible patients on the agenda for discussion unless a request was received from the participating urologist. At Site 3 and Site 8 discussion of patients was delayed until after receipt of the first post-operative PSA test result.

Secondary outcome data reporting the proportion of patients discussed at the MDT before and after the implementation of the flagging process are presented in Chapter Seven (Table 7.2) to determine if there was a significant increase in discussion of patients after the intervention.

Sensitivity analyses including potential effect modifiers of the effects of the intervention on likelihood of being discussed at the MDT are reported in Chapter Seven (Supplementary Table S7.2).

Due to inconsistencies in MDT record keeping it was not possible to accurately record the MDT recommendation across all sites. Nonetheless, recommendations that were recorded were included in subgroup analyses exploring the relationship between MDT recommendation and referral to radiotherapy or RAVES in Chapter Seven (Table 7.4).

6.4.3 Context

Eight of the nine MDTs held fortnightly meetings and one met monthly (Site 4). All nine MDTs included both public and private patients. All but one site had a designated MDT coordinator (administrator or nurse) responsible for scheduling and agendas. At the remaining site (Site 3), organisation of the MDT was delegated to the incumbent urology Registrars. Record keeping was variable across sites ranging from a formal MDT database documenting discussion and recommendations maintained by a data manager (Sites 8 and 9), MDT administration records maintained by the MDT coordinator (Sites 2, 3, 4 and 6), letters of recommendation produced by the MDT coordinator (Sites 1 and 5), a MDT "flag" in the electronic patient medical record (Site 3), or ad hoc notes taken by the MDT coordinator, cancer care nurse coordinator or Registrar (Site 7). The level of detail, timeliness and completeness of MDT records was variable.

6.4.4 Semi-structured interviews

All nine Clinical Leaders [CL] (100%) and 20 out of 28 participating urologists [PU] (71%) participated in an end of study interview resulting in a total sample of 29 (overall response rate 78%). Two of the interviewees (one Clinical Leader and one participating urologist) did not complete all interview questions due to time constraints. Responses are grouped by process evaluation domain and interview theme.

Table 6.5: Integration of the MDT flagging process into routine care (ranked by Discussed among those flagged)

		Flagged			Discussed[1] among those flagged	
Characteristic	**N1^**	**n1 (% of N1)**	**Adjusted # RR (95%CI)**	**N2^^**	**n2 (% of N2)**	**Adjusted # RR (95%CI)**
All patients:	**407**	**318 (78%)**		**318**	**220 (69%)**	
Hospital						
Site 6	36	34 (94%)	1.13 (1.03, 1.25)	34	34 (100%)	3.30 (2.70, 4.03)
Site 5	19	6 (32%)	0.46 (0.16, 1.32)	6	6 (100%)	3.14 (2.50, 3.95)
Site 1	48	32 (67%)	0.94 (0.81, 1.09)	32	30 (94%)	2.94 (2.29, 3.78)
Site 4	54	40 (74%)	0.96 (0.78, 1.17)	40	36 (90%)	2.92 (2.29, 3.72)
Site 8	52	48 (92%)	1.13 (1.07, 1.21)	48	40 (83%)	2.74 (2.23, 3.37)
Site 2	12	8 (67%)	0.79 (0.75, 0.84)	8	6 (75%)	2.47 (2.03, 3.02)
Site 7	34	25 (74%)	0.94 (0.67, 1.33)	25	18 (72%)	2.37 (1.59, 3.54)
Site 9	32	29 (91%)	1.42 (1.24, 1.63)	29	20 (69%)	2.09 (1.29, 3.37)
Site 3	120	96 (80%)	ref.	96	30 (31%)	ref.
***p*-value**			<0.001			<0.001
Insurance						
Private	329	280 (85%)	ref.	280	190 (68%)	ref.
Public	78	38 (49%)	0.56 (0.42, 0.75)	38	30 (79%)	1.15 (0.89, 1.49)
***p*-value**			<0.001			0.282

^ Intervention group patients

^^ Intervention group patients who were flagged

[1]Patient discussed at MDT meeting within 4 months after prostatectomy

Adjusted for hospital/MDT and insurance with urologist as the clustering variable

Participation and response

Understanding of role and work undertaken

All nine Clinical Leaders reportedly understood their role as to encourage urologist participation and facilitate implementation of CLICC elements and felt adequately informed about what they were expected to do. Only three of the nine (Sites 5, 6 and 7) additionally viewed their role as one of an opinion leader to actively influence and promote participating urologist behaviour change:

> *"To constantly remind the urologists that men with unfavourable histological results from surgery should at least have the discussion and be considered for radiotherapy and to keep that in focus." [CL – Site 7]*

Adequacy of information about what the study was hoping to achieve

18 of 20 urologists reported that they felt adequately informed about what the study was hoping to achieve. The remaining two reported that they were informed but were unsure if there was an undisclosed purpose to the study:

> *"I was informed but I'm not sure if what we were told is what it was really looking at … it's almost like an audit thing." {PU – Site 6]*

> *"Having [X] as the lead in this hospital, and I have the highest respect for him, but there seemed to be an element of not being able to discuss what the investigators were hoping to achieve on a theoretical basis." [PU – Site 4]*

Perceptions of study success

There was variability in participants' perceptions of whether the study was successful both within and across study sites.

More than three quarters of interviewees (22 of 29; 76%) considered that CLICC was successful in their hospital. The most commonly cited reason for perceived success (n=15) was increased discussion of patients at the MDT ensuring no patient got missed or "*slipped through the cracks"*:

> *"… every meeting there are generally CLICC patients that come up, there is always discussion about those patients and probably in more detail then would happen before. In the interest of time we wouldn't have always discussed every patient - if they have low volume cancer then a couple of the urologists would just keep an eye on them. Patients are presented courtesy of [the pathology provider] and that has increased discussion." [CL – Site 7]*

Several participants (n=7) viewed the study as successful in terms of general involvement of the MDT and contribution of patient data through medical record review but were unsure whether this would result in changes to clinical practice:

"Hard to comment – we are adhering to it and all urologists are on board and freely discussing patients at the MDT so successful from that point of view. Don't know if it's changed referral patterns or other behaviours." {PU – Site 6]

Three participants (10%) felt it was too early to tell if the study had been successful or not:

"I think there needed to be a longer study period to continue to have an effect. It has been successful in showing us how few patients get referred for adjuvant radiotherapy and demonstrated the variation in practice within and across hospitals." [PU – Site 7]

Of the four participants (14%) who did not think the study was successful: two cited low participation (both from Site 2); one thought the study unsuccessful because it had not changed their own practice (Site 4); and one (Site 3) noted:

"I think it could have been done better but we didn't give a lot of consideration about how to implement the changes from a logistical point of view. The problem is that we have too many cases so we could have had a better crack at discussing all of them." [CL – Site 3]

Most helpful intervention components

Flagging of cases by pathology for discussion at the MDT was considered the most helpful intervention component in achieving practice change and was mentioned by 21 of 29 interviewees (72%). The automatic nature of the system which ensured all patients were listed and required no action on the part of the urologist was frequently noted:

"[MDT flagging of high-risk cases was] most important especially for high volume cancer centres where it is easy to provide excellent care but patients still fall through the cracks due to sheer numbers. The MDT list was manageable because the patients flagged are the right ones that should be given priority over others." {CL – Site 6]

"The automated nature of the study, not requiring the urologist who is already stretched for time to fill out 400 pages of a clinical trial scenario is a big positive. Data collection and feedback is external. I think flagging will continue. We think we have almost 100% MDT coverage. It seems to be working and done by the team – I haven't had to do much more." {CL – Site 9]

A minority (2 of 29; 7%) did not find MDT flagging helpful because they considered it too early to discuss patients at the subsequent MDT following surgery:

"I think the flagging was not helpful because of the timing – two weeks after the operation there is no progress, no six-week PSA and continence status is not known so you don't have a feel if radiotherapy is appropriate, necessary or a hindrance. You almost become too pushy to force patients to have radiotherapy but if you wait for the PSA at six weeks (and it has been shown that there is no difference between two weeks and two months) you know better. The MDT has changed discussion to two months for that reason." [PU – Site 8]

"Initially [MDT flagging] was done through the MDT coordinator but I wasn't given enough pre-warning to be prepared to discuss [the patient]. It works better now cases are emailed direct and I put them up when I have the post-operative PSA and knowledge of the patient's recovery." [PU – Site 2]

Feedback reports were identified as a helpful intervention component by nearly half of the interviewees (14 of 29; 48%). While some were most interested in their own audit results others found it useful to make comparisons between sites and see how practice varied:

"Individual reporting to the urologists enables them to see their own results – some were surprised by their low referral rates. I'm not sure the overall pattern data made much difference because there were only one or two funny outliers. Personal information is more useful." [CL – Site 7]

"The study results and feedback help us keep an eye on our case load and allows us to monitor our margins and other factors that determine outcomes for patients." [PU – Site 5]

"Interesting to see how our performance compares with others in terms of at risk features, in terms of positive margins and extracapsular extension rates, especially as a regional centre." [CL – Site 5]

Seven interviewees (24%) found the printed educational materials useful with four of these highlighting them as the most helpful element of the trial.

"[Printed materials] were very clear about the way forward for the management of these patients." [PU – Site 5]

However, one participant noted:

"This information has been around for a while but there are problems with the results so I guess that's why we need to think about it." [PU – Site 3]

While five of the 29 (17%) found the CLICC introductory video helpful, others considered it impersonal and the content too lay:

"Flagging followed by the video – it was concise, pitched at the right level and did all the things a good educational video should." [CL – Site 4]

'Clinical content was too simple. If you are attending conferences and up to date with Continuing Professional Development then you would know about adjuvant radiotherapy." [PU – Site 4]

Of the 20 urologist participant interviewees, four (20%) (Sites 4, 5, 7 and 8) noted the influence of the Clinical Leader as important in achieving desired outcomes but none articulated a reason for this.

Effect(s) of the intervention on MDT decision-making

Only four of the 20 urologist participant interviewees (20%) perceived that CLICC had affected MDT decision-making. Two reflected that this change predominantly related to increased awareness of the need to present patients to the MDT:

"Personally no, I was already having robust MDT meetings but it did highlight certain deficiencies in the MDT. So yes, it has, people are more mindful now about the MDT meetings." [PU – Site 3]

"I think so – we had a little summary chat about it the other night when [Clinical Leader] brought it up again… making sure everyone has the full opinion about ongoing management.' [PU – Site 5]

One participant considered that discussion of patients at the MDT translated into increases in referral patterns:

"…patients who are eligible for discussion are discussed at the time and there is now a process in place for those patients to be presented. Discussing patients at the time encourages other referral to radiation oncology or medical oncology etc." [PU – Site 3]

Conversely, another participant reported that MDT discussion decreased referral of patients who were considered inappropriate for adjuvant radiotherapy:

"…it is helpful to discuss T3a cases – for guys with tiny volume extracapsular extension we don't need to clog up the radiation oncology clinic for discussion if we discuss the patient at the MDT and the radiation oncologist says they don't need to see them." [PU – Site 7]

Three quarters of urologist participants (15 of 20; 75%) did not consider that the trial had affected MDT decision-making. Four of these noted that although the MDT recommendations for patient management had not changed more cases were being discussed as a result of flagging:

"No we haven't changed – we have discussed more cases earlier than we normally would but we haven't changed what the decision would be." [PU – Site 7]

Three others felt that MDT decision-making had not changed because they perceived all high-risk patients were already being discussed by the MDT prior to the implementation of patient flagging through CLICC. It was noted,

however, that individuals had no way of knowing whether their colleagues put all patients to the MDT:

> *"Probably not because we were doing this before CLICC. I always put all my cases to the MDT – I am a stickler for it but I have no way of knowing if more cases are coming up from the others." [PU – Site 6]*

> *"Of course, it may only be a perception that all cases were presented prior to CLICC – will be very useful to see before and after data." [CL – Site 9]*

A group of three participant urologists reported that prior to CLICC they would generally not discuss high-risk patients at the MDT but would instead refer directly to a radiation oncologist for discussion of adjuvant radiotherapy:

> *"… to me, a lot of the decision should not be made in the MDT but in the consulting rooms with the patient and the radiation oncologist – the radiation oncologist needs to see the patient to know if it is appropriate. They should not decide on radiotherapy without seeing the patient." [PU – Site 8]*

One urologist participant (Site 7) was uncertain whether there had been a change in MDT decision-making but noted that he '*hoped so*'.

Effect(s) of the intervention on relationships with colleagues

The majority (23 of 28; 82%) did not perceive that CLICC had affected relationships with their colleagues. Predominantly these relationships were inferred to be with radiation oncology colleagues:

> *"I don't think the CLICC study has changed what is otherwise a very positive interaction. It's frequent; we all collaborate and are very respectful of each other. The personalities of the radiotherapists and pathologists and oncologists that turn up are collaborative. All keen to make sure patients get the best care. It is not uncommon for treatment plans to be changed at the MDT due to agreed protocols (from surgery to RT or vice versa) but I appreciate it being measured and to get the feedback." [CL – Site 9]*

"I don't think so – we've had an excellent MDT for a long time and a good relationship with our radiation oncology colleagues. We were putting [patients] on RAVES long before CLICC…" [PU – Site 6]

"Not really, people get on well with the radiation oncologist." {PU – Site 7]

Four participants (14%) considered that CLICC had positively affected relationships with colleagues, particularly with the radiation oncologists (n=3).

"It has brought us together again. Before we had drifted apart. Many more patients are discussed and the radiation oncologists are seeing more people." [CL – Site 8]

"Yes – relationships are better. It has facilitated discussion." [PU – Site 3]

One participant reflected that CLICC had negatively affected relationships with colleagues:

"It was annoying that my data were open and would be discussed at the MDT but colleagues were not prepared to present their own data." [PU – Site 2]

Concerns regarding the implementation of the intervention or unintended outcomes

There were few concerns regarding implementation of the intervention. One participant (Site 3) noted that his high caseload meant there was not enough time to discuss all flagged patients. Another participant from the same site corroborated this view.

One participant (Site 4) maintained the *"impression that you were looking for something that was not discussed."*

Two participants had concerns related to unwillingness of some urologists/MDTs to participate:

"Disappointed that externally the lack of enthusiasm for audit reduced participation." {CL – Site 8]

"It was annoying that as a small regional hospital we participated and some major city hospitals felt they did not need to and were not willing to have their practice looked at." {PU – Site 5]

There were no concerns about unintended outcomes. One participant (Site 1) noted as a positive outcome that the quality of public pathology reporting had improved due to the influence of the private pathology model, which he considered to be *"disseminating into the general pathological community"* as a result of MDT flagging.

Perceptions of the extent to which the intervention resulted in change in practice and any wider changes in patterns of care

Only one of the nine Clinical Leaders perceived that discussion of cases at the MDT meeting had changed their own referral patterns or those of colleagues:

"More patients are being discussed and referred definitely. The radiation oncologists are very positive about the changes." {CL – Site 8]

The other eight Clinical Leaders (89%) felt discussion at the MDT had not resulted in change in referral patterns - either because referral was already happening or because colleagues remained unwilling to change practice:

"No change in referral patterns – the MDT was saying the same thing we've been doing anyway, Our patients are offered observation or early adjuvant radiotherapy already then the radiation oncologist will mention RAVES if they decide to go for a consultation." {CL – Site 4]

"I think it stayed fairly much the same. Some of the group never referred unless the PSA rose so from that group you may sometimes get particularly high-risk cases being referred following discussion. It maybe changed that but otherwise no." {CL – Site 1]

"I tend to refer but some of the others for people with questionable extracapsular extension with low grade tumour at the margin or who have had a nerve sparing prostatectomy the don't say so but they tend to wait – they are running their own mini RAVES trial. I'm not sure they will

change for those patients but for those with higher risk an increase in referral will be a good thing." [CL – Site 7]

The collective group of Clinical Leaders and participating urologists were divided in their opinions as to whether that had been any wider changes in patterns of care for men with locally advanced prostate cancer. More than half (15 of 27; 56%) maintained there had been no change. Of those that considered there had been wider changes (12 of 27; 44%) these were suggested to involve:

1. Increased discussion with patients about the potential need for, and benefits of adjuvant radiotherapy, in consultation with the urologist (n=3) or through referral to radiation oncology (n=5)
2. A tendency toward more aggressive treatment of prostate cancer (n=1)
3. An increase in the use of robotic surgery (n=1)
4. Improvements in surgical outcomes and targeted radiotherapy techniques (n=1)
5. Declining use of adjuvant radiotherapy due to complications (n=1)

Contributions of CLICC to patient care

The perceived contributions of CLICC to patient care fell into five categories:

1. Increased discussion of patients with high-risk features at the MDT (8 of 27; 30%)

   "Enabling those patients who may benefit from adjuvant therapies to be identified and discussed on a routine basis." [PU – Site 3]

   "For high-risk men we all accept they need multi-modal treatment. The MDT discussion has developed better understanding about timing and appropriate use of adjuvant radiotherapy." [CL – Site 8]

2. Increased discussion between urologists and patients about the potential need for further adjuvant treatment (6 of 27; 22%)

"We have seen patients who were treated elsewhere who have not had optimum treatment and haven't had a discussion about radiotherapy – adjuvant or even salvage. Increasing that discussion is important." {CL – Site 5]

3. Audit of clinical practice to highlight differential patient outcomes and referral patterns between urologists and across institutions and the potential to use this data to drive change (6 of 27; 22%)

   "The most important thing is measurement against desirable patterns of care – you can't manage what you can't measure so the ability to provide us with data which drives patters of care is the main contribution CLICC has made and it's reassuring to know we're going the right way and out practice is good. It's a matter of influencing overall quality of care across NSW that will be the big contribution." [CL – Site 9]

   "Audit results are good to show the outcomes achieved by different surgeons – it allows a patient to select a surgeon with a full understanding of their performance." {PU – Site 7]

4. Increased patient referral to radiation oncology for discussion of adjuvant radiotherapy (4 of 27; 15%)

   "Exactly what the objective of the study is – to make sure all patients get referral in a timely fashion either before treatment or refer early. Don't leave the radiation oncologist out of the picture." [PU – Site 8]

5. Increased urologist awareness that adjuvant radiotherapy should be considered as a treatment option for men with high-risk features following radical prostatectomy (3 of 27; 11%)

   "Raising urologists awareness that adjuvant radiotherapy should be considered." [PU – Site 4]

   "To shed light on the issue. The study should be followed through and set the standard for care." [PU – Site 6]

Benefits for participants

The perceived benefits of CLICC for participants largely overlapped with contributions to patient care.

Ten of the 27 interviewees (37%) noted the provision of audit data as the main benefit of participation both as a means to understand their own practice and as a mechanism to identify inappropriate practice:

> *"The audit process is a very useful tool to show the percentage of high-risk men in different institutions – the presentation of results as proportions was very informative. Audit should be used to flag inappropriate surgery – if urologists have high percentages of cases with high-risk features then they shouldn't be operating on those patients." [PU – Site 7]*

> *"There is benefit in terms of measurement of high-risk parameters. It is nice to know what our overall margin rate is and whether we are operating on more high or low risk disease – so data has been very welcome and the reflection on patterns of care we currently have is important." [CL – Site 9]*

> *"The main message that came from this study is that pressure should be applied for all urologists to meet standards and be looked at by an outsider. We need to bring the recalcitrant into line and those who are not meeting the standard, their practice should be looked at." [PU – Site 5]*

A third of interviewees (9 of 27; 33%) noted that increased discussion of all potential treatment options was the main benefit to participation, be that at the MDT or in consultation with the patient:

> *"Because of the number of surgeries we always rationed the number of people discussed but we are developing systems to discuss more people, highlight the complex cases and deal with routine cases. In general, adherence to guidelines is a good thing and prior to CLICC and the MDT flagging there was very poor adherence to the adjuvant radiotherapy guideline." [CL – Site 8]*

> *"The fact that it's discussed at an open forum, that there is a benchmark of what is considered to be the best treatment. In our institute that is*

largely covered by our attachment to RAVES. Within the MDT we can't capture everybody but by providing the list the importance of following accepted evidence-based practice is being discussed." [CL – Site 7]

"I think no one knows what is the right answer in terms of treatment and there is variability in recommendations for care and what patients decide they want to have. Getting information will be helpful both for discussion of treatment options at the MDT then conveying that recommendation as discussed to patients." [PU – Site 9]

Six participants (22%) noted that CLICC would benefit participants by providing them with evidence. This evidence related to:

1. The efficacy of the MDT:

"…Whether the MDT makes a difference to the way we treat a patient and may also succeed in demonstrating that protocol driven referral to a MDT works." [CL – Site 4]

"Myself and other surgical colleagues are starting to question what difference the MDT makes in a well functioning centre if there are good relationships… where is the evidence that it makes a difference to patient outcomes." [PU – Site 6]

2. Whether embedding evidence-based care, specifically following the recommendation for adjuvant radiotherapy, will lead to improved patient outcomes:

"I think getting more information on whether there is any solid evidence that high-risk patients benefit from early treatment over monitoring and early salvage." [PU – Site 9]

"Whether or not patients are referred for a radiation oncology consult and whether they benefit from the adjuvant versus salvage radiotherapy opinion." [PU – Site 3]

Two interviewees (7%) noted that they had benefited from the provision of support to ensure best practice in a time poor environment:

"…People are busy and doing their own thing – it's good to have the nudging to remind you about best practice." [PU – Site 5]

"Acknowledgement of what urologists need – education and some logistical support such as setting up the mechanism by which those patients are automatically flagged." [PU – Site 8]

The final interviewee perceived that increased awareness of the potential need for adjuvant radiotherapy within the urological community was the main benefit of participating in the study.

Context

Factors that hindered or facilitated the role Clinical Leader

The majority (7 of 9) reported no factors that hindered their role as Clinical Leader. One noted that colleague's *"paranoia"* hindered participation of urologists at that site (Site 2). Another (Site 4) noted:

"The main difficulties have been getting everyone together in one place at one time including for presentation of feedback reports." [CL – Site 4]

Two Clinical Leaders cited the receptiveness or reasonableness of colleagues as a facilitator.

Two Clinical Leaders noted that support from the research team facilitated their role:

"…Calls and emails and follow up were excellent. As a clinician, that level of reminder is needed as studies are low on priority so without reminders and follow-up it wouldn't happen." [CL – Site 5]

Interaction with colleagues

All Clinical Leaders perceived that they were able to interact with colleagues where necessary. Three noted that colleagues were *"happy"*, *"already on*

side" and *"ultimately realised the importance of these sorts of studies"* so they did not need to do much to fulfill their role in CLICC.

Two Clinical Leaders (Sites 1 and 4) expressed that they did not perceive it as their role to influence colleagues or offer support to change practice:

> *"Didn't see my role was to tell my colleagues to follow the guideline and I didn't do it." [CL – Site 1]*

Contextual factors that hindered or facilitated the implementation of the project

MDT coordinators and pathologists were considered by Clinical Leaders to be critical to the success of the study. Across all four sites where the Clinical Leaders noted issues with implementation of the MDT flagging process these related to resourcing for public pathology services (Sites 1, 5, 6 and 7). In addition, the lack of a dedicated MDT coordinator (Site 3) and lack of a secretarial facility to support the MDT (Site 7) resulted in inconsistent record keeping of the MDT recommendation for care.

> *"The study demonstrates the variety in MDT structure as a tool for management of cancer patients. There is not enough regulation or impetus to get people to do it properly. Cancer Institute NSW provides funding but guidelines for MDT functioning are very vague. Funding should come with KPIs for administration and reporting etc." {CL – Site 8}*

Conditions critical to the project's success/lack of success

Conditions considered necessary for the successful implementation of CLICC: were:

1. Commitment and willingness of clinicians to participate (n=6)
2. Existence of a well-functioning MDT through which to implement the flagging process and discuss patients with high-risk disease (n=5)
3. The influence of the Clinical Leader or other champions (notably the radiation oncologist) in persuading people to participate (n=3)

4. Facilitation of the CLICC study team coupled with intervention elements that required minimal time commitment from participants (n=3)

The predominant reason for perceived lack of success was disagreement with the clinical practice guideline recommendation and lack of clarity about which patients will benefit from adjuvant radiotherapy (n=8):

> *"Whether the clinicians are convinced that hig- risk patients need certain interventions. The jury is still out about adjuvant radiotherapy so the result of the RAVES trial will be critical to the success of this study. The big confounder is not knowing the result of the RAVES trial." [CL – Site 4]*

> *"In spite of all the best efforts there is still an underlying uncertainty about the benefit of immediate adjuvant radiotherapy rather than early salvage. RAVES is struggling and most surgeons have an uncertainty about risk benefit analysis. The CLICC study really brought it to a head but showed there are some men who benefit from early rather than late radiotherapy. Surgeons are getting better but we all know it's the grade and stage of the cancer that matters." [PU – Site 4]*

> *"The difference is around margin status – a patient with negative margins won't get radiotherapy whoever you refer them to, and shouldn't." [PU – Site 4]*

Poor participation was noted as the reason for lack of success by both interviewees from Site 2 and was considered to be a reflection of general unwillingness to change practice or have current practice audited.

Perception of the supportiveness of, and interaction with, the Clinical Leader

Participating urologists from eight of the nine sites generally felt that the Clinical Leader was supportive of the study.

Interviewees from six sites (Sites 3, 4 and 6-9) communicated that the Clinical Leader initiated regular discussion about CLICC at the MDT or in shared

consulting rooms. Notably all participating urologist interviewees at Site 7 elaborated on the supportiveness of their Clinical Leader:

> *"Yes – he was supportive and we had an adequate amount of interaction. We all spoke about the study at the MDT every time we received the individual and group feedback." [PU – Site 7]*

> *"I share rooms with [Clinical Leader] so we spoke about the study a lot." [PU – Site 7]*

> *"Yes. He's been fantastic. We work in the same rooms." [PU – Site 7]*

At Site 5 two of three interviewees noted that while the Clinical Leader was supportive they had not had much interaction with him about CLICC:

> *"Yes he was supportive. There was not a lot of interaction with [Clinical Leader] but that's normal as he has a lot on so don't take it negatively." [PU – Site 5]*

> *"Not a lot of interaction but he was supportive." [PU – Site 5]*

At Site 3, none of the three interviewees felt they had sufficient interaction with the Clinical Leader about CLICC. One interviewee commented that the Clinical Leader was *"moderately supportive"*, one declined to comment claiming no direct interaction with him about CLICC but noting that the *"feedback report sometimes got discussed in a group setting'.* The third did not feel that the Clinical Leader was supportive of CLICC.

Sustainability

Continuation of CLICC elements

All CLICC materials including: the CLICC introductory video; the CLICC printed resource; and feedback report templates were made available to participants via a DropBox folder for continued use.

Clinical Leaders at six of the nine sites (Sites 4 – 9) reported that their colleagues had collectively decided flagging of patients for discussion at the

MDT would continue beyond the end of the active intervention phase of CLICC.

At one site (Site 3) a decision about continuation had not been made but the Clinical Leader indicated he was supportive if the department was favourable.

At Site 2 where the Clinical Leader reported MDT flagging would not continue (but acknowledged that it *"never really happened"*) the process was adapted such that patients were not listed for discussion by the MDT coordinator as per the study protocol but were only added to an agenda at the request of the urologists. The public pathologist at that site additionally noted that flagged cases were not routinely brought to the MDT.

At the remaining site (Site 1) the Clinical Leader commented:

> *"Certainly in my own practice I would always discuss high-risk patients anyway and send them to [the radiation oncologist] for a chat but I probably won't formally continue flagging." [CL – Site 1]*

The other interviewee from the same site felt that discussion of all high-risk patients was largely adhered to before the study and would likely continue beyond it:

> *"I think in many respects we had that process in track anyway with the MDT so anyone with high-risk disease would be discussed. We have a robust, frequent MDT so by and large it will continue." [PU – Site 1]*

6.5 Discussion

CLICC intervention elements were implemented with fidelity across the nine participating MDTs. All Clinical Leaders and participating urologists met the minimum requirement for exposure to: opinion leaders; the CLICC introductory video; printed educational materials; audit feedback reports; and flagging of eligible patients by pathology for discussion at multidisciplinary team meetings. Following implementation of the MDT flagging process, three

sites (Sites 2, 3 and 8) adapted the process by which flagged patients were added to a meeting agenda for discussion to suit local needs or preferences.

Participation was high across eight of nine CLICC sites with all eligible urologists participating from five MDTs (Sites 1, 4, 5, 6 and 8). More than three quarters (76%) of eligible urologists participated overall. Site 2 experienced low participation with the majority (nine of 11; 82%) declining or withdrawing consent. The Clinical Leader and the one other participating urologist at Site 2 considered poor participation due to lack of willingness to change practice and reluctance to provide access to medical records for review of current practice. The implementation of CLICC negatively affected relationships between participants and non-participants at Site 2, with the former annoyed by the latter's 'paranoia' and lack of transparency. Interviewees also commented on non-participation of colleagues at Site 7 and Site 9, which was unanimously perceived as 'lack of enthusiasm for the audit component' and unwillingness to contribute patient outcome data through medical record review. Interviewees considered these the same reasons for non-participation of the two eligible MDTs that declined.

Response to the CLICC implementation trial was varied. All nine Clinical Leaders and the majority of participating urologists (18 of 20; 90%) felt adequately informed about what the study was hoping to achieve. There was variability in participants' perceptions of whether the study was successful both within and across study sites. Implementation of the MDT flagging process was considered the main success and was perceived to have increased discussion of eligible patients by more than half the interviewees (secondary outcome data are reported in Chapter Seven). MDT record review demonstrated that pathologists were able to flag 78% of eligible patients for discussion overall, with 85% of private patients and 49% of public patients flagged. Of those flagged, 68% of private patients and 79% of public patients

were discussed at the MDT. However, there was uncertainty as to whether increased MDT discussion would translate into increased referral of patients to radiation oncology for discussion of adjuvant radiotherapy (primary outcome data are presented in Chapter Seven). Flagging of cases by pathology for discussion at the MDT was attributed to be the most helpful intervention component in achieving practice change being mentioned by nearly three quarters of interviewees. The automatic nature of the flagging system, which ensured all patients were listed without action on the part of the Clinical Leader or participating urologist, was frequently noted as beneficial in reducing the burden on time poor clinicians, especially in CLICC sites with high patient volume. This would suggest that the hypothesised *enabling* factors within the CLICC conceptual program logic model, which addressed systems and processes and cultural barriers, were the most essential element in achieving desired practice change in the current context. Only two interviewees articulated that they did not find the MDT flagging process useful due to the timing of discussion immediately after surgery. One of these was from Site 2 where the flagging process deviated from the study protocol after implementation such that patients were added to the MDT agenda at the discretion of the urologist rather than the MDT coordinator, which did not represent a change from routine practice. The other interviewee that did not initially find the MDT flagging process helpful was from Site 8 where a collaborative decision was made by the MDT to adapt the process such that patients were added to the MDT agenda two months after surgery so the 6-week post-operative PSA and continence status was known at the time of discussion.

Nearly half considered audit feedback reports to be a helpful intervention component both on a personal level to monitor their own practice and as a means make comparisons with other institutions and the provision of audit data was considered the main benefit of participation in the trial. There was a

competitive reaction to feedback and the majority perceived their own results and those of colleagues within their MDT to indicate that they were performing well in comparison with others in terms of clinical indicators such as surgical margins or other high-risk features. As one interviewee noted, *"it's reassuring to know we're going the right way and our practice is good."* [CL - Site 9]. Within the CLICC conceptual logic model, feedback reports were hypothesised to be a mechanism to *reinforce* desired behaviours (increased referral to radiation oncology for discussion of adjuvant radiotherapy) but participants placed more emphasis on clinical indicators than behavioural indicators in response to feedback and only one participant noted that his colleagues were *"surprised by their low referral rates"* [CL – Site 7]. Only one Clinical Leader perceived his role as one of a true opinion leader to reinforce desired behaviours and *"constantly remind the urologists that men with unfavourable histological results from surgery should at least have the discussion and be considered for radiotherapy..."* This would suggest that the *reinforcing* elements of CLICC might not have functioned as intended in relation to the primary outcome, defined a priori as patient referral within 4 months after prostatectomy to either radiation oncology or to the RAVES trial. There was necessarily a delay in the presentation of feedback on the primary outcome given the need to wait more than 4 months after surgery to determine whether a referral had been made within the specified time frame. This meant that Sites 6, 7 and 8, the latest to enter the trial, did not receive the third feedback report, which provided individual, site and aggregate study level pre- and post-intervention outcome data. There was, therefore, no opportunity for participants at those sites to determine if their referral practice had changed or how any potential change compared with that of other sites.

In view of participant response to the study and the perception of the importance of integration of the MDT flagging process as a measure of

success, a secondary outcome was added to the protocol during the trial but prior to any analysis, namely discussion of the patient at an MDT meeting within 4 months after prostatectomy. Data on the number of patients flagged and the proportion of those patients subsequently discussed at an MDT meeting was collected in real time meaning participants at all sites received at least one feedback report including individual, site and aggregate study level MDT discussion data following the implementation of the flagging process. This meant discussion rates could be directly compared with other sites and there was an opportunity to improve before the next quarterly feedback cycle. Results from participant interviews suggest that Clinical Leaders, through the presentation and discussion of feedback reports, may have served to *reinforce* this secondary outcome of discussion at the MDT rather than the primary outcome of referral. As one Clinical Leader noted *"I told them to up their game so we would be better than everywhere else."* [CL – Site 6]. Of note, this site (Site 6) had the highest rate of participation (100%) and response (100% of flagged cases discussed) highlighting the potential of the Clinical Leader to reinforce desired behaviours if they actively champion them.

The most frequently cited reason for potential lack of success in achieving an increase in the primary outcome of referral to radiation oncology was continued disagreement with the clinical practice guideline recommendation for adjuvant radiotherapy and lack of clarity about which patients will benefit. This suggests that the *predisposing* CLICC elements (CLICC video; CLICC printed resource and other printed materials) may have been ineffective in addressing clinician level barriers associated with knowledge, attitudes and perceptions for some participants who noted, for example, that 'this information has been around for a while but there are problems with the results…' Knowledge and attitudinal outcomes are presented in Chapter Eight.

The ongoing RAVES trial, hypothesised a priori as a contributor to persisting norms as a clinician level barrier, was noted as a confounder by a number of interviewees who considered that the trial supports their view that there is insufficient evidence in favour of adjuvant radiotherapy over early salvage radiotherapy. These participants used lack of definitive results from the ongoing RAVES trial as justification for non-referral for consideration of immediate adjuvant radiotherapy and this position was not successfully redressed by the CLICC predisposing elements.

A number of contextual factors adversely affected the implementation of CLICC elements. The most prominent of these was insufficient resourcing to support flagging of patients through public pathology services. This meant less than half of eligible public patients were flagged for discussion overall and no public patients were flagged at Sites 6, 7 or 8. Only two sites were able to achieve similar rates of public patients flagged as private patients. Both of these sites had higher public patient volume and had a lead pathologist that took responsibility for flagging and reporting on public patients at the MDT. Private pathology flagging was inconsistent across sites that did not exclusively use the predominant pathology provider and this suggests that centralised services are necessary for the successful implementation of these types of new systems and processes. The majority of sites integrated the flagging process into routine practice with a high proportion of flagged patients added to the MDT agenda for discussion. Site 3 was an outlier with only one third of flagged patients discussed at the MDT. High patient volume, insufficient logistical planning for implementation of the flagging process and lack of support from the Clinical Leader were all identified as issues at this site. In addition, this was the only site that did not have a designated MDT coordinator.

The MDT flagging process was the most sustainable CLICC element and was in continuation at six of the nine sites at the time of writing. The provision of support for implementation was noted as a key facilitator in conjunction with the automatic nature of the process, requiring no action on the part of the urologist. Adequate resourcing for pathology services and MDT coordination will be necessary for sustainability of the flagging process in the long term. Many participants considered provision of audit feedback data beneficial, however, medical record review was time and labour intensive and found to be intrusive or inappropriate by some participants. The establishment of the NSW Prostate Cancer Registry may facilitate ongoing provision of feedback.

The process evaluation of the CLICC trial demonstrates that CLICC elements could be implemented as they were designed. Within the CLICC conceptual program logic model, the hypothesised *enabling* factor, namely flagging of eligible cases by the pathologist to the MDT coordinator for discussion at the MDT, was considered by participants to be the most essential and sustainable element in achieving desired practice change and was integrated and adopted into routine practice at the end of the trial at a number of sites. Analyses reporting whether there was significant change in the secondary outcome, discussion of the patient at an MDT meeting within 4 months after prostatectomy, and whether discussion translated into change in the primary outcome of patient referral within 4 months after prostatectomy to either radiation oncology or to the RAVES trial are presented in Chapter Seven.

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Chapter 7: Changes in provider behaviour

7.1 Introduction

This chapter presents results of Phase I of the CLICC implementation trial (1) in relation to the effects of the CLICC intervention on provider behaviour, specifically referral to radiation oncology and discussion of patients at a MDT meeting. Knowledge and attitudinal outcomes measured in Phase II are reported in Chapter Eight.

7.2 Methods

7.2.1 Study Design

The CLICC implementation trial used a stepped wedge cluster randomised design. Participating MDTs crossed over from the control phase to the intervention phase at different time points throughout the study period across nine randomisation steps (Figure 7.1). The stepped wedge design increases statistical power compared with a parallel-group design (2, 3) because the intervention effect is estimated through both between-hospital and within-hospital comparisons. The order in which MDTs entered the intervention phase was determined randomly using a computer generated random number sequence. The intervention was rolled out during nine separate regularly scheduled MDT meetings between 13 December 2013 and 27 August 2014.

7.2.3 Study participants

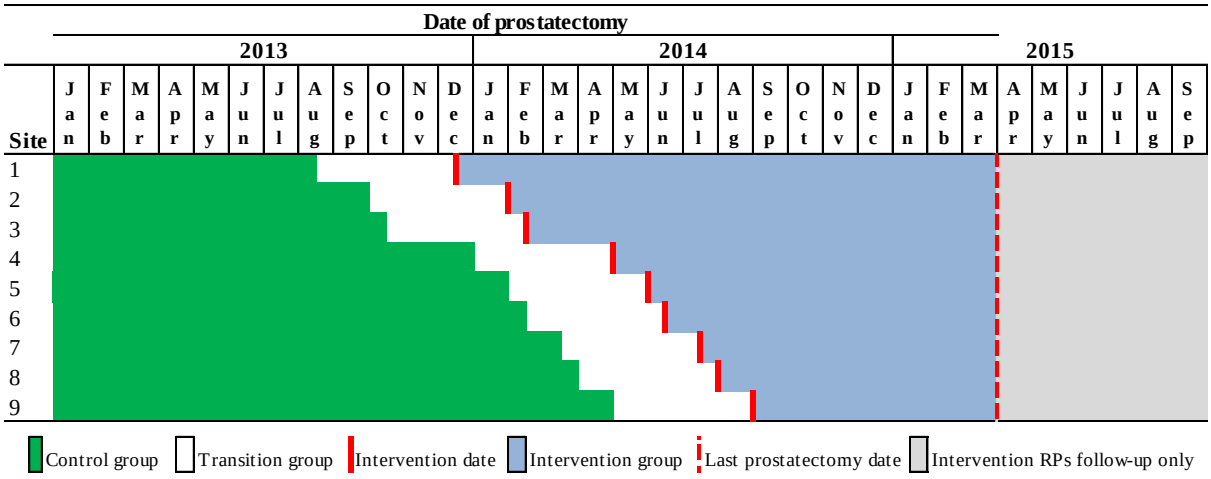
Hospital sample

All NSW hospitals that met the inclusion criteria of having: (i) a urological MDT; and (ii) a member(s) of the ACI Urology Network. Through the involvement of Network members the MDT represented the local Network node at each hospital.

Urologist sample

Urologist who were eligible for inclusion were members of a participating MDT, who: (i) performed radical prostatectomy during the control or intervention phase; and (ii) reviewed their high-risk prostate cancer cases (post-radical prostatectomy) at the participating MDT at the time the intervention commenced at that site. The latter two eligibility criteria were specified after publication of the study protocol (1) to enable exclusion of urologists who: (i) did not perform any radical prostatectomies during the study period and, therefore, would not contribute any clinical data; and (ii) are members of a participating MDT for the purposes of other urological conditions but present radical prostatectomy patients for review at a different non-participating MDT.

Figure 7.1: Timing of the intervention rollout in relation to date of prostatectomy



7.2.4 Data collection methods

Data were extracted from clinical records for all patients who underwent radical prostatectomy by a participating urologist between 3 January 2013 and 31 March 2015, and who were subsequently found to have one or more of three pre-specified adverse features (extracapsular extension, seminal vesicle invasion or positive surgical margins) upon pathological examination of the prostate specimen. Clinical data for included patients were obtained from a review of medical records for a minimum of 6 months after their prostatectomy.

Data extraction from patient's medical records

Information was collected through data extraction from urologists' and radiotherapy patients' medical records by independent, trained research assistants who were blind to the date that the intervention commenced at the hospital. Pre-intervention period data were collected retrospectively for patients who underwent radical prostatectomy between 1 January 2013 and the end of the month preceding cross over from the control to intervention phase.

Information from medical records

Data collected through medical record review were: referral to radiotherapy, taken from the urologist's notes (including dates of surgery and referral) or the recorded reasons for not referring; uptake of radiotherapy and the date of commencement; enrolment into the RAVES trial from the radiation oncology database; and whether the patient was referred to a MDT meeting, date of the meeting and the MDT recommendation.

Data were extracted from medical records at hospitals, cancer centres and urologists' private consulting rooms using previously established methods.(4) MDT data obtained from medical records on whether the patient was referred to a MDT, date of the meeting and the MDT recommendation were supplemented with data extracted from MDT administrative records to increase accuracy and completeness.

Patient level factors were collected from medical and hospital records including: month, year and country of birth, comorbidities, post-operative Gleason score, PSA level at diagnosis, maximum PSA level within four months of radical prostatectomy and private health insurance status (data collection forms are provided in Appendix XI). These patient level factors were considered to be potential barriers to referral to radiation oncology for consideration of radiotherapy.

7.2.5 Outcomes

The primary outcome was defined a-priori as patient referral within 4 months after prostatectomy to either radiation oncology or to the RAVES trial.(1) The RAVES trial was designed to compare survival and quality of life outcomes for Australasian patients through randomisation to either salvage radiotherapy if and when a rise in Prostate Specific Antigen (PSA) is detected or immediate adjuvant radiotherapy. Referral to the RAVES trial was included as a primary outcome because the CLICC intervention could result in increased referral to radiation oncology for consideration of enrolment in the trial rather than for consideration of immediate adjuvant radiotherapy at sites actively recruiting to RAVES.

Secondary outcomes were: an initial patient consultation with a radiation oncologist; enrolment in the RAVES trial; and commencement of radiotherapy. Each of the secondary outcomes was measured at 6 months after prostatectomy. Enrolment in the RAVES trial could not be measured due to insufficient data (date of enrolment in RAVES was documented in medical records for only 11 patients). An additional secondary outcome was added to the protocol during the trial but prior to any analysis: discussion of the patient at a MDT meeting within 4 months after prostatectomy.

7.2.6 Statistical methods

Data were systematically checked for errors and cleaned where appropriate. Patients were defined to be in the intervention group if their prostatectomy was performed after the introductory CLICC intervention session at the MDT to which the urologist belonged. Patients were defined to be in the control group if their prostatectomy was performed 4 months or more before the introductory CLICC intervention session. Those who underwent prostatectomy between the date of the introductory CLICC intervention session and 4 months prior were in the transition group (Figure 7.1). This latter group was formed because some patients could potentially benefit from the intervention while others could be referred or discussed before the

intervention date and thus received no such benefit. Results relating to the transition group are reported for completeness but are of marginal importance to the main study hypothesis. Moreover, the transition group was included in all regression analyses because the additional sample size increases the reliability of confounder effect estimates, which in turn increases the reliability of intervention effect estimates.

Generalised linear regression models with a Poisson distribution and log link, and generalised estimating equation (GEE) adjustment for the clustering of patients within urologists were used to estimate the relative proportions (RR) of patients who, within 4 months after prostatectomy, were: (1) referred to a radiation oncologist or to the RAVES trial; and (2) discussed at a MDT meeting. The same methods were used to estimate the relative proportions (RR) of patients who, within 6 months after prostatectomy, had a consultation with a radiation oncologist and/or who commenced radiotherapy (with patients who were referred to RAVES excluded from these analyses because their patterns of care are dependent on the RAVES study protocol). The dichotomous dependent variable in each regression model was one of the defined outcomes mentioned above. Independent variables were study group (control, transition, intervention), age at prostatectomy (40-59, 60-69, 70+), extracapsular extension (No, Yes, Unsure), positive surgical margin (No, Yes, Unsure), seminal vesicle invasion (No, Yes, Unsure), regional lymph node involvement (No, Yes, Unsure), post-operative Gleason score (6-7, 8, 9-10, Unsure), maximum PSA level within 4 months after RP (<0.1 ng/ml, $\geq$ 0.1ng/ml, no PSA test recorded) number of co-morbidities (0, 1, 2+) and Site. The results for individual sites are de-identified to maintain confidentiality. Exchangeable working correlation structures and robust standard errors were used in all models.

Interaction terms were added where appropriate to assess potential modifiers of the effects of the intervention. In addition, a number of sensitivity analyses were also performed for the 2 outcomes “referred to a radiation oncologist or to the RAVES

trial" and "discussed at a MDT meeting": (1) Excluding patients who were referred to radiation oncologist before radical prostatectomy; (2) Excluding patients whose urologist recorded the reason as salvage therapy, or no reason was recorded but they had a PSA level >0.1 (ng/ml) within 4 months after radical prostatectomy; (3) Excluding patients who were deemed to be lost to follow-up as they did not have at least one follow-up consultation with their urologist within 4 months after their radical prostatectomy; (4) Fitting minimally adjusted regression models to the data, adjusting only for study group, date of surgery, age at prostatectomy, and site with urologist again defined as the clustering variable; (5) Excluding patients of the urologist with the highest case-load comprising 13.9% of all radical prostatectomies in the study; (6) Excluding patients from the site with the highest case-load comprising 21.2% of all radical prostatectomies in the study; (7) Using linear mixed models with random effect terms for site and urologists nested within sites; (8) The two outcomes of referred and discussed were assessed at 6 months rather than 4 months.

Previously we have reported that our stepped wedge study design will have at least 80% power to detect an increase in referral to a radiation oncologist from 15% to 35%, or 20% to 40% if approximately 400 high-risk patients contributed data to the study (with roughly half allocated to the control and intervention groups respectively), and from 20% to 35% if approximately 670 high-risk patients contributed data to the study (1).

7.3 Results

Eleven NSW hospitals met the inclusion criteria. The urological MDTs from two of these declined to participate resulting in a total sample of nine sites. From these nine sites 55 urologists were invited to participate in the trial. Eight declined, six were ineligible as they performed no radical prostatectomies during the specified study period, and four withdrew consent, resulting in a total of 37 participants. The 37 participating urologists operated on 1087 high-risk patients during the study (Figure

7.2). Of these, 1071 had sufficient clinical information to be included in one or more analyses comprising 505, 159 and 407 patients in the control, transition and intervention groups respectively.

Figure 7.2: Participant flow diagram

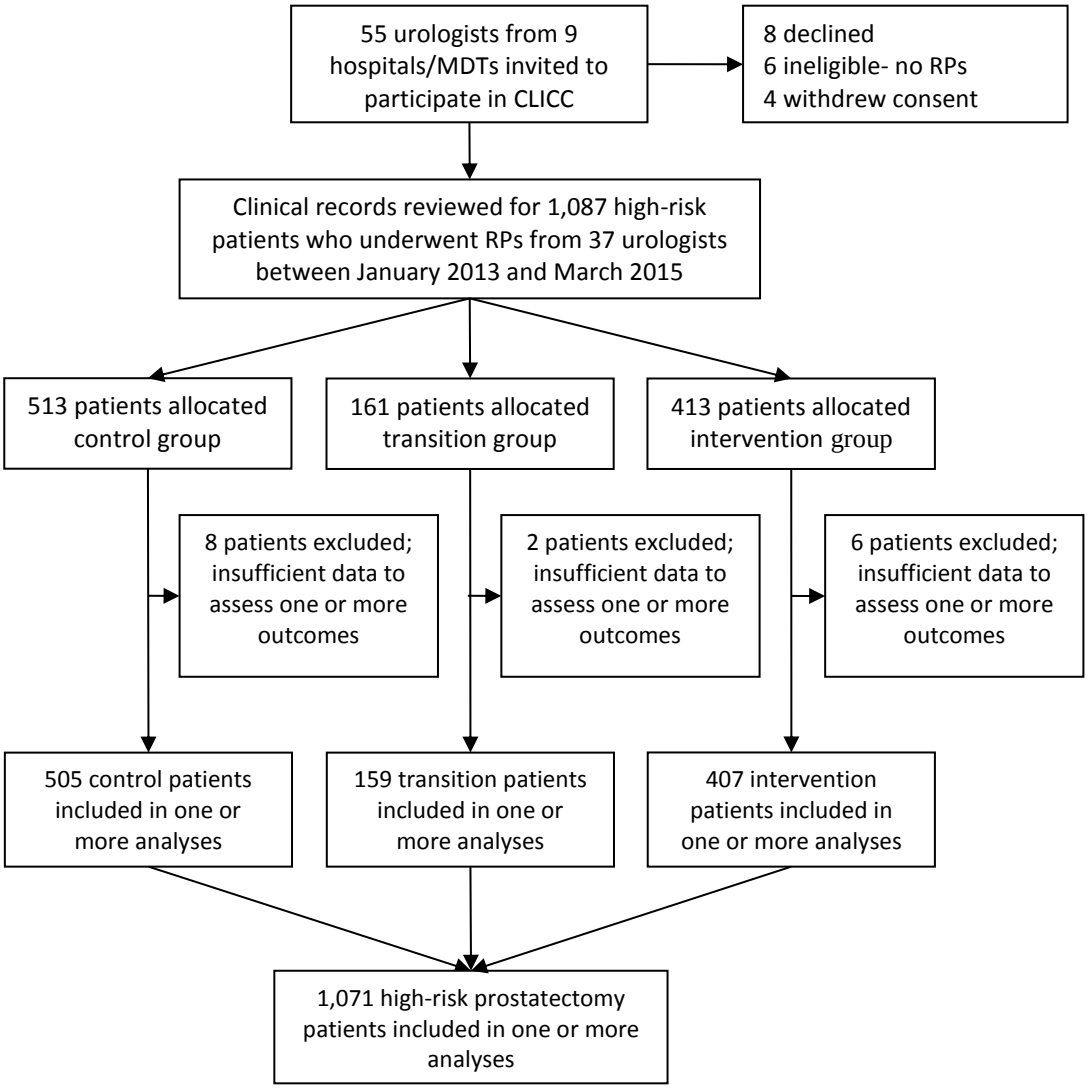


Table 7.1: Patient characteristics by study group

	Study group				
	Control	Transition	Intervention	TOTAL:	
Characteristic	**n (%)**	**n (%)**	**n (%)**	**N (%)**	***p*-value^**
All patients:	505 (100%)	159 (100%)	407 (100%)	1071 (100%)	
Age					
Median (years)	65.0	65.0	65.0	65.0	
Quartiles (years)	59-68	58-69	61-69	60-69	
Age group					
40-59	128 (25%)	43 (27%)	81 (20%)	252 (24%)	0.145
60-69	284 (56%)	84 (53%)	231 (57%)	599 (56%)	
70+	93 (18%)	32 (20%)	95 (23%)	220 (21%)	
Extracapsular extension					
No	96 (19%)	27 (17%)	69 (17%)	192 (18%)	0.511
Yes	406 (80%)	131 (82%)	338 (83%)	875 (82%)	
Unsure	3 (1%)	1 (1%)	0 (0%)	4 (0%)	
Positive surgical margin					
No	229 (45%)	69 (43%)	198 (49%)	496 (46%)	0.087
Yes	276 (55%)	89 (56%)	204 (50%)	569 (53%)	
Unsure	0 (0%)	1 (1%)	5 (1%)	6 (1%)	
Seminal vesicle invasion					
No	395 (78%)	131 (82%)	339 (83%)	865 (81%)	0.231
Yes	109 (22%)	28 (18%)	66 (16%)	203 (19%)	
Unsure	1 (0%)	0 (0%)	2 (0%)	3 (0%)	
Regional lymph node involvement					
No	305 (60%)	98 (62%)	278 (68%)	681 (64%)	0.035
Yes	30 (6%)	5 (3%)	25 (6%)	60 (6%)	
Unsure	170 (34%)	56 (35%)	104 (26%)	330 (31%)	
Post-operative Gleason grade					
6-7	395 (78%)	133 (84%)	344 (85%)	872 (81%)	0.132
8	30 (6%)	3 (2%)	18 (4%)	51 (5%)	
9-10	77 (15%)	22 (14%)	42 (10%)	141 (13%)	
Unsure	3 (1%)	1 (1%)	3 (1%)	7 (1%)	
Number of co-morbidities					
0	103 (20%)	19 (12%)	67 (16%)	189 (18%)	0.149
1	313 (62%)	108 (68%)	268 (66%)	689 (64%)	
2+	89 (18%)	32 (20%)	72 (18%)	193 (18%)	
Maximum PSA level within 4 months after RP (ng/ml)					
< 0.1	399 (79%)	137 (86%)	339 (83%)	875 (82%)	0.224
≥0.1	83 (16%)	16 (10%)	51 (13%)	150 (14%)	
No PSA test recorded	23 (5%)	6 (4%)	17 (4%)	46 (4%)	
Hospital					
Site 1	27 (5%)	14 (9%)	48 (12%)	89 (8%)	<0.001
Site 2	11 (2%)	2 (1%)	12 (3%)	25 (2%)	
Site 3	68 (13%)	39 (25%)	120 (29%)	227 (21%)	
Site 4	51 (10%)	12 (8%)	54 (13%)	117 (11%)	
Site 5	23 (5%)	3 (2%)	19 (5%)	45 (4%)	
Site 6	77 (15%)	21 (13%)	36 (9%)	134 (13%)	
Site 7	81 (16%)	26 (16%)	34 (8%)	141 (13%)	
Site 8	120 (24%)	26 (16%)	52 (13%)	198 (18%)	
Site 9	47 (9%)	16 (10%)	32 (8%)	95 (9%)	

Data are n (%) unless otherwise stated ^ p-values are for differences in % across the 3 groups from chi-squared tests

Patient characteristics (Table 7.1) were similar across groups with the exception of regional lymph node involvement (p=0.035). However, the proportions of patients *with* regional lymph node involvement were similar in the control and intervention groups (both 6%).

7.3.1 Primary Outcome

Referral within 4 months after prostatectomy to either radiation oncology or to the RAVES trial

In the intervention group, 32% (130 of 407) of patients were referred within 4 months after prostatectomy to either a radiation oncologist or to the RAVES trial compared with 30% (154 of 505) in the control group (Table 7.2). After adjustment for potential confounders, referral was not significantly different between the intervention and control groups (adjusted RR=1.05; 95% CI [0.74, 1.49]; p=0.892).

A number of patient characteristics other than study group were associated with referral to a radiation oncologist or to the RAVES trial within 4 months of radical prostatectomy, including having extracapsular extension (RR=1.30; 95% CI [1.04, 1.63]; p=0.023), seminal vesicle invasion (RR=1.78; 95% CI [1.46, 2.18]; p<0.001) and PSA ≥0.1ng/ml (RR=1.54 compared to PSA<0.1 ng/ml; 95% CI [1.26, 1.88]; p<0.001 for overall PSA variable). Having positive surgical margins or regional lymph node involvement was not significantly associated with referral to a radiation oncologist or to the RAVES trial within 4 months of radical prostatectomy (p=0.059 and p=0.291 respectively).

The effect of the intervention on referral was not significantly modified by any of the potential effect modifiers examined (Supplementary Table S7.1) with the exceptions of comorbidities (p=0.029) and site (p<0.001). We found evidence that the intervention worked better in some sites than others. Specifically, the intervention appeared to work best in four sites, each with similar increases in referral rates: Site 1 (RR=1.37; 95% CI [0.42-4.46]); Site 4 (RR=1.27; 95% CI [0.75-2.17]); Site 7 (RR=1.60;

95% CI [0.80-3.19]) and Site 8 (RR=1.57; 95% CI [1.01-2.43]). The intervention also worked better in those with two or more comorbidities (RR=1.27; 95% CI [1.02, 1.58]).

Table 7.2: Referral to radiation oncologist or RAVES, or case discussed at MDT within 4 months after prostatectomy

		Referred[1]		Discussed[2]	
Characteristic	**N**	**n (%)**	**Adjusted # RR (95%CI)**	**n (%)**	**Adjusted # RR (95%CI)**
All patients:	1071	325 (30%)		354 (33%)	
Study group					
Control	505	154 (30%)	ref.	88 (17%)	ref.
Transition	159	41 (26%)	0.99 (0.68, 1.44)	26 (16%)	1.53 (0.90, 2.59)
Intervention	407	130 (32%)	1.05 (0.74, 1.49)	240 (59%)	4.31 (2.40, 7.75)
***p*-value**			0.892		<0.001
Age group					
40-59	252	75 (30%)	ref.	79 (31%)	ref.
60-69	599	200 (33%)	1.05 (0.92, 1.21)	196 (33%)	0.94 (0.82, 1.07)
70+	220	50 (23%)	0.85 (0.70, 1.04)	79 (36%)	0.98 (0.82, 1.19)
***p*-value**			0.068		0.587
Extracapsular extension					
No	192	42 (22%)	ref.	52 (27%)	ref.
Yes	875	282 (32%)	1.30 (1.04, 1.63)	302 (35%)	1.14 (0.88, 1.48)
Unsure	4	1 (25%)	n/a^	0 (0%)	n/a^
***p*-value**			0.023		0.321
Positive surgical margin					
No	496	133 (27%)	ref.	167 (34%)	ref.
Yes	569	192 (34%)	1.19 (0.99, 1.42)	184 (32%)	1.01 (0.84, 1.20)
Unsure	6	0 (0%)	n/a^	3 (50%)	n/a^
***p*-value**			0.059		0.947
Seminal vesicle invasion					
No	865	206 (24%)	ref.	275 (32%)	ref.
Yes	203	118 (58%)	1.78 (1.46, 2.18)	78 (38%)	1.15 (0.95, 1.38)
Unsure	3	1 (33%)	n/a^	1 (33%)	n/a^
***p*-value**			<0.001		0.141
Regional lymph node involvement					
No	681	208 (31%)	ref.	225 (33%)	ref.
Yes	60	35 (58%)	0.84 (0.57, 1.24)	31 (52%)	1.22 (0.83, 1.79)
Unsure	330	82 (25%)	0.89 (0.76, 1.04)	98 (30%)	1.01 (0.81, 1.27)
***p*-value**			0.291		0.609
Post-operative Gleason grade					
6-7	872	243 (28%)	ref.	282 (32%)	ref.
8	51	12 (24%)	0.81 (0.62, 1.06)	17 (33%)	1.16 (0.84, 1.60)
9-10	141	67 (48%)	1.17 (0.93, 1.46)	51 (36%)	1.17 (0.88, 1.55)
Unsure	7	3 (43%)	n/a^	4 (57%)	n/a^
***p*-value**			0.074		0.481
Number of co-morbidities					
0	189	58 (31%)	ref.	53 (28%)	ref.
1	689	207 (30%)	0.99 (0.85, 1.16)	232 (34%)	1.12 (0.92, 1.36)
2+	193	60 (31%)	1.13 (0.94, 1.36)	69 (36%)	1.27 (1.02, 1.58)
p-value			0.383		0.094

Table 7.2 (continued): Referral to radiation oncologist or RAVES, or case discussed at MDT within 4 months after prostatectomy

		Referred[1]		Discussed[2]	
Characteristic	**N**	**n (%)**	**Adjusted # RR (95%CI)**	**n (%)**	**Adjusted # RR (95%CI)**
All patients:	1071	325 (30%)		354 (33%)	
Maximum PSA level within 4 months after RP (ng/ml)					
< 0.1	875	231 (26%)	ref.	284 (32%)	ref.
≥0.1	150	80 (53%)	1.54 (1.26, 1.88)	57 (38%)	1.11 (0.89, 1.38)
No PSA test recorded	46	14 (30%)	1.12 (0.73, 1.73)	13 (28%)	0.91 (0.53, 1.57)
p-value			<0.001		0.538
Hospital					
Site 1	89	22 (25%)	1.63 (0.82, 3.25)	53 (60%)	2.74 (1.86, 4.02)
Site 2	25	23 (92%)	2.38 (1.27, 4.47)	8 (32%)	1.84 (0.88, 3.84)
Site 3	227	34 (15%)	ref.	51 (22%)	ref.
Site 4	117	16 (14%)	1.14 (0.32, 4.03)	40 (34%)	1.72 (1.13, 2.61)
Site 5	45	18 (40%)	2.18 (1.09, 4.35)	15 (33%)	1.79 (0.94, 3.38)
Site 6	134	61 (46%)	3.14 (1.66, 5.94)	75 (56%)	3.76 (2.40, 5.91)
Site 7	141	43 (30%)	1.75 (0.94, 3.27)	27 (19%)	1.49 (0.76, 2.91)
Site 8	198	69 (35%)	1.68 (0.84, 3.34)	52 (26%)	1.89 (1.26, 2.83)
Site 9	95	39 (41%)	2.11 (1.13, 3.95)	33 (35%)	2.21 (1.36, 3.60)
***p*-value**			<0.001		<0.001

[1]Patient referral within 4 months after RP to either a radiation oncologist or the RAVES trial
[2]Patient discussed at MDT meeting within 4 months after RP
Adjusted for study group, age at prostatectomy, extracapsular extension, positive surgical margin, seminal vesicle invasion, regional lymph node involvement, post-operative Gleason score, number of co-morbidities, maximum PSA within 4 months of RP, date of surgery, hospital/MDT and urologist as the clustering variable
^ 7 control, 3 transition and 10 intervention patients within these categories were excluded from regression modelling due to the low numbers prohibiting the convergence of model estimates

7.3.2 Secondary outcomes

Discussion of the patient at a MDT meeting within 4 months after prostatectomy

Discussion of the patient at a MDT meeting within 4 months after prostatectomy was significantly higher in the intervention group (adjusted RR=4.31; 95% CI [2.40, 7.75]; p<0.001) (Table 7.2). Fifty-nine per cent of intervention patients (240 of 407) were discussed at a MDT meeting within 4 months after prostatectomy compared with 17% of control patients (88 of 505).

The effect of the intervention on discussion of the patient at a MDT meeting within 4 months after prostatectomy was significantly modified by a number of patient characteristics (Supplementary Table S7.2) including seminal vesicle invasion

(p=0.039), regional lymph node involvement (p < 0.001), post-operative Gleason score (p<0.019) and maximum PSA level within 4 months after prostatectomy (p<0.001). In general for these characteristics, categories corresponding to lower risk of prostate cancer recurrence, such as no seminal vesicle invasion, Gleason score 6-7, or PSA ≤ 0.1 ng/ml, corresponded to larger relative increases in the rates of discussion at a MDT meeting.

The effect of the intervention on discussion of the patient at a MDT meeting was significantly modified by site (p<0.001).

An initial patient consultation with a radiation oncologist

Ninety-four per cent of patients (137 of 146) referred to radiotherapy within four months after prostatectomy (excluding those referred to the RAVES trial) attended an initial consultation with a radiation oncologist within 6 months after prostatectomy (Supplementary Table S7.3). Patients with a PSA ≥ 0.1ng/ml were more likely to attend an initial consultation with a radiation oncologist than those with a PSA <0.1ng/ml (RR=1.14; 95% CI [1.03, 1.27]; p=0.016). Patients with comorbidities were less likely to attend an initial consultation with a radiation oncologist than those with none (p<0.001). There was no significant variation in the proportion referred to radiotherapy within 4 months after prostatectomy that subsequently attended an initial consultation with a radiation oncologist between sites (p=0.059).

Commencement of radiotherapy

After excluding 186 patients who were referred to RAVES (who would be randomised to adjuvant radiotherapy or observation as per the RAVES protocol), 83 of 885 patients (9%) commenced radiotherapy within 6 months after prostatectomy. Twenty-eight of 330 patients (8%) with adverse pathological features post-surgery commenced radiotherapy with 6 months after prostatectomy in the intervention group compared with 39 of 361 (11%) in the control group (RR 0.93; 95% CI [0.26,

3.31]; p=0.957) (Table 7.3). After excluding an additional 710 patients who were not referred to radiotherapy within 4 months after prostatectomy, 47% (27 of 57) commenced radiotherapy within 6 months after prostatectomy compared with 61% (38 of 62) in the control group (RR 0.40; 95% CI [0.13, 1.24]; p=0.067). The likelihood of commencing radiotherapy within 6 months after prostatectomy varied significantly by site (p<0.001).

A number of patient characteristics other than study group were associated with patients referred within 4 months after RP commencing radiotherapy within 6 months after prostatectomy. Specifically, there was an increased likelihood of referred patients commencing radiotherapy within 6 months after prostatectomy for those with post-operative Gleason grade 9-10 (RR 1.37 compared to grade 6-7; 95% CI [1.05, 1.77]; p=0.015 for overall Gleason grade variable) and a maximum PSA level within 4 months of prostatectomy ≥0.1ng/ml (RR 1.61 compared to PSA<0.1ng/ml; 95% CI [1.17, 2.21]; p=0.011 for overall maximum PSA variable), perhaps indicating these patients commenced salvage rather than adjuvant radiotherapy.

Referred patients with 2 or more co-morbidities were less likely to commence radiotherapy than those with no co-morbidities (RR 0.53; 95% CI [0.33, 0.87]; p=0.029 for overall co-morbidities variable). The effect of the intervention on commencement of radiotherapy within 6 months after prostatectomy was also significantly modified by site (p<0.001).

Table 7.3: Proportion of patients who commenced radiotherapy within 6 months after prostatectomy

	Excludes patients referred to RAVES			Excludes patients referred to RAVES and patients not referred to a radiation oncologist within 4 months after RP		
		Started radiation within 6 months after RP			Started radiation within 6 months after RP	
Characteristic	**N~**	**n (%)**	**Adjusted # RR (95%CI)**	**N~@**	**n (%)**	**Adjusted # RR (95%CI)**
All patients:	885	82 (9%)		146	80 (55%)	
Study group						
Control	361	39 (11%)	ref.	62	38 (61%)	ref.
Transition	194	15 (8%)	0.91 (0.43, 1.95)	27	15 (56%)	0.36 (0.15, 0.87)
Intervention	330	28 (8%)	0.93 (0.26, 3.31)	57	27 (47%)	0.40 (0.13, 1.24)
***p*-value**			0.957			0.067
Age group						
40-59	204	18 (9%)	ref.	30	18 (60%)	ref.
60-69	488	52 (11%)	1.08 (0.71, 1.64)	91	52 (57%)	1.06 (0.73, 1.54)
70+	193	12 (6%)	0.58 (0.32, 1.05)	25	10 (40%)	0.68 (0.34, 1.36)
***p*-value**			0.051			0.230
Extracapsular extension						
No	168	9 (5%)	ref.	18	8 (44%)	ref.
Yes	713	72 (10%)	1.73 (0.99, 3.03)	127	71 (56%)	1.43 (0.85, 2.41)
Unsure	4	1 (25%)	n/a^	1	1 (100%)	n/a^
***p*-value**			0.053			0.180
Positive surgical margin						
No	404	23 (6%)	ref.	47	23 (49%)	ref.
Yes	475	59 (12%)	1.40 (0.93, 2.10)	99	57 (58%)	1.01 (0.81, 1.27)
Unsure	6	0 (0%)	n/a^	0	0 (.)	n/a^
***p*-value**			0.111			0.904
Seminal vesicle invasion						
No	729	39 (5%)	ref.	77	38 (49%)	ref.
Yes	154	42 (27%)	2.24 (1.21, 4.13)	69	42 (61%)	1.33 (0.89, 1.96)
Unsure	2	1 (50%)	n/a^	0	0 (.)	n/a^
***p*-value**			0.010			0.160
Regional lymph node involvement						
No	558	50 (9%)	ref.	91	48 (53%)	ref.
Yes	56	19 (34%)	0.85 (0.41, 1.76)	31	19 (61%)	0.87 (0.64, 1.19)
Unsure	271	13 (5%)	0.68 (0.36, 1.29)	24	13 (54%)	1.17 (0.81, 1.68)
***p*-value**			0.488			0.475
Post-operative Gleason grade						
6-7	719	51 (7%)	ref.	97	50 (52%)	ref.
8	47	2 (4%)	0.45 (0.14, 1.44)	8	2 (25%)	0.37 (0.09, 1.54)
9-10	114	28 (25%)	1.83 (1.18, 2.83)	40	27 (68%)	1.37 (1.05, 1.77)
Unsure	5	1 (20%)	n/a^	1	1 (100%)	n/a^
***p*-value**			0.008			0.015
Number of co-morbidities						
0	149	14 (9%)	ref.	20	13 (65%)	ref.
1	573	55 (10%)	1.00 (0.66, 1.53)	95	54 (57%)	0.69 (0.47, 1.03)
2+	163	13 (8%)	0.87 (0.46, 1.66)	31	13 (42%)	0.53 (0.33, 0.87)
p-value			0.905			0.029

Continued next page

Characteristic	Excludes patients referred to RAVES			Excludes patients referred to RAVES and patients not referred to a radiation oncologist within 4 months after RP		
		Started radiation within 6 months after RP			Started radiation within 6 months after RP	
	N~	n (%)	Adjusted # RR (95%CI)	N~@	n (%)	Adjusted # RR (95%CI)
Maximum PSA level within 4 months after RP (ng/ml)						
< 0.1	710	34 (5%)	ref.	73	34 (47%)	ref.
≥0.1	137	46 (34%)	3.36 (1.85, 6.12)	67	44 (66%)	1.61 (1.17, 2.21)
No PSA test recorded	38	2 (5%)	0.65 (0.21, 2.07)	6	2 (33%)	0.88 (0.49, 1.59)
p-value			<0.001			0.011
Hospital						
Site 1	89	14 (16%)	5.57 (2.30, 13.49)	22	13 (59%)	3.05 (1.84, 5.08)
Site 2	11	5 (45%)	11.97 (3.56, 40.22)	9	5 (56%)	1.85 (1.15, 3.00)
Site 3	207	6 (3%)	ref.	14	5 (36%)	ref.
Site 4	108	5 (5%)	1.73 (0.50, 6.00)	8	5 (63%)	2.44 (1.46, 4.08)
Site 5	38	7 (18%)	5.33 (2.11, 13.44)	12	7 (58%)	1.34 (0.76, 2.38)
Site 6	86	10 (12%)	3.99 (1.43, 11.18)	16	10 (63%)	1.42 (0.88, 2.29)
Site 7	116	12 (10%)	2.87 (1.04, 7.92)	19	12 (63%)	2.06 (1.34, 3.18)
Site 8	153	13 (8%)	2.04 (0.66, 6.26)	24	13 (54%)	1.58 (1.15, 2.17)
Site 9	77	10 (13%)	4.07 (1.32, 12.52)	22	10 (45%)	1.31 (0.70, 2.45)
***p*-value**			<0.001			<0.001

~Excludes 186 patients referred to the RAVES trial

@ Excludes an additional 710 patients who were not referred to a radiation oncologist within 4 months after RP

Adjusted for study group, age at prostatectomy, extracapsular extension, positive surgical margin, seminal vesicle invasion, regional lymph node involvement, post-operative Gleason score, number of co-morbidities, maximum PSA within 4 months after RP, time period of surgery, hospital/MDT and urologist as the clustering variable

^ Patients within these categories were excluded from regression modelling due to the low numbers prohibiting the convergence of model estimates

7.3.3 Subgroup analyses

MDT recommendation

The MDT recommendation was known for 217 of 240 patients discussed at a MDT meeting within 4 months after prostatectomy. The MDT recommendation was referral to radiotherapy or RAVES for 58% of discussed patients (140 of 240). Only sixty-two of these 140 patients (44%) with a MDT recommendation for referral were actually referred to radiation oncology within 4 months after prostatectomy (Table 7.4).

Table 7.4: MDT recommendations by referral status among intervention patients discussed at a MDT meeting within 4 months after prostatectomy

		Actual referral	
		Referred within 4 months after RP[1]	Referred within 6 months after RP[2]
MDT recommendation	**N**	**n (%)**	**n (%)**
Referral to RT or RAVES	140	62 (44%)	67 (48%)
Watch and wait	42	6 (14%)	8 (19%)
Other recommendation	35	14 (40%)	14 (40%)
Recommendation not recorded	23	12 (52%)	12 (52%)
Case not discussed within 4 months after RP	167	36 (22%)	47 (28%)
TOTAL (all intervention patients):	**407**	**130 (32%)**	**148 (36%)**

[1]Patient referral within 4 months after prostatectomy to either a radiation oncologist or the RAVES trial
[2]Patient referral within 6 months after prostatectomy to either a radiation oncologist or the RAVES trial

Reasons for non-referral among patients with a MDT recommendation for referral

Among the 78 patients with a MDT recommendation for referral who were not referred the most common reason for non-referral, as recorded in urologists notes, was a low or undetectable post-operative PSA (45 of 78; 58%), followed by good post-operative continence (28 of 78; 36%), then watch and wait for salvage radiotherapy (12 of 78; 15%), (Table 7.6). This is consistent with the documented reasons for non-referral among all 746 patients (351 baseline, 118 transition, 277 intervention) that were not referred to radiotherapy or RAVES within 4 months after prostatectomy: reasons recorded were a low or undetectable post-operative PSA (407 of 746; 55%), followed by good post-operative continence (92 of 746; 12%), then watch and wait for salvage radiotherapy (92 of 746; 12%) (data not shown). There were no instances where the reason for non-referral of one of the 78 discussed patients with a MDT recommendation for referral was documented as patient preference. Overall, patient preference was recorded as the reason for non-referral 2% of patients (14 of 746) who were not referred. It should be noted, however, that there was no recorded reason for non-referral for more than a third of these patients (274 of 746; 37%).

Table 7.6: Reasons for non-referral as recorded in urologist notes among the 78 intervention group cases with a MDT recommendation for referral who were not referred within 4 months of prostatectomy

Possible reasons recorded	# of responses	% of n=78 non-referred cases^
PSA low or undetectable	45	58%
Continence is good	28	36%
Watch and wait for salvage	12	15%
Continence is bad	4	5%
Patient preference	0	0%
Other	4	5%
No reason recorded in notes	25	32%

^ Total of percentages exceeds 100% because each patient could have more than one reason recorded for non-referral

7.3.4 Sensitivity analyses

Sensitivity analyses showed that our results were robust to a variety of different assumptions and/or statistical methods (Supplementary Figure S7.1).

7.4 Discussion

The CLICC implementation trial did not result in a significant increase in the primary outcome of referral to radiotherapy or the RAVES trial within 4 months after prostatectomy. Nevertheless, there was evidence that the CLICC intervention was more effective in certain sites than others.

As a result of the CLICC intervention, there was a more than threefold proportional increase in the secondary outcome of patient discussion at a MDT meeting within 4 months after prostatectomy with 56% being discussed in the intervention group compared with 17% in the control group. Of note, the four sites that had the highest proportional increases in referral to radiotherapy or RAVES within 4 months after prostatectomy (Sites 1, 4, 7 and 8) were amongst the 5 sites with the highest proportional increases in patients discussed at a MDT meeting. This is consistent with the notion that increasing discussion of patients at a MDT meeting has the potential to enable change in subsequent referral behaviours. The intervention had less of an

effect on patient discussion at a MDT meeting within 4 months after prostatectomy at Site 3. Through the CLICC process evaluation (Chapter Six), several issues were revealed at Site 3 including high patient volume, insufficient logistical planning for implementation of the flagging process and lack of support from the Clinical Leader. In addition, this was the only site that did not have a designated MDT coordinator to add flagged patients to the MDT agenda for discussion.

Within the CLICC conceptual program logic model, flagging of eligible cases by the pathologist to the MDT coordinator for discussion at a MDT meeting was hypothesised to enable referral to radiotherapy or RAVES within 4 months after prostatectomy by overcoming clinician level barriers associated with variable engagement with, and selective presentation of cases to, the MDT. The significant increase in the proportion of patients with adverse pathological features discussed at the MDT demonstrates that the MDT flagging element of CLICC successfully addressed selective presentation of cases. Following discussion at the MDT, however, less than half of patients with a MDT recommendation for referral were actually referred to radiotherapy or RAVES within 4 months after prostatectomy. This could indicate that, while they adhered to the MDT flagging process, some participants were still not actively engaged with the MDT and, therefore, did not change their referral behaviour in line with the MDT recommendation. This may in part be due to the larger relative increase in the number of patients who could be considered at the lower end of the 'high risk" spectrum such as those without seminal vesicle invasion, a lower Gleason score, or low or undetectable PSA (≤ 0.1 ng/ml). In the CLICC process evaluation (Chapter Six), a number of features were suggested to reduce the likelihood of patients being referred to radiation oncology, including "*tiny volume extracapsular extension" [PU - Site 7],* "*low grade tumour at the margin" (CL – Site 7]* or *"negative margins" [PU – Site 3]*. As another participant noted, "*Surgeons are getting better but we all know it's the grade and stage of the cancer that matters." [PU – Site 4].* While the clinical practice guideline recommendation for adjuvant radiotherapy does not distinguish between high-risk

features, established post-prostatectomy nomograms indicate that not all adverse pathologic features are equal in terms of risk of relapse.(5) For example, a patient with a pre-operative PSA of 5, Gleason 7 disease with some extracapsular extension and clear margins has a less than 10% risk of relapse compared with an 89% risk of relapse in a patient with Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension, seminal vesicle involvement and positive surgical margins. This could explain the uncertainty expressed in the CLICC process evaluation (Chapter Six) as to whether increased MDT discussion based on flagging all patients with any of the three adverse pathological features would translate into increased referral of patients to radiation oncology.

Where documented, the reason for non-referral of patients with a MDT recommendation for referral was predominantly attributed to a low or undetectable post-operative PSA. This is contrary to the clinical practice guideline, which does not specify PSA level but recommends that all men with extracapsular extension, seminal vesicle invasion or positive surgical margins should be referred to radiation oncology for discussion of adjuvant radiotherapy.(6-8) By its definition, adjuvant radiotherapy is that delivered when the patient has an undetectable or low PSA (<0.1ng/ml). Radiotherapy commenced when the patient has a post-operative PSA equal to or greater than 0.1ng/ml would, therefore, be classified as salvage, rather than adjuvant, due to detection of residual or recurrent disease. Data obtained from radiation oncology records for men who commenced radiotherapy within 6 months after prostatectomy showed that patients with PSA levels ≥0.1ng/ml were more likely to commence radiation than those with PSA levels <0.1ng/ml. However, those with PSA levels ≥0.1ng/ml were actually receiving salvage rather than adjuvant radiotherapy. This aligns with the CLICC process evaluation (Chapter Six) in which a number of participants indicated post-intervention that their preference continued to be referral for early salvage radiotherapy at the time of a confirmed PSA rise rather than referral for immediate adjuvant radiotherapy.

The overall proportion of patients that commenced radiotherapy within 6 months was 9% with a slight non-significant decrease from 11% in the control group to 8% in the intervention group. This is consistent with data from a number of published studies, which consistently report only 10-20% of eligible patients receive adjuvant treatment in Australia (4, 9-11), Canada (12, 13) and the US (14-17). The most recent Australian data, from eligible patients who were notified to the Victorian Prostate Cancer Registry between 2008 and 2011, showed that only 9.4% (78 of 833) of men with an adverse pathologic feature received adjuvant radiotherapy within 6 months after prostatectomy.(11) In part, low rates of adjuvant radiotherapy are due to low rates of referral; a patient cannot commence radiotherapy without first being referred to a radiation oncologist. However, within the subset of patients who were referred to a radiation oncologist only a little over half commenced radiotherapy within 6 months of prostatectomy despite more than 90% attending an initial consultation. Further, the proportion commencing radiotherapy within 6 months after prostatectomy decreased between the control, transition and intervention groups. This is consistent with a retrospective analysis of data from the US National Cancer Data Base that indicated *declining* use of radiotherapy for adverse features after radical prostatectomy in line with the trend in our data. That study, including nearly 100,000 patients, found receipt of postoperative radiotherapy significantly decreased from 9.1% to 7.3% between 2005 and 2011 ($p < 0.001$).(18) While that study did not explore the reason for the decrease in adjuvant radiotherapy in men with adverse pathologic features, a US survey found urologists were less confident in the benefit of adjuvant radiotherapy in terms of overall survival or durable biochemical control and predicted higher rates of erectile dysfunction due to radiotherapy than radiation oncologists.(19) Results from the CLICC process evaluation (Chapter Six) highlight similar concerns and indicate that continued disagreement with the clinical practice guideline recommendation and lack of clarity about which patients will benefit from adjuvant radiotherapy are the most likely

reasons for lack of success in increasing rates of referral to radiotherapy or RAVES within 4 months after prostatectomy within the local context.

Limitations

Power calculations were based on estimated sample sizes from Medicare claims data, extrapolating that 3,517 NSW men would undergo radical prostatectomy in 2013 and that 46% would have surgery in one of the nine participating sites. This equated to 1,348 radical prostatectomies over the 10 months of CLICC implementation trial with 20% to 50% or 270 to 671 men at 'high risk' following surgery. A downward trend in prostate cancer diagnoses and a plateau in the proportion undergoing radical prostatectomy during the study period resulted in an overestimate of the number of cases treated with surgery. However, this was balanced by an underestimate of the proportion of men with high-risk features, meaning more men than anticipated contributed data to the study, giving a total sample of 1,087 men. Overall these trends balanced out and did not affect the power of the study to find a significant result.

Medicare claims data for the period 1 January 2013 to 30 June 2014 indicate that nearly half (47%) of all radical prostatectomies in NSW over that period were performed in the nine study sites consistent with our estimate. While this implies results should be generalisable it is acknowledged that the effect of the intervention on primary and secondary outcomes was significantly modified by site due to inconsistencies in practice and contextual factors so there is potential for this variation to be evident more widely.

The effect size of the CLICC implementation trial was a 2% increase in referrals at 4 months after prostatectomy (30% to 32%) and a 4% increase at 6 months after prostatectomy (32% to 35%) (Figure S7.1). This is considerably less than the estimated 15% to 20% increase in referrals which was perhaps unrealistic given that many implementation trials show only small to moderate effects (20) and typically

interventions such as audit and feedback or educational outreach result in a 4% to 5% increase respectively in dichotomous outcomes.(21)

In order to determine whether the lack of significant change in the primary outcome of referral to radiotherapy or RAVES within 4 months after prostatectomy is related to the persisting clinician level barriers identified in the CLICC process evaluation (Chapter Six), knowledge and attitudinal outcomes are presented in Chapter Eight.

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Supplementary Appendix for Chapter Seven

Table S7.1: Potential effect modifiers of the effects of the intervention on prevalence of referral to radiation oncologist or RAVES within 4 months after prostatectomy

	Referred[1]/Total (%)			
Potential effect modifier	**Control**	**Intervention**	**Adjusted RR# for intervention effect (95%CI)**	***p-value* for interaction**
All patients:	154/505 (30%)	130/407 (32%)	1.05 (0.74, 1.49)^^	n/a
Age group				
40-59	36/128 (28%)	28/81 (35%)	1.25 (0.81, 1.94)	0.198
60-69	96/284 (34%)	78/231 (34%)	0.93 (0.62, 1.39)	
70+	22/93 (24%)	24/95 (25%)	1.17 (0.80, 1.70)	
Extracapsular extension				
No	22/96 (23%)	15/69 (22%)	0.85 (0.53, 1.36)	0.168
Yes	131/406 (32%)	115/338 (34%)	1.10 (0.76, 1.58)	
Unsure	1/3 (33%)	0/0 (.)	n/a^	
Positive surgical margin				
No	64/229 (28%)	54/198 (27%)	1.01 (0.71, 1.42)	0.680
Yes	90/276 (33%)	76/204 (37%)	1.07 (0.72, 1.61)	
Unsure	0/0 (.)	0/5 (0%)	n/a^	
Seminal vesicle invasion				
No	93/395 (24%)	88/339 (26%)	1.03 (0.71, 1.49)	0.473
Yes	61/109 (56%)	41/66 (62%)	1.14 (0.77, 1.70)	
Unsure	0/1 (0%)	1/2 (50%)	n/a^	
Regional lymph node involvement				
No	94/305 (31%)	87/278 (31%)	1.07 (0.76, 1.52)	0.891
Yes	19/30 (63%)	14/25 (56%)	1.18 (0.66, 2.10)	
Unsure	41/170 (24%)	29/104 (28%)	1.01 (0.65, 1.56)	
Post-operative Gleason score				
6-7	109/395 (28%)	103/344 (30%)	1.08 (0.75, 1.55)	0.517
8	8/30 (27%)	3/18 (17%)	0.67 (0.32, 1.40)	
9-10	35/77 (45%)	23/42 (55%)	1.03 (0.60, 1.76)	
Unsure	2/3 (67%)	1/3 (33%)	n/a^	
Number of co-morbidities				
0	32/103 (31%)	19/67 (28%)	0.74 (0.52, 1.05)	0.029
1	98/313 (31%)	85/268 (32%)	1.05 (0.71, 1.56)	
2+	24/89 (27%)	26/72 (36%)	1.34 (0.85, 2.11)	
Maximum PSA level within 4 months after RP (ng/ml)				
< 0.1	103/399 (26%)	99/339 (29%)	1.13 (0.79, 1.60)	0.445
≥0.1	44/83 (53%)	26/51 (51%)	0.89 (0.53, 1.48)	
No PSA test recorded	7/23 (30%)	5/17 (29%)	0.91 (0.37, 2.25)	
Hospital				
Site 1	5/27 (19%)	14/48 (29%)	1.37 (0.42, 4.46)	<0.001
Site 2	10/11 (91%)	12/12 (100%)	0.83 (0.56, 1.23)	
Site 3	15/68 (22%)	16/120 (13%)	0.80 (0.58, 1.10)	
Site 4	4/51 (8%)	9/54 (17%)	1.27 (0.75, 2.17)	
Site 5	9/23 (39%)	8/19 (42%)	0.75 (0.35, 1.60)	
Site 6	36/77 (47%)	20/36 (56%)	1.13 (0.82, 1.55)	
Site 7	20/81 (25%)	15/34 (44%)	1.60 (0.80, 3.19)	
Site 8	33/120 (28%)	24/52 (46%)	1.57 (1.01, 2.43)	
Site 9	22/47 (47%)	12/32 (38%)	0.75 (0.46, 1.21)	

[1]Patient referral within 4 months after RP to either a radiation oncologist or the RAVES trial

(continued next page)

Adjusted for study group, age at RP, extracapsular extension, positive surgical margin, seminal vesicle invasion, regional lymph node involvement, post-operative Gleason score, number of co-morbidities, maximum PSA within 4 months after RP, time period of surgery and site where appropriate, and urologist as the clustering variable
¥ Time after intervention is the time between RP and intervention for patients with RPs that occurred after the intervention or equal to zero otherwise
^^ Results from original analyses repeated here for convenience
^ 7 control and 9 intervention patients were excluded from regression modelling due to low numbers prohibiting the convergence of model estimates

Table S2: Potential effect modifiers of the effects of the intervention on prevalence of patients being discussed at MDT meeting within 4 months after prostatectomy

	Discussed[1]/Total (%)			
Potential effect modifier	**Control**	**Intervention**	**Adjusted RR# for intervention effect (95%CI)**	***p-value* for effect modification**
All patients:	88/505 (17%)	240/407 (59%)	4.31 (2.40, 7.75)^^	n/a
Age group				
40-59	23/128 (18%)	50/81 (62%)	4.09 (2.25, 7.44)	0.326
60-69	45/284 (16%)	136/231 (59%)	4.78 (2.43, 9.40)	
70+	20/93 (22%)	54/95 (57%)	3.62 (1.94, 6.78)	
Extracapsular extension				
No	13/96 (14%)	35/69 (51%)	4.83 (2.41, 9.68)	0.613
Yes	75/406 (18%)	205/338 (61%)	4.22 (2.32, 7.68)	
Unsure	0/3 (0%)	0/0 (.)	n/a^	
Positive surgical margin				
No	39/229 (17%)	115/198 (58%)	4.70 (2.31, 9.56)	0.548
Yes	49/276 (18%)	122/204 (60%)	4.07 (2.29, 7.23)	
Unsure	0/0 (.)	3/5 (60%)	n/a^	
Seminal vesicle invasion				
No	59/395 (15%)	199/339 (59%)	5.01 (2.67, 9.38)	0.039
Yes	29/109 (27%)	40/66 (61%)	2.90 (1.46, 5.76)	
Unsure	0/1 (0%)	1/2 (50%)	n/a^	
Regional lymph node involvement				
No	53/305 (17%)	154/278 (55%)	3.86 (2.02, 7.38)	<0.001
Yes	18/30 (60%)	12/25 (48%)	1.06 (0.50, 2.25)	
Unsure	17/170 (10%)	74/104 (71%)	7.94 (4.16, 15.14)	
Post-operative Gleason score				
6-7	58/395 (15%)	205/344 (60%)	4.84 (2.53, 9.28)	0.019
8	5/30 (17%)	11/18 (61%)	4.41 (1.86, 10.47)	
9-10	24/77 (31%)	21/42 (50%)	2.22 (1.17, 4.22)	
Unsure	1/3 (33%)	3/3 (100%)	n/a^	
Number of co-morbidities				
0	15/103 (15%)	35/67 (52%)	4.53 (2.55, 8.06)	0.937
1	56/313 (18%)	162/268 (60%)	4.25 (2.30, 7.88)	
2+	17/89 (19%)	43/72 (60%)	4.56 (2.17, 9.59)	
Maximum PSA level within 4 months after RP (ng/ml)				
< 0.1	58/399 (15%)	204/339 (60%)	5.04 (2.64, 9.61)	<0.001
≥0.1	25/83 (30%)	29/51 (57%)	2.50 (1.44, 4.35)	
No PSA test recorded	5/23 (22%)	7/17 (41%)	2.46 (1.17, 5.14)	

Continued next page

Potential effect modifier	Discussed[1]/Total (%) Control	Intervention	Adjusted RR# for intervention effect (95%CI)	*p-value* for effect modification
Hospital				
Site 1	7/27 (26%)	38/48 (79%)	4.77 (1.98, 11.44)	<0.001
Site 2	1/11 (9%)	6/12 (50%)	8.78 (0.89, 86.52)	
Site 3	14/68 (21%)	33/120 (28%)	1.87 (0.79, 4.47)	
Site 4	4/51 (8%)	36/54 (67%)	11.24 (3.63, 34.84)	
Site 4	2/23 (9%)	12/19 (63%)	7.09 (2.74, 18.33)	
Site 6	34/77 (44%)	36/36 (100%)	2.54 (1.24, 5.21)	
Site 7	7/81 (9%)	19/34 (56%)	6.74 (3.20, 14.20)	
Site 8	9/120 (8%)	40/52 (77%)	11.37 (6.48, 19.98)	
Site 9	10/47 (21%)	20/32 (63%)	3.01 (1.30, 7.01)	

[1]Patient discussed at MDT meeting within 4 months after RP

Adjusted for study group, age at RP, extracapsular extension, positive surgical margin, seminal vesicle invasion, regional lymph node involvement, post-operative Gleason score, number of co-morbidities, maximum PSA within 4 months after RP, time period of surgery and hospital/MDT where appropriate, and urologist as the clustering variable

¥ Time after intervention is the time between RP and intervention for patients with RPs that occurred after the intervention or equal to zero otherwise

^^ Results from original analyses repeated here for convenience

^ 7 control and 9 intervention patients within these categories were excluded from regression modelling due to the low numbers prohibiting the convergence of model estimates

Table S7.3: Had consultation with radiation oncologist within 6 months of prostatectomy

	All patients excluding RAVES referrals			Patients referred to a radiation oncologist within 4 months after RP excluding RAVES referrals		
		Had consultation with radiation oncologist within 6 months after RP			Had consultation with radiation oncologist within 6 months after RP	
Characteristic	**N˜**	**n (%)**	**Adjusted # RR (95%CI)**	**N˜@**	**n (%)**	**Adjusted # RR (95%CI)**
All patients:	885	152 (17%)		146	137 (94%)	
Study group						
Control	361	65 (18%)	ref.	62	59 (95%)	ref.
Transition	194	28 (14%)	1.20 (0.81, 1.78)	27	26 (96%)	0.93 (0.79, 1.09)
Intervention	330	59 (18%)	1.45 (0.77, 2.70)	57	52 (91%)	0.97 (0.80, 1.18)
***p*-value**			0.514			0.638
Age group						
40-59	204	34 (17%)	ref.	30	29 (97%)	ref.
60-69	488	94 (19%)	1.05 (0.75, 1.47)	91	87 (96%)	1.00 (0.91, 1.11)
70+	193	24 (12%)	0.69 (0.48, 0.98)	25	21 (84%)	0.86 (0.70, 1.05)
***p*-value**			0.005			0.269
Extracapsular extension						
No	168	18 (11%)	ref.	18	16 (89%)	ref.
Yes	713	133 (19%)	1.59 (1.13, 2.24)	127	120 (94%)	1.08 (0.90, 1.30)
Unsure	4	1 (25%)	n/a^	1	1 (100%)	n/a^
***p*-value**			0.008			0.430
Positive surgical margin						
No	404	49 (12%)	ref.	47	45 (96%)	ref.
Yes	475	103 (22%)	1.35 (1.00, 1.82)	99	92 (93%)	0.94 (0.85, 1.04)
Unsure	6	0 (0%)	n/a^	0	0 (.)	n/a^
***p*-value**			0.047			0.236
Seminal vesicle invasion						
No	729	83 (11%)	ref.	77	72 (94%)	ref.
Yes	154	68 (44%)	1.74 (1.37, 2.22)	69	65 (94%)	1.02 (0.93, 1.12)
Unsure	2	1 (50%)	n/a^	0	0 (.)	n/a^
***p*-value**			<0.001			0.632
Regional lymph node involvement						
No	558	96 (17%)	ref.	91	86 (95%)	ref.
Yes	56	31 (55%)	0.93 (0.56, 1.54)	31	30 (97%)	0.97 (0.87, 1.09)
Unsure	271	25 (9%)	0.67 (0.42, 1.08)	24	21 (88%)	0.95 (0.81, 1.12)
***p*-value**			0.257			0.819
Post-operative Gleason grade						
6-7	719	101 (14%)	ref.	97	91 (94%)	ref.
8	47	6 (13%)	0.61 (0.36, 1.03)	8	6 (75%)	0.75 (0.52, 1.09)
9-10	114	44 (39%)	1.36 (0.96, 1.92)	40	39 (98%)	1.04 (0.95, 1.15)
Unsure	5	1 (20%)	n/a^	1	1 (100%)	n/a^
***p*-value**			0.024			0.202
Number of co-morbidities						
0	149	22 (15%)	ref.	20	20 (100%)	ref.
1	573	98 (17%)	1.11 (0.83, 1.48)	95	88 (93%)	0.87 (0.81, 0.94)
2+	163	32 (20%)	1.31 (0.91, 1.88)	31	29 (94%)	0.91 (0.83, 0.99)
***p*-value**			0.350			<0.001

Table S7.3 (continued): Had consultation with radiation oncologist within 6 months of prostatectomy

	All patients excluding RAVES referrals			Patients referred to a radiation oncologist within 4 months after RP excluding RAVES referrals		
		Had consultation with radiation oncologist within 6 months after RP			Had consultation with radiation oncologist within 6 months after RP	
Characteristic	**N~**	**n (%)**	**Adjusted # RR (95%CI)**	**N~@**	**n (%)**	**Adjusted # RR (95%CI)**
All patients:	885	152 (17%)		146	137 (94%)	
Maximum PSA level within 4 months after RP (ng/ml)						
< 0.1	710	73 (10%)	ref.	73	65 (89%)	ref.
≥0.1	137	71 (52%)	2.68 (1.90, 3.78)	67	66 (99%)	1.14 (1.03, 1.27)
No PSA test recorded	38	8 (21%)	1.39 (0.72, 2.66)	6	6 (100%)	1.19 (1.04, 1.36)
***p*-value**			<0.001			0.016
Hospital						
Site 1	89	24 (27%)	2.22 (1.18, 4.17)	22	21 (95%)	1.11 (0.93, 1.33)
Site 2	11	8 (73%)	3.86 (1.41, 10.54)	9	8 (89%)	1.01 (0.83, 1.23)
Site 3	207	16 (8%)	ref.	14	13 (93%)	ref.
Site 4	108	11 (10%)	1.26 (0.44, 3.59)	8	8 (100%)	1.16 (0.93, 1.45)
Site 5	38	11 (29%)	2.60 (1.21, 5.59)	12	11 (92%)	0.96 (0.81, 1.15)
Site 6	86	15 (17%)	2.46 (1.21, 5.01)	16	15 (94%)	0.96 (0.83, 1.11)
Site 7	116	18 (16%)	1.45 (0.67, 3.13)	19	18 (95%)	1.05 (0.86, 1.29)
Site 8	153	25 (16%)	1.47 (0.71, 3.06)	24	22 (92%)	1.01 (0.85, 1.21)
Site 9	77	24 (31%)	2.68 (1.33, 5.38)	22	21 (95%)	1.05 (0.90, 1.23)
***p*-value**			<0.001			0.059

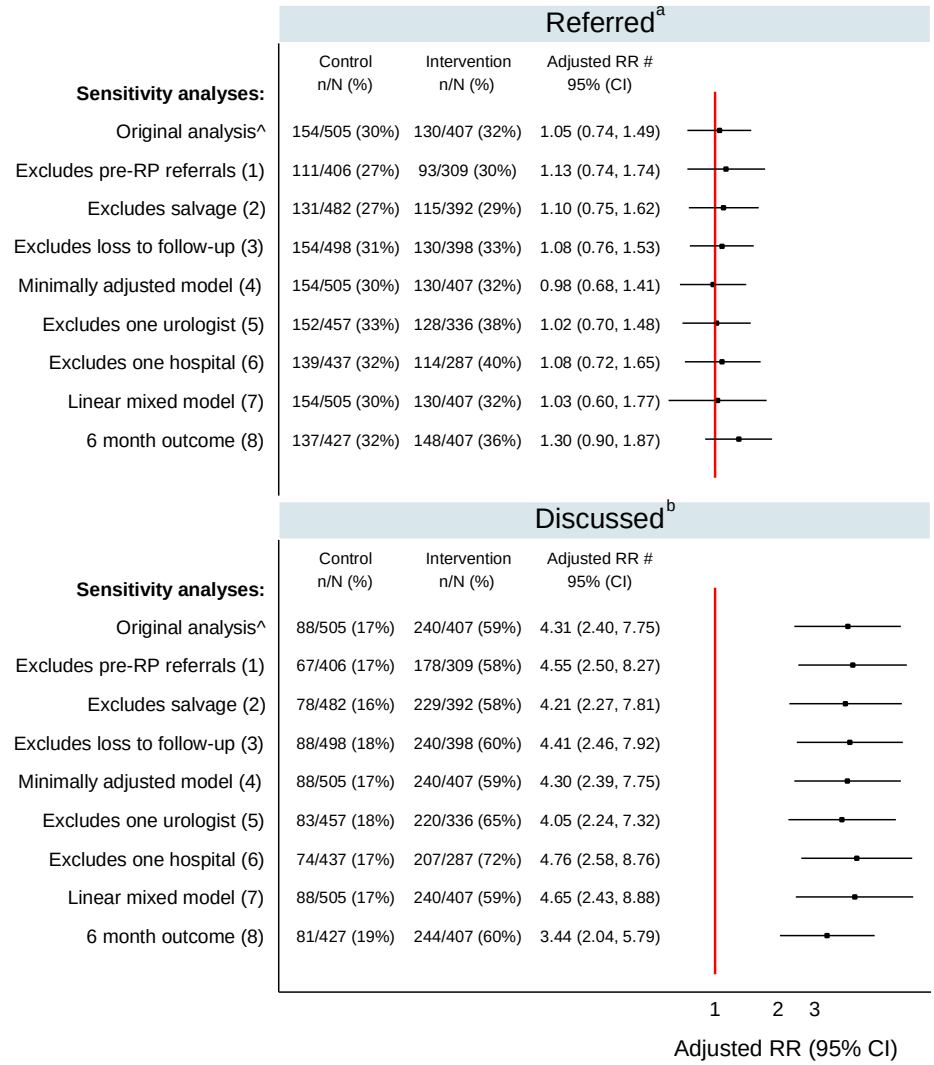
~Excludes 186 patients referred to the RAVES trial (includes 7 patients referred to RAVES after the 4 month CLICC cut off within 6 months after RP as per the RAVES recruitment protocol)

@ Excludes an additional 739 patients who were not referred to a radiation oncologist within 4 months after RP

Adjusted for study group, age at prostatectomy, extracapsular extension, positive surgical margin, seminal vesicle invasion, regional lymph node involvement, post-operative Gleason score, number of co-morbidities, maximum PSA within 4 months after RP, time period of surgery, site and urologist as the clustering variable

^ Patients within these categories were excluded from regression modelling due to low numbers prohibiting the convergence of model estimates

Figure S7.1: Sensitivity Analyses



[a] Patient referral within 4 months after RP to either a radiation oncologist or to the RAVES trial
[b] Patient discussed at MDT meeting within 4 months after RP
All analyses with the exception of #4 were adjusted for study group, age at prostatectomy, extracapsular extension, positive surgical margin, seminal vesicle invasion, regional lymph node involvement, post-operative Gleason score, number of co-morbidities, maximum PSA within 4 months of RP and time period of surgery. In addition: GEE analyses (analyses #1-6 and #8) included site as a fixed effect and urologist as the panel variable; the linear mixed model analysis (analyses #7) included random effect terms for sitel and urologists nested within sites
^ Results from original analyses repeated convenience
(1) Excludes patients referred to radiation oncologist before RP
(2) For each of the 2 outcomes, respectively, patients were excluded if they were referred or discussed within 4 months after RP but their urologist recorded the reason as salvage therapy or they had a PSA ≥0.1ng/ml within 4 months after RP
(3) Excludes patients who did not have a post surgical consultation within 4 months after RP
(4) Adjusted only for time period of surgery, age at RP and site with urologist defined as the panel variable and includes 7 control and 10 intervention patients excluded from original analyses because of missing clinical data
(5) Excludes patients of the urologist with highest caseload comprising 13.9% of all RPs
(6) Excludes patients from the site with highest caseload comprising 21.2% of all RPs (continued next page)

(7) Results from a linear mixed model analyses with random effect terms for site and urologists nested within sites
(8) The two outcomes of referred and discussed assessed at 6 months rather than 4 months

Chapter 8: Changes in provider knowledge, attitudes and beliefs

8.1 Introduction

Results presented in Chapter Seven, show that while the CLICC implementation trial significantly increased the secondary outcome of discussion of the patient at an MDT meeting within 4 months after prostatectomy, it did not result in significant change in the primary outcome of patient referral within 4 months after prostatectomy to either radiation oncology or to the RAVES trial. To understand the reasons for this lack of change in the primary outcome it is necessary to further explore participants' r*esponse* to the intervention through assessment of knowledge and attitudinal outcomes.(1)

As outlined in Chapter Six, *response* was defined as the extent to which multidisciplinary teams integrated and adopted new knowledge, systems and processes into their routine practice. The significant increase in the secondary outcome, discussion of the patient at an MDT meeting within 4 months after prostatectomy, indicates that flagging of eligible cases through the pathologist to the MDT coordinator successfully addressed the systems and processes and cultural barriers of variable engagement with, and selective presentation of cases to, the MDT. However, subgroup analyses (Chapter Seven; Table 7.4) demonstrated that for patients where the MDT recommendation was referral to radiotherapy, only 44% were actually referred within 4 months after radical prostatectomy. Where recorded, the main reasons for non-referral were an undetectable or low PSA (58%) and good continence (36%). This suggests that persisting clinician knowledge or attitudinal barriers are the reason there was no increase in the primary outcome of referral to radiotherapy or RAVES within four months of prostatectomy.

Clinician level barriers, identified through the needs and barriers analysis presented in Chapter Four, predominantly related to negative attitudes regarding the evidence to support the clinical practice recommendation for adjuvant radiotherapy for locally

advanced disease. This was coupled with perceptions of the potential for overtreatment in some patients whose cancer may not recur and concerns about radiotherapy associated toxicity or side effects such as impotence, urinary or fecal incontinence and urethral stricture; proposed by radiation oncologist interviewees to be due to insufficient knowledge about current radiotherapy techniques. The ongoing RAVES trial (2), comparing survival and quality of life outcomes for Australasian patients at high-risk of recurrence post-prostatectomy through randomisation to either salvage radiotherapy at the time of a PSA rise or immediate adjuvant radiotherapy, contributed to persisting norms.

Through the CLICC conceptual program logic model these knowledge and attitudinal barriers were mapped to physician-focused intervention components, specifically:

- Non-didactic, interactive provider education: CLICC introductory session facilitated by the Clinical Leader; CLICC introductory video (*predisposing* factors
- Dissemination of printed materials: CLICC printed resource; full copy of the Australian Cancer Network Clinical Practice Guideline for the Management of Men with Locally Advanced and Metastatic Prostate Cancer; peer review journal publications reporting the results and long-term follow up of the EORTC (3, 4), SWOG (5-7) and ARO (8, 9) randomised controlled trials that form the evidence base for the clinical practice guideline recommendation for adjuvant radiotherapy for locally advanced disease (*predisposing* factor)

To evaluate the extent to which participants integrated and adopted new knowledge from these CLICC intervention elements, and the degree to which they addressed clinician level barriers, we conducted baseline and post-intervention surveys to assess knowledge, attitudes and beliefs.

We hypothesised that compared with pre-intervention measures, urologists post-intervention would have increased knowledge about the evidence for appropriate adjuvant radiotherapy for high-risk prostate cancer patients after radical prostatectomy and the associated risks and benefits of treatment; and more positive attitudes towards the need for referral to radiation oncology as a means to support fully informed patient decision making.(1)

8.2 Methods

8.2.1 Study sample

Nine Clinical Leaders and 28 urologist participants involved in the CLICC implementation trial.

8.2.2 Survey domains

The CLICC baseline and post-intervention surveys were abbreviated versions of that developed for the nationwide surveys of urologist members of the Urological Society of Australia and New Zealand (USANZ) reported in Chapters Three and Nine. Briefly, the CLICC participant surveys related to: clinical equipoise; and knowledge, attitudes and beliefs regarding the clinical practice recommendation for adjuvant radiotherapy for men with locally advanced prostate cancer following radical prostatectomy. The baseline survey additionally collected demographic information. Where a baseline survey was not received from a participant this was collected in the post-intervention survey. Full surveys and the scoring key are included in Appendix XI. The survey predominantly used a five-point Likert scale ("strongly disagree" = 1 to "strongly agree" = 5) coded as consecutive integers for analysis (with an additional "don't know" option coded as missing). Negatively worded items were reverse coded around the mid-point ("strongly disagree" = 5 to "strongly agree" = 1). A summary score was calculated from respondents' total scores on questions within domains by summing the values for all non-missing items and dividing by the total number of items completed to assess overall attitudes and beliefs relating to the clinical practice

recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive adjuvant radiotherapy within 4 months of surgery. The CLICC participant survey was provided in hard copy only.

8.2.3 Clinical Equipoise

Three clinical scenarios were given to urologists as outlined in Box 8.1. Each reflected a different risk of recurrence but all fell under the "high-risk" category as outlined in the Australian Cancer Network Guidelines.(10) Cases 1, 2 and 3 had a 19%, 10% and 89% 10-year risk of biochemical relapse respectively according to Memorial Sloan Kettering Cancer Center nomograms (11). Respondents were asked to indicate the strength of their preference for watchful waiting or adjuvant radiotherapy on a linear analog scale with one treatment option anchored at each end of the scale. The scale was centered on zero to represent ''undecided'' and marked from ''1'' to ''5'' toward each end to represent increasing certainty in the treatment approach.(12).

For descriptive analysis, treatment preferences were categorised as follows: 0 – 3 = watchful waiting is preferable; 4 – 6 = undecided; 7 – 10 = adjuvant radiotherapy is preferable. Consistent with the definition used in the 2012 USANZ survey (13) and other equipoise studies (12), we define clinical equipoise as a situation in which less than 80% of clinicians are in agreement about the most appropriate treatment for a given scenario. For regression analysis, responses to clinical scenarios were transposed to a continuous 0 to 10 point scale, with lower scores indicating greater preference for watchful waiting.

8.2.4 Survey administration

Pre-intervention surveys were included in the information pack provided at the CLICC introductory session (or mailed to participants who did not attend the session). Three reminders, including further copies of the survey, were sent according to established protocols.

Post-intervention surveys were mailed to all Clinical Leaders and participating urologists on 31 March 2015 at the end of the active intervention phase. Three

reminders, including further copies of the survey, were sent according to established protocols.

In a deviation to the published study protocol (1) the survey was conducted at two time points (baseline and post-intervention) rather than three (baseline, 6 months after roll-out of the intervention, and end of study). This was because the six-month survey coincided with the post-intervention survey for Sites 8 and 9, which were the last to enter the active intervention phase of the study.

Box 8.1: Clinical case scenarios

Case 1 – A 64 year old man, previously well, presented with a screening PSA 12.2. Patient had radical prostatectomy 10 weeks ago. Pathology results show a Gleason 3+4=7 carcinoma with extracapsular extension and positive margins near apex over a 2mm front. Seminal vesicle and lymph nodes were clear. Post radical prostatectomy he has good urinary control. Post-op PSA 0.01. No return of erections.

Case 2 – A 58 year old man had a nerve sparing radical prostatectomy 3 months ago for a low volume Gleason 3+4=7 carcinoma (20% high grade) with 0.2mm extracapsular extension in left peripheral zone but clear surgical margin. No perineural or lymphovascular invasion. Seminal vesicles clear. 0/12 nodes involved. Post op PSA <0.01. Some dribbling on straining but pad free. Partial erections but inadequate for intercourse.

Case 3 - A 62 year old man had a non nerve sparing prostatectomy for a clinical T3 prostate cancer with pre-op PSA of 14. Histopathology demonstrates a widespread Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension and involvement of base of right seminal vesicle. Multiple sites of positive surgical margins. Post op PSA 0.04. No lymph node involvement. Good urinary function and no erections.

8.2.5 Statistical methods

Data were analysed using IBM SPSS Statistics Version 23.0 and STATA version 11.0. To compare differences between responses to baseline and post-intervention survey questions, generalised estimating equations (GEEs) were used to account for repeat responses from the same urologists across both surveys in instances where the

urologist had complete both surveys. Participants who completed only one survey, either baseline or post-intervention, were necessarily analysed as though they were unique in each survey and, as a consequence, confidence intervals for effect estimates are likely to be conservative, but point estimates should remain unbiased. Responses to survey questions were treated as the outcomes in regression models. Link functions and distributions for the GEEs were dependent on the nature of the responses options. Binomial distributions and logit link functions were assumed for dichotomous response items producing odds ratios as the measure of effect. Gaussian distributions and identity link functions were assumed for Likert and other ordinal scale response items producing mean differences as the measure of effect. P-values for multinomial outcomes were calculated using multinomial regression with a random effect to account for repeat responses from the same urologists (where relevant).

Qualitative textual data were explored thematically to identify collective attitudes and beliefs relating to the clinical practice recommendation that '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery*'.

8.3 Results

8.3.1 Response rate

29 of 37 participants (78%) completed the baseline survey and 24 of 37 (65%) completed the post-intervention survey. More than half (20 of 37; 54%) completed both surveys. Participant characteristics by survey are included in Table 8.1.

Table 8.1: Participant characteristics by survey

Characteristic	Survey: Baseline (n=29)	Survey: Post-intervention (n=24)	*p*-value^
Sex			
Male	28 (97%)	19 (79%)	0.080
Female	0 (0%)	0 (0%)	
Missing	1 (3%)	5 (21%)	
Age at survey			
20-30	0 (0%)	0 (0%)	0.154
31-40	4 (14%)	4 (17%)	
41-50	10 (34%)	8 (33%)	
51-60	5 (17%)	1 (4%)	
>60	10 (34%)	7 (29%)	
Missing	0 (0%)	4 (17%)	
Type of practice			
VMO/Consultant	28 (97%)	20 (83%)	0.036
Registrar/Junior Medical Officer	0 (0%)	0 (0%)	
Salaried University Academic	0 (0%)	0 (0%)	
Staff Specialist	1 (3%)	0 (0%)	
Other	0 (0%)	0 (0%)	
Missing	0 (0%)	4 (17%)	
Years of practice			
0-5	4 (14%)	4 (17%)	0.528
6-10	4 (14%)	3 (13%)	
11-15	6 (21%)	5 (21%)	
16-20	4 (14%)	2 (8%)	
21-25	1 (3%)	1 (4%)	
26-30	7 (24%)	4 (17%)	
>30	3 (10%)	1 (4%)	
Missing	0 (0%)	4 (17%)	
Perform radical prostatectomy			
Yes	29 (100%)	20 (83%)	0.036
No	0 (0%)	0 (0%)	
Missing	0 (0%)	4 (17%)	
Practice location			
Capital city	16 (55%)	11 (46%)	0.185
Other major urban area	8 (28%)	6 (25%)	
Rural	5 (17%)	3 (13%)	
Missing	0 (0%)	4 (17%)	
Setting for majority of patients			
Private	19 (66%)	14 (58%)	0.101
Public	10 (34%)	6 (25%)	
Missing	0 (0%)	4 (17%)	
New patients per month (mean)	10.9	11.7	0.544
% of practice for PC patients (mean)	26.3	27.9	0.264
% of PC patients in active treatment (mean)	39.5	35.8	0.187

^ *p*-values correspond to tests of no difference between surveys
Numbers are n (%) unless otherwise stated

There was a significant difference in type of practice between the baseline and post-intervention groups (p=0.036); however, this is likely due to the higher proportion of participants with missing demographic information in the post-intervention survey. There was also a significant difference in the number who reported that they perform radical prostatectomy (p=0.036). This was due to missing demographic information since eligibility criteria specified that CLICC participants must have performed one or more radical prostatectomies during the baseline and/or study period.

8.3.2 Treatment preference for adjuvant versus salvage radiotherapy post-prostatectomy

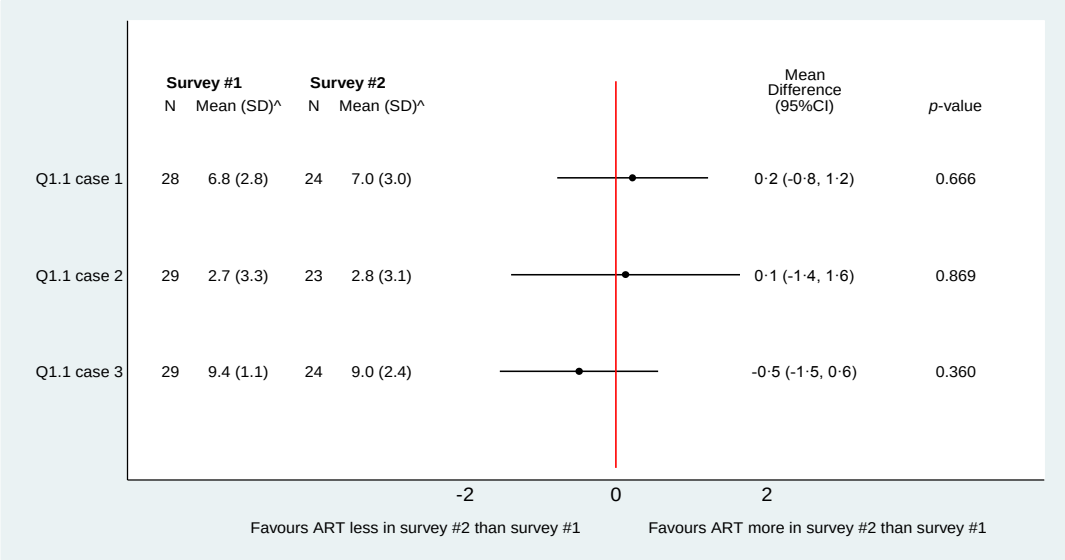
Treatment preferences for the three hypothetical clinical scenarios (Box 8.1) are detailed in Table 8.2 and Figure 8.1.

Table 8.2: Comparison between baseline and post-intervention survey responses - current level of certainty about which treatment option is better

	Watchful waiting is preferable			Undecided			Adjuvant radiotherapy is preferable			Missing		
	N	%	95% CI (%)	N	%	95% CI (%)	N	%	95% CI (%)	N	%	95% CI (%)
Case 1 Baseline	5	**17**	3, 31	6	**21**	6, 36	17	**59**	41, 77	1	3	-
Case 1 Post-intervention	4	**17**	2, 32	3	**18**	3, 33	17	**71**	53, 89	0	0	-
Case 2 Baseline	21	**72**	56, 88	2	**7**	0, 16	6	**21**	6, 36	0	0	-
Case 2 Post-intervention	17	**71**	52, 90	2	**8**	0, 19	4	**17**	2, 32	1	4	-
Case 3 Baseline	0	**0**	-	1	**3**	0, 9	28	**97**	91, 100	0	0	-
Case 3 Post-intervention	2	**8**	0, 19	0	**0**	-	22	**92**	81, 100	0	0	-

There was no change in CLICC participants' treatment preferences between baseline and post-intervention surveys. At baseline, according to our definition, there was clinical equipoise for Case 1 (19% 10-year risk of biochemical relapse). However, a greater proportion indicated a preference for adjuvant radiotherapy than watchful waiting: 59% indicated that adjuvant radiotherapy is preferable, 21% were undecided and 17% indicated that watchful waiting is preferable. Post-intervention for Case 1 71% indicated a preference for adjuvant radiotherapy, 18% were undecided and 17% indicated a preference for watchful waiting. While there was an increase in the proportion that indicated a preference for adjuvant radiotherapy post-intervention, this change was not significant; urologists were on average 0.2 more favourable towards Case 1 receiving adjuvant radiotherapy post-intervention than they were at baseline with mean scores of 6.8 and 7.0 respectively (mean difference 0.2; 95% CI [-0.8, 1.2]; p=0.666). There was also clinical equipoise for Case 2 (10% 10-year risk of biochemical relapse) at baseline, with a stronger preference for watchful waiting, and this did not change post-intervention. Seventy-two per cent indicated a preference for watchful waiting at baseline compared with 71% post-intervention while the proportion that considered adjuvant radiotherapy preferable decreased from 21% at baseline to 17% post-intervention but this change was not significant (mean scores 2.7 and 2.8 respectively; mean difference 0.1; 95% CI [-1.4, 1.6]; p=0.869). For Case 3 (89% 10-year risk of biochemical relapse) adjuvant radiotherapy was considered preferable by 97% at baseline decreasing to 92% post-intervention (mean scores 9.4 and 9.0). This change was not significant (mean difference -0.5; 95% CI [-1.5, 0.6]; p=0.360).

Figure 8.1: Comparison between baseline and post-intervention survey responses - level of certainty about which treatment option is better



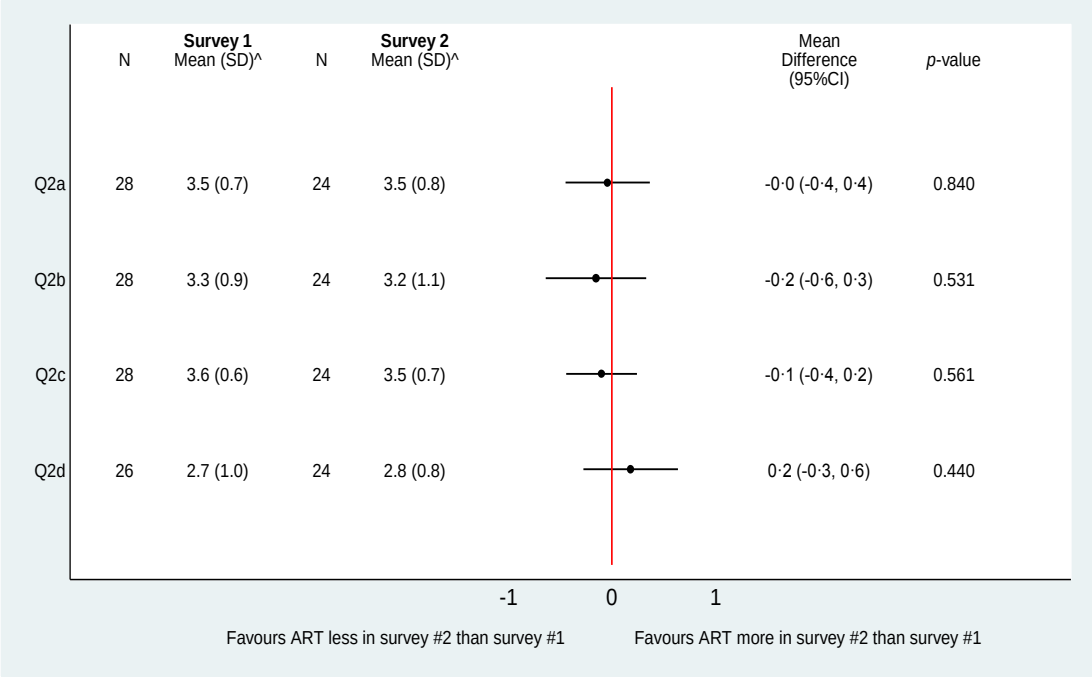
^ Scores were measured on a scale from 0 to 10 with lower scores indicating greater preference for watchful waiting, higher scores indicating greater preference for adjuvant radiotherapy and a score of 5 indicating undecided
Survey #1 = Baseline Survey #2 = Post-intervention

8.3.4 Knowledge

There were no significant changes in participants' understanding of the current literature and evidence for the treatment of prostate cancer (Figure 8.2). There was no difference in agreement between baseline and post-intervention surveys that immediate external irradiation after radical prostatectomy improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 prostate cancer who are at high risk of progression (Q2a. mean difference -0.0; 95% CI [-0.4, 0.4]; p=0.840). There was less agreement post-intervention that relapse after local therapy is defined by prostate-specific antigen (PSA) values >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir PSA after radiation therapy (RT) but this was not significant (Q2b. mean difference -0.2; 95% CI [-0.6, 0.3]; p=0.531]. Notably, there was less agreement post-intervention that all high risk patients should have multidisciplinary input and be referred by their urologist to a radiation oncologist before treatment to

ensure informed decision making based on discussion of the relative advantages and disadvantages of adjuvant radiotherapy or watchful waiting but this change was not significant (Q2c. mean difference -0.1; 95% CI [-0.4, 0.2]; p=0.561). Further, there was slightly more agreement post-intervention that there are no data from randomised controlled trials to define the benefits of salvage radiation versus adjuvant therapy or salvage radiation versus systemic therapy (either at time of PSA rise or at time of radiographic progression) but this was not significant (Q2d. mean difference 0.2; 95% CI [-0.3, 0.6]; p=0.440).

Figure 8.2: Comparison between baseline and post-intervention survey responses - understanding of current literature and evidence for the treatment of prostate cancer



^ Scores correspond to a 4-point Likert type scale with scoring 1=Strongly disagree, 2=Somewhat disagree, 3=Somewhat agree, 4=Strongly agree; "Don't know" and missing responses were excluded from analyses
Survey #1 = Baseline Survey #2 = Post-intervention
*Full survey questions are available in Appendix X.

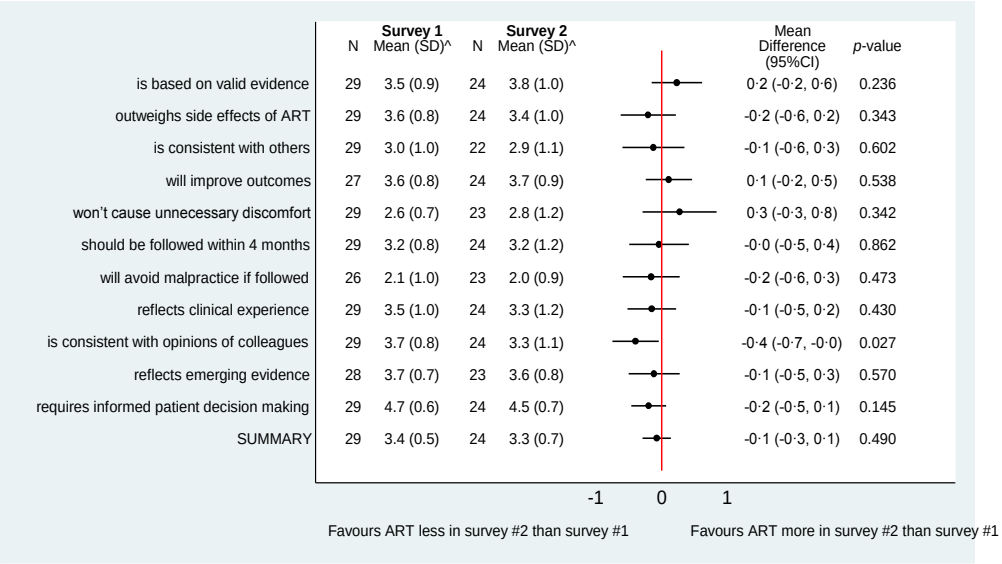
8.3.5 Attitudes

Overall there was no change in agreement with the clinical practice recommendation for adjuvant radiotherapy for locally advanced disease

between baseline and post-intervention (mean difference -0.1; 95% CI [-0.3, 0.1]; p=0.490) (Figure 8.3). This reflects lack of significant change across the majority of underlying attitudes within this domain. Notably, there was no change in the level of agreement that the recommendation is based on a valid interpretation of underpinning evidence (mean difference 0.2; 95% CI [-0.2, 0.6]; p=0.236). Further, there was no change in agreement post-intervention that the recommendation reflects evidence that is emerging on the topic (mean difference -0.1; 95% CI [-0.5, -0.3]; p=0.570). The only significant change in attitudes was less agreement post-intervention that the recommendation is consistent with the opinions of respected clinical colleagues (mean difference -0.4; 95% CI [-0.7, 0.0]; p=0.027).

Figure 8.3: Comparisons between baseline and post-intervention responses - attitudes towards recommendation that '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery*'

**This recommendation:*



^ Scores correspond to a 5-point Likert type scale with scoring 1=Strongly disagree, 2=Disagree, 3=Neither agree nor disagree, 4=Agree, 5=Strongly agree; "Don't know" and missing responses were excluded from analyses
Survey #1 = Baseline Survey #2 = Post-intervention
*Full survey questions are available in Appendix X. Some items were reverse coded for analyses and these are reflected in question labels.

8.3.6 Beliefs

Post-operative treatment decisions

There was no significant difference between the baseline and post-intervention surveys in opinions about who is best placed to make post-operative treatment decisions (p=0.75; Table 8.3). The majority of participants in both surveys (76% baseline and 74% post-intervention) considered that the MDT is best placed to decide on the most appropriate post-operative treatment followed by the urological surgeon. No participants considered the radiation oncologist best placed to make post-operative treatment decisions at either baseline or post-intervention.

Table 8.3: Comparison between baseline and post-intervention responses - following radical prostatectomy, who is the person best placed to decide on the most appropriate post-operative treatment option?

	Survey	
	Baseline	Post-intervention
Following surgery who should decide further treatment?	**(n=29)**	**(n=23)**
The urological surgeon is best placed to decide	6 (21%)	4 (17%)
The radiation oncologist is best placed to decide	0 (0%)	0 (0%)
The MDT is best placed to decide	22 (76%)	17 (74%)
The patient is best placed to decide	1 (3%)	2 (9%)
The medical oncologist is best placed to decide	0 (0%)	0 (0%)

p=0.75 for test equal proportions across surveys
n and % are for frequencies and % of individuals; missing responses were excluded from analysis

Survival benefit and toxicity associated with adjuvant radiotherapy

Participants did not vary significantly between baseline and post-intervention in their views of the minimum survival benefit considered acceptable for them to follow the recommendation for adjuvant radiotherapy for locally advanced disease (mean difference -0.3; 95% CI [-1.5, 1.0]; p=0.690). Nor was there a significant change in the maximum proportion of men who suffer from rectal damage or develop faecal incontinence as a result of radiotherapy for this treatment to be unacceptable (mean difference -2.1; 95% CI [-9.4, 9.2]; p=0.572) (data not shown).

Open text responses

Eighteen of 29 (62%) of participants provided comments in the baseline survey and 13 of 24 (54%) provided comments in the post-intervention survey. Thematic analysis of open text indicated a number of common beliefs evident in the baseline surveys that persisted in the post-intervention surveys:

1. *Concerns about side effects / overtreatment resulting in a preference for early salvage over adjuvant radiotherapy* – 6 of 18 (33%) at baseline and 5 of 13 (38%) post-intervention noted that:

   > *"in men who are low to moderate risk of recurrence it is difficult to push adjuvant radiation as it has side effects which are often understated by the Radiation Oncologist." [Baseline]*
   >
   > *"High % of patient will have treatment & side effects unnecessarily. With ultra-sensitive PSA, f/u [follow up] selective salvage Rx [radiotherapy] may give specific similar benefit i.e. RAVES trial." [Post-intervention]*

2. *Need for individualised care* – a number of participants (4 of 18 (22%) at baseline and 3 of 13 (23%) post-intervention) noted that post-operative adjuvant radiotherapy should be considered on a case-by-case basis:

   > *"Nuanced decision. Depends on risk of relapse. Positive margin group is different from ECE group with negative margins. Some patients clearly benefit. Others are best to wait for any PSA recurrence. A 'one size fits all' recommendation is poor medicine." [Baseline]*
   >
   > *"Recommendations strongly depend on grade of glands at margin, extent of margin + PSA. For some patients it is appropriate. For some it is not. The recommendation is not nuanced enough."[Post-intervention]*

3. *Perceived lack of evidence / lack of confidence in trial data* – 22% (4 of 18) commented on the level of evidence supporting adjuvant radiotherapy following radical prostatectomy at baseline:

"I remain unconvinced on the quality of benefit of adjuvant RTx [radiotherapy] over early salvage RTx [radiotherapy], but agree the available evidence supports early intervention." [Baseline].

Only one participant (8%) expressed similar concerns about evidence post-intervention:

"Absolute numbers in randomised trials to date who have had events (e.g. death) is low. So evidence is not as strong as Rad Onc [radiation oncologist] likes to think." [Post-intervention]

4. *Positive beliefs about adjuvant radiotherapy* - In both baseline (4 of 18; 22%) and post-intervention (3 of 13; 33%) surveys a number commented favourably on adjuvant radiotherapy following radical prostatectomy and indicated they support its use:

   "I support it but less so if: lower risk - local positive margins and 3+3 at margin; young and wants erection." [Baseline]

   "Adjuvant radiotherapy has a place in selected patients after risk stratification for progression of disease." [Baseline]

   Post-intervention comments were more positive without caveats, with participants noting it is *"really good", "I do it"* and there should be *"more"*.

Discussion

The results of CLICC participant surveys did not support the hypothesis that post-intervention urologists would have increased knowledge about the evidence for appropriate adjuvant radiotherapy for high-risk prostate cancer patients after radical prostatectomy and the associated risks and benefits of treatment post-intervention; and more positive attitudes towards the need for referral to radiation oncology as a means to support fully informed patient decision-making.

It is a limitation that not all CLICC participants completed both baseline and

post-intervention surveys. Those that only completed one survey, either baseline or post-intervention, were necessarily analysed as though they were unique in each survey and, as a consequence, confidence intervals for effect sizes are likely to be conservative but point estimates should remain unbiased. More than half (54%), however, completed both surveys enabling comparison of differences in responses between baseline and post-intervention surveys. "Don't know" responses were coded as missing which reduced the denominator for some questions but there were very few instances (less than 10 in the baseline survey and 2 in the post-intervention survey) where "don't know" responses were selected across all survey questions. It is a further potential limitation that the psychometric properties of the survey have not been assessed. The response rate (78% baseline and 65% post-intervention) is higher than that reported for similar clinician surveys.(14, 15)

The results correspond with comments made in semi-structured interviews, conducted as part of the CLICC process evaluation (Chapter Six), and in open text survey responses in which a number of participants noted that they had knowledge of the evidence from these trials but continued to challenge its efficacy; *"Absolute numbers in randomised trials to date who have had events (e.g. death) is low. So evidence is not as strong as [the radiation oncologist] likes to think."* [Post-intervention survey] CLICC printed materials included all data relating to the three randomised controlled trials (EORTC Trial 22911 (3, 4); SWOG S8794 (5, 6, 16); ARO Trial 96–02/AUP AP 09/95 (8, 9)) that form the evidence base for this clinical practice recommendation published at the commencement of the active intervention phase. However, with the exception of longer-term follow-up results for the EORTC Trial (4) no new data were published between the release of clinical practice guidelines (10, 17-20) and commencement of CLICC in 2014. Results from the RAVES trial (2) which were anticipated to provide evidence directly comparing outcomes and quality of life associated with adjuvant radiotherapy and early salvage

radiotherapy were frequently mentioned. This highlights the continued influence of RAVES as a confounder to reinforce the normative behaviour of watchful waiting rather than immediate referral for consideration of adjuvant radiotherapy, which is the evidence-based guideline recommended care. As one participant in the baseline survey noted, *"My own practice is to refer to practitioners involved in the RAVES trial as I feel that time will show one can watch safely these men rather than commence immediate RT."* In recognition of the potential for RAVES to act as a confounder in the CLICC implementation trial, the primary outcome included patient referral within 4 months after prostatectomy to either radiation oncology or to the RAVES trial. Subgroup analysis of RAVES referral patterns (Chapter Seven) showed that only 15% of eligible patients (75 of 505 baseline; 24 of 159 transition) were referred to RAVES within 4 months of radical prostatectomy prior to CLICC and referral rates did not change post-intervention (16%; 64 of 407 intervention patients). The RAVES trial was closed to accrual on 31 December 2015 due to poor recruitment and the low event rate, which the RAVES Independent Data Monitoring Committee considered would make it "highly unlikely that early salvage radiotherapy will be shown to be 10% inferior to adjuvant therapy in biochemical control, even if a further 140 patients were recruited to the study to reach the original sample size of 470".(21) This means that the current randomised controlled trial data from the EORTC (3, 4); SWOG (5, 6, 16) and ARO trials (8, 9) remains the best evidence to inform the treatment of men with locally advanced prostate cancer following radical prostatectomy.

In addition to the summary of evidence, the CLICC printed resource provided high-level information on current radiotherapy techniques. It was not appropriate to provide more detailed information, as decisions regarding dose should be made by the treating radiation oncologist who has full knowledge of the patient's functional status, history and toxicity tolerance.(22) The CLICC printed resource, therefore, advocated referral to radiation oncology to

discuss what radiation treatment would involve at the patient's local radiotherapy unit. However, survey responses indicate that post-intervention participants did not have more positive attitudes towards the need for referral to radiation oncology as a means to support fully informed patient decision-making. In fact, while the change was not significant, fewer participants post-intervention agreed that all high risk patients should have multidisciplinary input and be referred by their urologist to a radiation oncologist before treatment to ensure informed decision making based on discussion of the relative advantages and disadvantages of adjuvant radiotherapy or watchful waiting. Open text responses indicated this is likely due to perceptions that radiation oncologists do not present a balanced view of radiotherapy associated side effects and toxicity: *"The side effects, when they occur, are not managed by radiation oncologists. As a result, radiation oncologists do not present a balanced view of risks versus benefits."* [Baseline] Post-intervention, however, one participant acknowledged that the lack of a balanced view was equally applicable to urologists: *"Urologists overestimate side effects. Rad Oncs [radiation oncologists] underestimate side effects."*

Somewhat contrarily, while participants did not have more positive attitudes towards the need for referral to radiation oncology as a means to support fully informed patient decision-making, there was persisting belief, evident in both baseline and post-intervention surveys, in the need for individualised care. This, however, was perceived by participants to relate to consideration of clinical factors such as margin status, post-operative PSA and continence rather than providing patients with an opportunity to discuss adjuvant treatment options with a radiation oncologist.

Whilst acknowledging the potential limitations associated with self-reported practice, there was an increase in the proportion of participants who indicated a preference for adjuvant radiotherapy for the hypothetical Case 1 but this

change was not significant and overall there was no change in treatment preference for any of the three given scenarios. This is consistent with results from independent, blinded medical record review (Chapter Seven), which found no increase in actual rates of referral to radiotherapy or RAVES within 4 months after prostatectomy, and reflects a lack of change in attitudes towards adjuvant radiotherapy for locally advanced disease. The only underlying attitude to change within the domain was a significant decrease in the proportion post-intervention that agreed the recommendation for adjuvant radiotherapy is consistent with the opinions of respected colleagues. This suggests that within the wider urological community there is potentially less agreement with the recommendation for adjuvant radiotherapy than was considered the case at baseline.

To determine whether urologists' attitudes towards adjuvant radiotherapy for locally advanced disease following radical prostatectomy have shifted nationally, outside of the CLICC participant group, we conducted a follow up survey of urologist members of the Urological Society of Australia (USANZ). Results of that survey are presented in Chapter Nine.

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Chapter 9: Changing attitudes toward management of men with locally advanced prostate cancer following radical prostatectomy: a follow-up survey of Australian-based urologists

Publication arising from this chapter

Publication arising from this chapter: Brown B, Egger S, Young J, Kneebone AB, Brooks AJ, Dominello A & Haines M. Changing Attitudes toward Management of Men with Locally Advanced Prostate Cancer following Radical Prostatectomy: A Follow-up Survey of Australian-based Urologists. *Journal of Medical Imaging and Radiation Oncology.* 2016 June 27. doi:10.1111/1754-9485.12483.

9.1 Abstract

Introduction: This study examined whether there has been change among Australia-based urologists' knowledge, attitudes and beliefs relating to guideline-recommended adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy since a prior survey in 2012 and investigated associations between attitudes and treatment preferences.

Methods: A nationwide survey of Australia-based urologist members of the Urological Society of Australia and New Zealand.

Results: 96 respondents completed the 2015 survey (30% response rate) compared with 157 (45% response rate) in 2012. There was no significant change in awareness of national clinical practice guidelines for the management of prostate cancer. When considering adjuvant against salvage radiotherapy, urologists were significantly less favourable towards adjuvant radiotherapy in 2015 than in 2012 for two of three hypothetical clinical case scenarios with a high 10-year risk of biochemical relapse according to

Memorial Sloan Kettering Cancer Center nomograms (p<0.001 for both cases). In 2015, urologists' were less positive overall towards the recommendation for post-operative adjuvant radiotherapy for men with locally advanced prostate cancer than in 2012 (p<0.001), reflecting a significant change across a number of attitudes and beliefs. Of note, urologists felt other urologists would more likely be critical if they routinely referred the target patient group for radiotherapy in 2015 compared with 2012 (p=0.007).

Conclusion: In 2015 Australian-based urologists were less favourable towards adjuvant radiotherapy over watchful waiting for men with high-risk pathologic features post-prostatectomy than in 2012. We could find no new published research that precipitated this change in attitude.

9.2 Introduction

On the basis of evidence from three randomised controlled trials demonstrating the efficacy of adjuvant radiotherapy after radical prostatectomy for patients with high-risk pathologic features, (1-5) several international clinical practice guidelines (CPGs) (6-10) were published between 2010 and 2013 with a recommendation that men with extracapsular extension, seminal vesicle invasion or positive surgical margins should be offered adjuvant radiotherapy after radical prostatectomy.

In 2012, two years after release of the Australian Cancer Network Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer (8), we conducted a nationwide survey to investigate Australian urologists' knowledge, attitudes and beliefs, and the association of these with treatment preferences relating to guideline-recommended adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy.(11) The survey provided baseline data to inform the development of the "Clinician-Led Improvement in Cancer Care (CLICC)" implementation trial.(12)

Results from the 2012 survey indicated that urologists varied in their attitudes and beliefs regarding adjuvant radiotherapy after radical prostatectomy for men with adverse pathologic features.(11) Less than one third agreed that adjuvant radiotherapy would lead to improved outcomes, while more than two thirds agreed that it may result in unnecessary patient discomfort. Consequently there was clinical equipoise for a hypothetical clinical scenario that would indicate its use (Box 9.1; Case 1). Forty per cent of respondents in 2012 expressed concerns about the appropriateness of adjuvant radiotherapy for patients with post-surgical incontinence or those worried about impotence. This was reflected in a preference to keep those patients under surveillance and refer for early salvage radiotherapy if there is a Prostate Specific Antigen (PSA) rise. This finding was in line with the results of a US survey, which indicated urologists were less confident in the benefit of adjuvant radiotherapy in terms of overall survival or durable biochemical control and predicted higher rates of side effects and toxicity due to radiotherapy than radiation oncologists.(13)

Numerous patterns of care studies demonstrate that ongoing controversy surrounding adjuvant radiotherapy and persisting clinical uncertainty is reflected in historically low rates of utilisation of adjuvant radiation in this patient group. These studies consistently report only 10-20% of eligible patients receive treatment in Australia (14-17), Canada (18, 19) and the US (20-23) and rates did not increase following publication of randomised controlled trial data. Further, a retrospective analysis of data from the US National Cancer Data Base indicates *declining* use of radiotherapy for adverse features after radical prostatectomy. That study, including 97,270 patients diagnosed with prostate cancer between 2005 and 2011, found receipt of postoperative radiotherapy significantly decreased from 9.1% to 7.3% ($p < 0.001$).(24)

Box 9.1: Clinical Case Scenarios

Case 1 – A 64 year old man, previously well, presented with a screening PSA 12.2. Patient had radical prostatectomy 10 weeks ago. Pathology results show a Gleason 3+4=7 carcinoma with extracapsular extension and positive margins near apex over a 2mm front. Seminal vesicle and lymph nodes were clear. Post radical prostatectomy he has good urinary control. Post-op PSA 0.01. No return of erections.

Case 2 – A 58 year old man had a nerve sparing radical prostatectomy 3 months ago for a low volume Gleason 3+4=7 carcinoma (20% high grade) with 0.2mm extracapsular extension in left peripheral zone but clear surgical margin. No perineural or lymphovascular invasion. Seminal vesicles clear. 0/12 nodes involved. Post op PSA <0.01. Some dribbling on straining but pad free. Partial erections but inadequate for intercourse.

Case 3 - A 62 year old man had a non nerve sparing prostatectomy for a clinical T3 prostate cancer with pre-op PSA of 14. Histopathology demonstrates a widespread Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension and involvement of base of right seminal vesicle. Multiple sites of positive surgical margins. Post op PSA 0.04. No lymph node involvement. Good urinary function and no erections.

Therefore, we conducted a follow up survey in 2015 to determine whether there has been a shift in prevailing attitudes and beliefs among Australian urologists regarding adjuvant radiotherapy after radical prostatectomy and their preferences for adjuvant or salvage radiotherapy for men with adverse pathological features.

9.3 Subjects and Methods

Study sample

Australia-based currently practicing urologists and trainees of the Urological Society of Australia and New Zealand (USANZ). Urologist participants in the CLICC implementation trial (n=37) (12) who have been exposed to an intervention strategy to increase referral for discussion of guideline recommended radiation treatment following surgery were ineligible to

participate in this survey, which they completed as a requirement of CLICC (reported elsewhere).

Survey domains

Full details of survey development have been previously published.(11) Briefly, the survey comprised 6 sections relating to: 1. clinical equipoise; 2. the use of, and attitudes and beliefs towards, clinical guidelines in practice; 3. innovation and current clinical practice; 4. barriers to adherence to a clinical practice recommendation; 5 perceptions of organisational readiness for change; and 6. demographic information. The full survey and the scoring key can be found in Appendix IV. The survey predominantly used a five-point Likert scale ("strongly disagree" = 1 to "strongly agree" = 5) coded as consecutive integers for analysis (with an additional "don't know" option coded as missing). Negatively worded items were reverse coded around the mid-point ("strongly disagree" = 5 to "strongly agree" = 1). A summary score was calculated from respondents' total scores on questions within domains by summing the values for all non-missing items and dividing by the total number of items completed to assess overall attitudes and beliefs relating to clinical practice guidelines (CPGs). The survey was formatted in both web-based and hard copy versions.

Clinical Equipoise

Three clinical scenarios were given to urologists as outlined in Box 9.1. Each reflected a different risk of recurrence but all fell under the "high-risk" category as outlined in the Australian Cancer Network Guidelines.(8) Cases 1, 2 and 3 had a 19%, 10% and 89% 10-year risk of biochemical relapse respectively according to Memorial Sloan Kettering Cancer Center nomograms (25) highlighting the heterogeneity of patients in the "high-risk" cohort.
For descriptive analysis (Table 2), treatment preferences were categorised as follows: 0 – 3 = watchful waiting is preferable; 4 – 6 = undecided; 7 – 10 =

adjuvant radiotherapy is preferable. Consistent with the definition used in the 2012 survey (11) and other equipoise studies (26), we define clinical equipoise as a situation in which less than 80% of clinicians are in agreement about the most appropriate treatment for a given scenario. For regression analysis, responses to clinical scenarios were transposed to a continuous 0 to 10 point scale, with lower scores indicating greater preference for watchful waiting (Figure 9.1).

Survey administration

The survey was administered following an established protocol used for the prior 2012 survey.(11) Respondents who completed the survey were eligible to enter a competition to win an iPad.

Statistical methods

Data were analysed using IBM SPSS Statistics Version 23.0 and STATA version 11.0. Only surveys that provided responses beyond the three clinical scenarios were included in analyses.

To compare differences between responses to 2012 and 2015 survey questions, generalised estimating equations (GEEs) were used to account for repeat responses from the same urologists across both surveys in instances where the urologist could be identified. However, because name disclosure was voluntary in both surveys to comply with confidentiality and ethical requirements, we were unable to match urologists who participated in both surveys but chose to remain anonymous in at least one of the surveys. These participants were necessarily analysed as though they were unique in each survey and, as a consequence, confidence intervals for effect estimates are likely to be conservative, but point estimates should remain unbiased.

Responses to survey questions were treated as the outcomes in regression models. Link functions and distributions for the GEEs were dependent on the

nature of the responses options. Binomial distributions and logit link functions were assumed for dichotomous response items producing odds ratios as the measure of effect. Gaussian distributions and identity link functions were assumed for Likert and other ordinal scale response items producing mean differences as the measure of effect. P-values for multinomial outcomes were calculated using multinomial regression with a random effect to account for repeat responses from the same urologists (where identifiable).

T-tests were used to explore relationships between knowledge and treatment preference.

Two lots of sensitivity analysis were conducted. First, regression models were additionally adjusted for age, sex and type of practice to account for any imbalances on these variables between surveys. Second, Likert and other ordinal outcomes were analysed alternatively using proportional odds ordinal logistic regression with cluster robust standard errors. This second sensitivity analysis was performed because the debate over the most appropriate statistical method for analysing Likert-type scales has been ongoing for more than 50 years.(27) In our main analyses, we chose to analyse Likert and other ordinal scales continuously using linear regression because, in our opinion, there is good evidence that this method is robust while providing more statistical power than other methods.(28, 29) Nonetheless, we also accept that ordinal logistic regression is an alternative appropriate method for analysing these data.

Qualitative textual data were explored thematically to identify persisting barriers to the implementation of the clinical practice recommendation that '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery'*.

9.4 Results

Response Rate

Ninety-five of 322 urologists (30%) invited to participate responded in 2015, compared with 157 of 350 (45%) in 2012. Respondent characteristics for the 2012 and 2015 surveys are summarized in Table 1. There was no significant difference in respondent demographics in the two surveys.

Table 9.1: Participant characteristics by survey

	Survey		
	2012	2015	
Characteristic	**(n=157)**	**(n=96)**	***p*-value^**
Sex			
Male	126 (80%)	78 (81%)	0.131
Female	14 (9%)	13 (14%)	
Missing	17 (11%)	5 (5%)	
Age at survey			
20-30	1 (1%)	1 (1%)	0.124
31-40	38 (24%)	22 (23%)	
41-50	48 (31%)	35 (36%)	
51-60	27 (17%)	25 (26%)	
>60	26 (17%)	7 (7%)	
Missing	17 (11%)	6 (6%)	
Type of practice			
VMO/Consultant	117 (75%)	79 (82%)	0.643
Registrar/Junior Medical Officer	5 (3%)	2 (2%)	
Salaried University Academic	5 (3%)	2 (2%)	
Staff Specialist	11 (7%)	6 (6%)	
Other	2 (1%)	2 (2%)	
Missing	17 (11%)	5 (5%)	
Years of practice			
0-5	38 (24%)	19 (20%)	0.494
6-10	24 (15%)	20 (21%)	
11-15	19 (12%)	13 (14%)	
16-20	17 (11%)	13 (14%)	
21-25	16 (10%)	14 (15%)	
26-30	11 (7%)	6 (6%)	
>30	15 (10%)	6 (6%)	
Missing	17 (11%)	5 (5%)	
Perform radical prostatectomy			
Yes	113 (72%)	79 (82%)	0.131
No	27 (17%)	12 (13%)	
Missing	17 (11%)	5 (5%)	

Continued next page

Characteristic	Survey 2012 (n=157)	Survey 2015 (n=96)	*p*-value^
Practice location			
Capital city	91 (58%)	54 (56%)	0.238
Other major urban area	28 (18%)	24 (25%)	
Rural/remote	20 (13%)	13 (14%)	
Missing	18 (11%)	5 (5%)	
Setting for majority of patients			
Private	78 (50%)	48 (50%)	0.684
Public	59 (38%)	39 (41%)	
Missing	20 (13%)	9 (9%)	
New patients per month (mean)	10.1	8.8	0.150
% of practice for PC patients (mean)	31.1	28.2	0.228
% of PC patients in active treatment (mean)	44.5	37.4	0.057

^ *p*-values correspond to tests of no difference between surveys
Numbers are n (%) unless otherwise stated

Knowledge – awareness of the Australian Cancer Network Clinical Practice Guidelines

Just over half of respondents (54%) reported that they were aware of the Guidelines in 2012 and there was no increase in awareness in 2015 (53%). Of those who were aware of the guideline, the primary source of referral was USANZ in both 2012 and 2015 (45% and 56% respectively).

Treatment preference for adjuvant versus salvage radiotherapy post-prostatectomy

Treatment preferences for the three hypothetical clinical scenarios (Box 9.1) are detailed in Table 9.2 and Figure 9.1. In 2012 there was clinical equipoise for Case 1 (19% 10-year risk of biochemical relapse): 45% indicated that watchful waiting is preferable; 12% were undecided; 43% indicated that adjuvant radiotherapy is preferable. In 2015 for Case 1, while there remained clinical equipoise according to our definition, urologists indicated a preference for watchful waiting (71%) over adjuvant radiotherapy (23%), with only 5% undecided. Urologists were on average 1.8 points less favourable towards Case 1 receiving adjuvant radiotherapy in 2015 than they were in 2012 with mean scores of 2.9 and 4.7 respectively (mean difference -1.8; 95% CI [-2.6, -

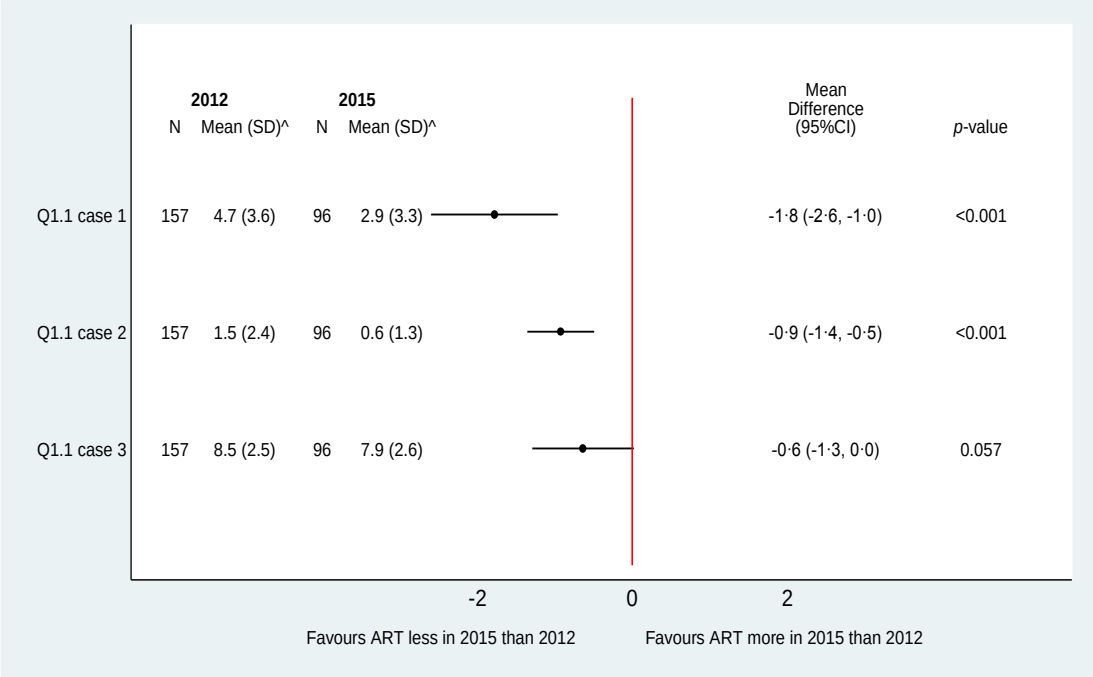
1.0]; p<0.001) representing a significant shift away from adjuvant radiotherapy as the preferred treatment choice. Treatment preference for Case 2 (10% 10-year risk of biochemical relapse) was watchful waiting in both 2012 (86%) and 2015 (97%) (mean scores 1.5 and 0.6 respectively) with urologists significantly less likely to favour adjuvant radiotherapy in 2015 than 2012 (mean difference -0.9; 95% CI [-1.4, -0.5]; p<0.001). For Case 3 (89% 10-year risk of biochemical relapse) adjuvant radiotherapy was considered preferable by 89% in 2012 decreasing to 82% in 2015 (mean scores 8.5 and 7.9). This change was not significant (mean difference -0.6; 95% CI [-1.3, 0.0]; p=0.057) but does provide weak evidence that adjuvant radiotherapy might be less preferred in 2015 than 2012, even for very high-risk patients.

Consistent with findings of the 2012 survey, for Case 1 where there was clinical equipoise, there was no significant difference in treatment preferences in 2015 between those who were aware of the Guidelines (M=2.68, SD=3.242) and those who were not (M=3.32, SD=3.476); t (92)=0.921, p=0.36.

Table 9.2: Current level of certainty about which treatment option is better

	Watchful waiting is preferable			**Undecided**			**Adjuvant radiotherapy is preferable**		
	N	**%**	**95% CI (%)**	**N**	**%**	**95% CI (%)**	**N**	**%**	**95% CI (%)**
Case 1 2012	71	**45**	37, 53	18	**12**	7, 17	68	**43**	35, 51
Case 1 2015	67	**71**	61, 79	5	**5**	2, 12	22	**23**	16, 33
Case 2 2012	135	**86**	81, 91	11	**7**	3, 11	11	**7**	3, 11
Case 2 2015	91	**97**	91, 99	2	**2**	1, 7	1	**1**	0, 6
Case 3 2012	14	**9**	5, 13	3	**2**	0, 4	140	**89**	84, 94
Case 3 2015	9	**10**	5, 17	8	**8**	4, 16	77	**82**	73, 88

Figure 9.1: Level of certainty about which treatment option is better^



^ Scores were measured on a scale from 0 to 10 with lower scores indicating greater preference for watchful waiting, higher scores indicating greater preference for adjuvant radiotherapy and a score of 5 indicating undecided
ART: Adjuvant radiotherapy

Attitudes and beliefs related to the recommendation for adjuvant radiotherapy for locally advanced disease

Overall there was less agreement with the clinical practice recommendation for adjuvant radiotherapy for locally advanced disease in 2015 than in 2012 (mean difference -0.3; 95% CI [-0.4, -0.1]; p<0.001) (Figure 2). This is a reflection of significant change across a number attitudes and beliefs. In 2015, there was significantly less agreement than 2012 that the recommendation is based on a valid interpretation of underpinning evidence (mean difference -0.4; 95% CI [-0.6, -0.1]; p=0.004 or that following the recommendation would lead to improved patient outcomes (mean difference -0.2; 95% CI [-0.4, 0.0]; p=0.019). Specifically, there was significantly less agreement in 2015 than 2012 that published literature provides evidence that immediate external irradiation after radical prostatectomy improves biochemical progression-free

survival and local control (mean difference -0.2; 95% CI [-0.4, -0.0]; p=0.012) (data not shown). Further, there was significantly less agreement in 2015 than in 2012 that the recommendation is consistent with the urologist's clinical experience with this patient group (mean difference -0.4 95% CI [-0.7, -0.2]; p<0.001) or with the opinions of respected clinical colleagues (mean difference -0.5; 95% CI [-0.8, -0.3]; p<0.001). There was significantly more agreement in 2015 than 2012 that the side effects of adjuvant radiotherapy for patients with locally advanced prostate cancer outweigh the benefits (mean difference -0.3; 95% CI [-0.5, -0.1]; p=0.007) and that the recommendation does not reflect evidence that is emerging on the topic (mean difference -0.3; 95% CI [-0.5, -0.0]; p=0.024). Significantly more urologists supported external beam radiation therapy for patients but not within four months of surgery (mean difference -0.3; 95% CI [-0.6, -0.1]; p=0.004).

Other factors related to the recommendation for adjuvant radiotherapy for locally advanced disease

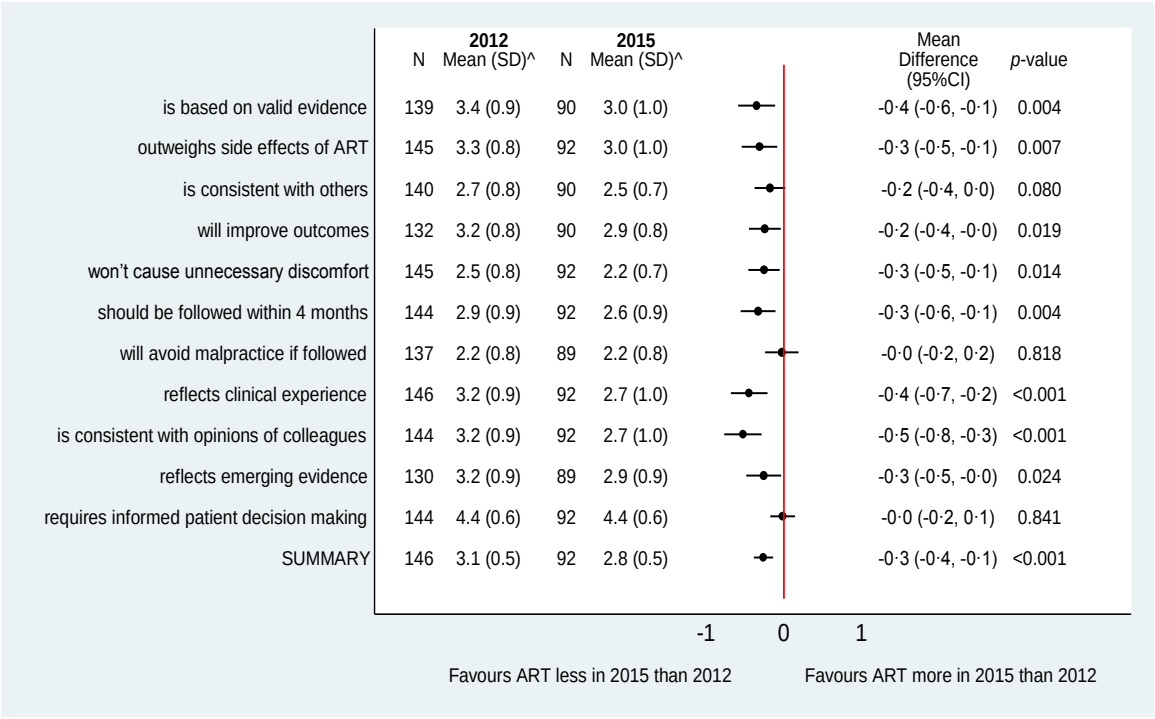
Urologists were significantly more agreeable in 2015 than 2012 to the proposition that other urologists would be critical if they routinely referred this patient group for radiotherapy (mean difference 0.3; 95% CI [0.1, 0.5]; p=0.007) (Figure 9.3). There was no significant change in attitudes across others factors

Evidence from randomised controlled trials

There were no significant changes in the levels of evidence considered necessary for urologists to be convinced of the benefit of adjuvant radiotherapy. See Table 9.3.

Figure 9.2: Comparisons between 2012 and 2015 survey responses - attitudes towards the Australia Cancer Network Guidelines recommendation that '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery*'^

**This recommendation:*



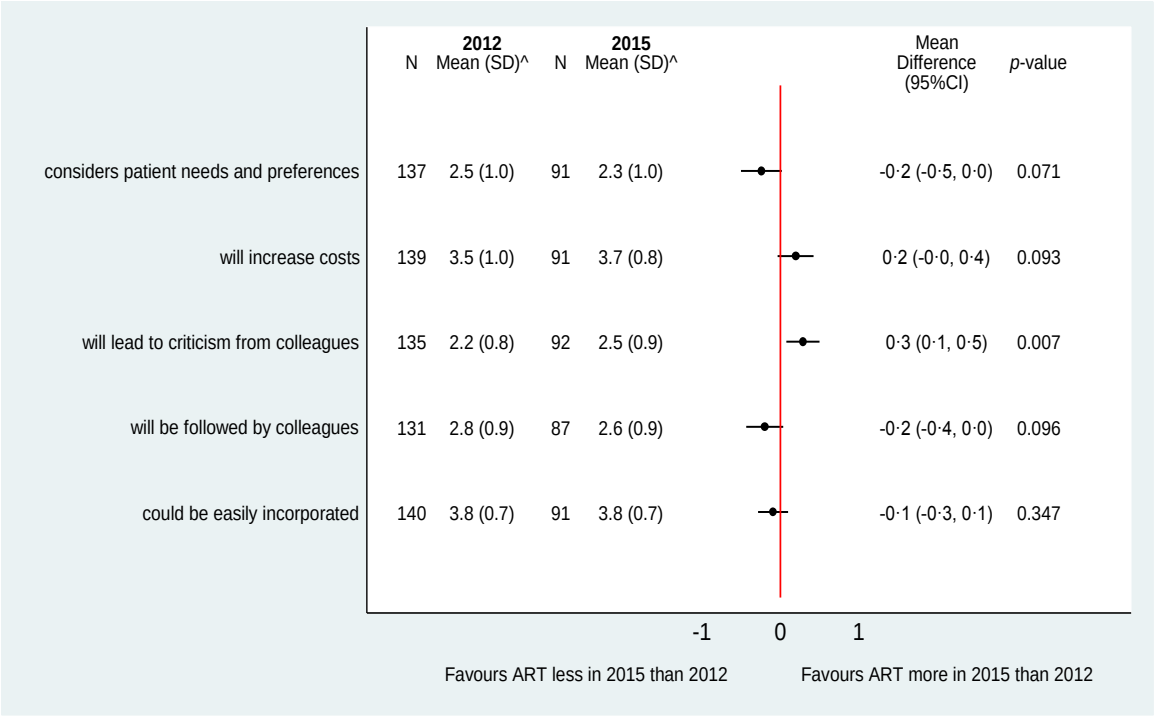
^ Scores correspond to a 5-point Likert type scale with scoring 1=Strongly disagree, 2=Disagree, 3=Neither agree nor disagree, 4=Agree, 5=Strongly agree; "Don't know" and missing responses were excluded from analyses

*Full survey questions are available from the corresponding author. Some items were reverse coded for analyses and these are reflected in question labels.

ART: Adjuvant radiotherapy

Figure 9.3: Comparisons between 2012 and 2015 survey responses - other factors relating to the recommendation '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery*'^

**This recommendation:*



^ Scores correspond to a 5-point Likert type scale with scoring 1=Strongly disagree, 2=Disagree, 3=Neither agree nor disagree, 4=Agree, 5=Strongly agree; "Don't know" and missing responses were excluded from analyses

*Full survey questions are available from the corresponding author.

ART: Adjuvant radiotherapy

Table 9.3: Comparison between 2012 and 2015 survey responses – levels of evidence to support the recommendation '*patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery*'

	2012		2015			
	N	Mean (SD)	N	Mean (SD)	Mean difference (95%CI)	*p*-value
Number of trials necessary to provide an acceptable level of evidence	139	3.2 (1.2)	84	3.1 (1.2)	-0.1 (-0.5, 0.2)	0.439
Number of years follow-up necessary	140	8.9 (2.2)	92	8.7 (2.4)	-0.2 (-0.8, 0.5)	0.613
Number of years of survival benefit	135	2.3 (2.6)	88	2.1 (2.3)	-0.2 (-0.8, 0.4)	0.560
Maximum proportion of men suffering rectal damage or faecal incontinence as a result of radiotherapy	141	14.5 (12.0)	90	13.3 (11.0)	-1.1 (-3.9, 1.6)	0.422

Post-operative treatment decisions

There was no significant difference between the two surveys in opinions about who is best placed to make post-operative treatment decisions (p=0.88; Table 9.4).

Table 9.4: Comparison between 2012 and 2015 survey responses – following radical prostatectomy who is the person best placed to decide on the most appropriate post-operative treatment option?

	Survey	
Q2.4 Who should decide future treatment	**2012 (n=149)**	**2015 (n=92)**
The urological surgeon is best placed to decide	42 (28%)	25 (27%)
The radiation oncologist is best placed to decide	1 (1%)	0 (0%)
The MDT is best placed to decide	85 (57%)	55 (60%)
The patient is best placed to decide	19 (13%)	12 (13%)
The medical oncologist is best placed to decide	2 (1%)	0 (0%)

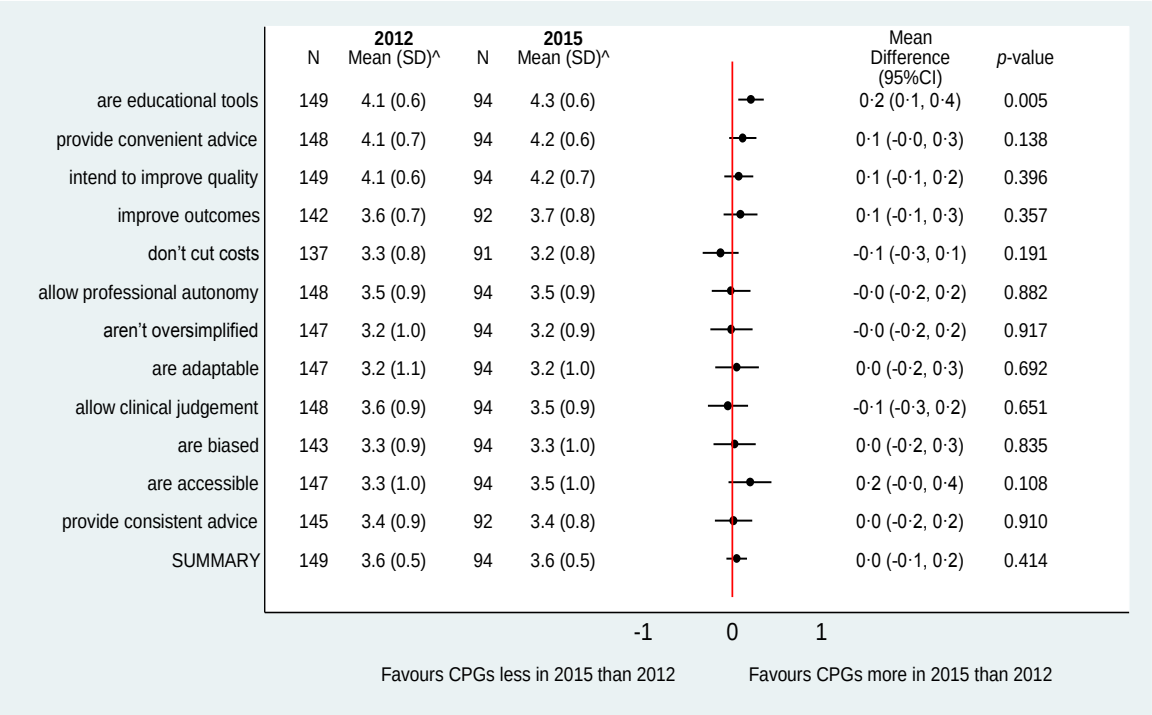
p=0.88 for test equal proportions across surveys, adjusted for sex and age at survey
n and % are for frequencies and % of individuals; missing responses were excluded from analysis

Attitudes and beliefs related to clinical practice guidelines in general

Overall, attitudes towards CPGs in general were positive and remained relatively unchanged from 2012 to 2015 (mean difference 0.0 95% CI [-0.1, 0.2]; p=0.414; Figure 9.4). The proportion of urologists reporting they use CPGs in their practice increased marginally from 78% to 85% but this change was not significant (odds ratio 1.59; 95% CI [0.75, 3.49]; p=0.187; data not shown) and there was no change in the number of different guidelines used in practice (mean difference 0.2; 95% CI [-0.7, 1.0]; p=0.710; data not shown). There was significantly more agreement in 2015 than 2012 that CPGs are good educational tools (mean difference 0.2; 95% CI [0.1, 0.4]; p=0.005).

Figure 9.4: Comparisons between 2012 and 2015 survey responses – attitudes and beliefs related to clinical practice guidelines in general^

**In general, clinical practice guidelines:*



^ Scores correspond to a 5-point Likert type scale with scoring 1=Strongly disagree, 2=Disagree, 3=Neither agree nor disagree, 4=Agree, 5=Strongly agree; "Don't know" and missing responses were excluded from analyses

*Full survey questions are available in Appendix IV. Some items were reverse coded for analyses and these are reflected in question labels.

CPG: Clinical Practice Guidelines

Barriers to implementation

Thematic analysis of open text responses indicated that barriers to the implementation of the Australian Cancer Network Guidelines recommendation for adjuvant radiotherapy for locally advanced disease consistently fell into the three main categories identified in the 2012 survey:

1. *Need for individualised care* - 40% (32/80) and 39% (18/46) of respondents in 2012 and 2015 respectively noted that post-operative radiotherapy *"needs to be individualised on a case by case basis dependent not just on pathology but age, life expectancy,*

comorbidities, continence and potency post-surgery". A number also reported that referral is dependent upon the post-operative PSA *"Given super-sensitive PSA assays I think it is reasonable to wait until a rise is confirmed before initiating adjuvant XRT".*

2. *Perceived lack of evidence / lack of confidence in trial data* – 30% (24/80) in 2012 and 28% (13/47) in 2015 reported concerns about the evidence base underlying the recommendation. *"ARO, EORTC and SWOG were flawed studies. There is a difference between early salvage versus late salvage. The question of adjuvant versus early salvage has not been addressed." "Improved biochemical recurrence but not difference in overall survival. SWOG study fundamentally flawed (poor recruitment/mid study alteration of intended analysis/one sided significance analysis) and should be discounted."*

3. *Concerns about side effects / overtreatment* – 25% (20/80) of respondents in 2012 and 35% (16/46) in 2015 noted that toxicities related to radiotherapy and potential unnecessary treatment are a barrier to the implementation of this recommendation. *"Other specialists underestimate the side effects e.g. bladder neck contracture, haemorrhagic cysts, stricture, LUTS of this modality. Causes decreased QoL, increased return to theatres, IDC usage etc. Needs to be INDIVIDUALISED!" "Whilst I refer patients for adjuvant radiotherapy selectively, it would not take much more evidence of long term negative side effects to convince me not to recommend it at all."*

Innovation, current practice and readiness for change

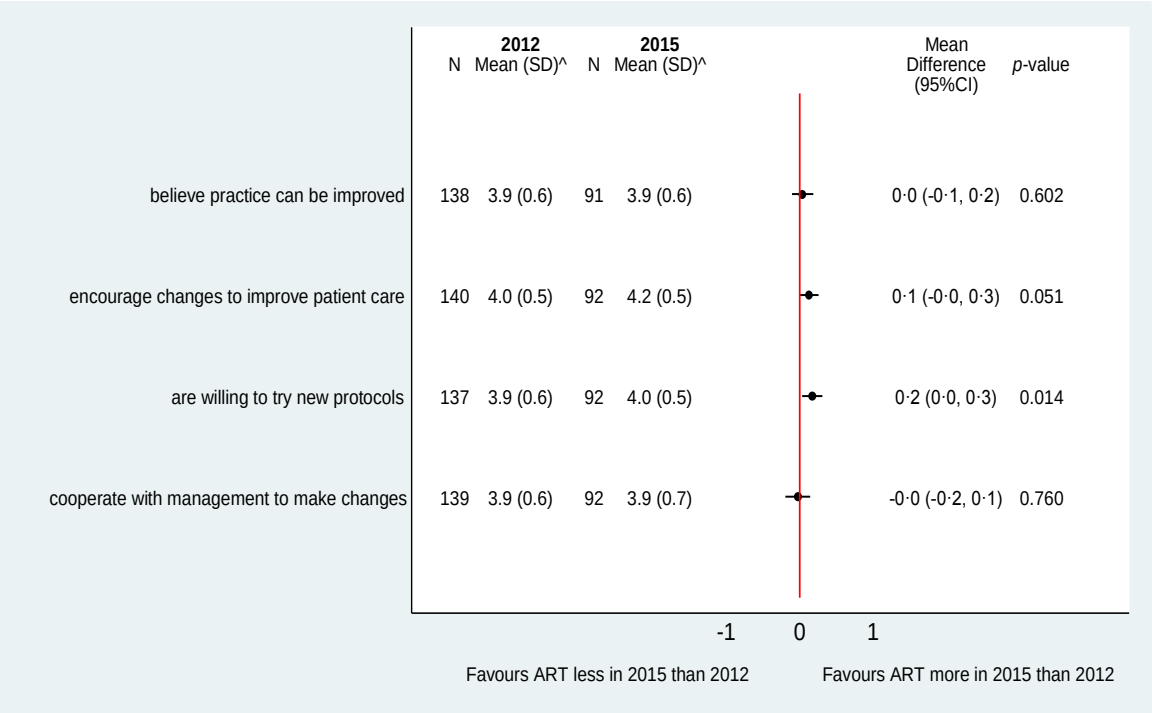
There was no significant difference between 2012 and 2015 in the proportions of urologists' willing to experiment with new procedures in their practice (13% versus 20%), who prefer to wait until others have tried new procedures (29% versus 34%) or who prefer to wait until procedures have been established for

a while (52% versus 43%) (p=0.23; data not shown). Consistent with 2012, no urologists in 2015 reported that they only try new procedures when regulations require them.

Urologists generally believed there is readiness for change in their organisation and this largely remained unchanged over time (Figure 9.5). However, urologists were significantly more agreeable in 2015 than 2012 to the proposition that urology leaders are willing to try new protocols (mean difference 0.2; 95% CI [0.0, 0.3]; p=0.014).

Figure 9.5: Comparisons between 2012 and 2015 survey responses – readiness for change^

**Urology leaders in my organisation:*



^ Scores correspond to a 5-point Likert type scale with scoring 1=Strongly disagree, 2=Disagree, 3=Neither agree nor disagree, 4=Agree, 5=Strongly agree; "Don't know" and missing responses were excluded from analyses
*Full survey questions are available in Appendix IV.
ART: Adjuvant radiotherapy

Sensitivity analyses

Sensitivity analyses adjusting for age and type of practice, both significantly correlated with treatment preference in the 2012 survey, found results to be

similar to non-adjusted analyses. Sensitivity analyses using proportional odds regression provided almost identical results in terms of statistically significant p-values.

9.5 Discussion

We conducted a follow up survey of urologists across Australia. There was no increase in awareness of the Australia Cancer Network Clinical Practice Guidelines for the Management of Men with Locally Advanced and Metastatic Prostate Cancer (8) over the three year period from 2012 to 2015. This suggests a need for improved knowledge translation that goes beyond passive dissemination of evidence through publication of guidelines.

The results highlight a persisting view that early salvage radiotherapy at the first sign of a PSA relapse is likely to have similar efficacy to adjuvant radiotherapy following radical prostatectomy, whilst avoiding radiotherapy associated toxicity in some patients who might not need further treatment. Urologists were significantly less favourable towards adjuvant radiotherapy for scenarios that would indicate its use according to clinical practice recommendations in 2015 than in 2012. The proportion indicating a preference for watchful waiting over adjuvant radiotherapy for a patient with a 10% 10-year risk of biochemical relapse increased significantly between 2012 and 2015. There remained clinical equipoise for a scenario describing a patient with a 19% 10-year risk of biochemical relapse, however, there was a significant increase in the proportion that favoured watchful waiting over adjuvant radiotherapy (less than half in 2012 and nearly three quarters in 2015). Continuing this trend, even for a given clinical scenario with an 89% 10-year risk of biochemical relapse there was a small, non-significant decrease in the proportion that considered adjuvant radiotherapy preferable in 2015. This is consistent with figures from the US National Cancer Data Base (24), which demonstrated less than one third of patients at the highest risk of recurrence

(pT3-4 disease with a positive margin and Gleason 8-10) with no comorbidities and a projected long life expectancy (<60 years old) received postoperative radiotherapy. In combination, these results suggest an increasing divergence between clinical opinion and the recommendations of published CPGs. Urologists' attitudes and beliefs and the lesser overall agreement with the clinical practice recommendation for adjuvant radiotherapy may help explain why there is reduced self-reported compliance. From 2012 to 2015 there was increased perception that the recommendation is not based on valid interpretation and does not reflect emerging evidence, perhaps due to frequently cited criticisms relating to the absence of a well-defined salvage radiotherapy arm in the randomised trials on which it is based and the lack of a consistent survival benefit at longer term follow up.(1-5) There was significantly less agreement in 2015 than 2012 that the recommendation is consistent with current clinical practice or with the opinions of colleagues, while there was more agreement with the proposition that other urologists would be critical if they routinely referred this patient group for radiotherapy. Coupled with greater agreement that side effects of adjuvant radiotherapy outweigh the benefits, and less agreement that it will lead to improved patient outcomes, these beliefs provide a powerful disincentive. Paradoxically, urologists were significantly more agreeable in 2015 than 2012 to the proposition that they support external beam radiation therapy for patients but not within four months of surgery. This aligns with the commonly held view that treatment should not be initiated until there is optimal postoperative recovery, particularly in urinary continence and potency and supports the need for individualised care that was raised in both the 2012 and 2015 surveys. The propensity to delay treatment may also be due in part to the emergence of ultra-sensitive PSA assays, which enable referral for salvage radiotherapy at the time of a confirmed PSA rise at lower levels than were previously detectable. However, the most recent US patterns of care study

(24) did not find a rise in radiotherapy between six months (their cut off point for adjuvant radiotherapy) and five years after radical prostatectomy leading the authors to conclude that a shift to salvage radiotherapy does not entirely explain the declining use of adjuvant radiotherapy.

Overall, attitudes towards CPGs in general remained positive and they were consistently viewed as good educational tools. This reinforces the need to optimise usability and adaptability of CPGs to increase impact on practice, for example, by offering alternate versions across different communication platforms including electronic versions that can be embedded within decision support systems. This can be achieved through appropriate planning to ensure guidelines are implementable.(30)

A potential limitation of this study is the lower response rate (30%) in the 2015 survey than that of the 2012 survey (45%). However, it is similar to the average response rate for other online surveys (33%) (31) and higher than other published clinician surveys.(13) Tests of no difference between the 2012 and 2015 survey samples indicated that there were no major differences in respondent demographics. It is a further potential limitation that the psychometric properties of the survey have not been assessed.

While this study necessarily presents self-reported practice, the CLICC implementation trial will provide independent data from medical record review on actual referral patterns for nearly 1000 men with adverse pathological features who underwent radical prostatectomy between 2011 and 2015 in participating NSW hospitals. Full details of CLICC elements and data collection methods are detailed in the study protocol.(12)

In conclusion, this survey highlights persisting clinical equipoise among Australian urologists in relation to adjuvant radiotherapy for men with adverse pathologic features following radical prostatectomy. Further it

suggests declining use of adjuvant radiotherapy in practice contrary to Guideline recommended care.

9.6 Authors' contributions

BB, in collaboration with all other authors, conceptualised the survey and interpreted the results presented in this paper. SE and BB conducted statistical analyses. All authors provided input into various aspects of the study, provided ongoing critique, and approved the final version of the manuscript.

9.7 Ethics Approval

Ethical approval for this study was obtained from the University of Sydney Human Research Ethics Committee, September 2012 (Protocol No: 15222).

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Chapter 10: Discussion and conclusion

This thesis presents a series of iterative studies to develop and test a clinical network embedded intervention to increase referral of men with adverse pathological features post-prostatectomy to radiation oncology for discussion of adjuvant radiotherapy in line with clinical practice guideline recommended care. It is the first rigorous evaluation involving a clinical network in the implementation of an intervention through a phased randomised cluster trial.

The systematic review presented in Chapter Two provided evidence that the ACI Urology Network was an appropriate vehicle through which to develop and embed the CLICC implementation trial within NSW hospitals linked to the network. While noting limitations with the quality of included quantitative studies, which predominantly used observational designs, the review found that clinical networks were able to achieve improvements based on several endpoints relating to both service delivery (such as adherence to clinical practice guidelines and protocols, development of clear patient pathways, and use of clinical tools) and patient outcomes (such as reduced mortality or improved time to treatment) across a range of clinical specialties. Of relevance to this thesis, the review found some evidence that clinical networks may be effective in engaging clinicians in developing and implementing clinical practice guidelines.

Through a survey of Australian-based urologist members of the Urological Society of Australia and New Zealand (USANZ) (1) (Chapter Three) a number of barriers to the implementation of the Australian Cancer Network Guidelines recommendation for adjuvant radiotherapy for locally advanced disease were identified. The most commonly cited barrier was the need for individualised care, taking account of the patient's post-operative recovery and treatment preference. There was also a lack of confidence in the randomised controlled

trial data that were the basis for the recommendation. This particularly related to the absence of a salvage radiotherapy arm to provide direct comparison of the efficacy of adjuvant versus early salvage radiotherapy. Survey participants also expressed concerns about the potential for overtreatment in patients whose cancer may never recur, as well as concerns about radiotherapy associated toxicity and side effects. Similar concerns were identified through the needs and barriers analysis to inform the development of the CLICC implementation trial (Chapter Four). Barriers were considered at three levels: (i) clinician; (ii) patient; and (iii) hospital systems and processes. In addition to some lack of knowledge, clinician level barriers included concerns about the quality of evidence, the potential for overtreatment, and radiotherapy associated toxicity and side effects. In addition, the ongoing RAVES clinical trial (2) comparing the efficacy of adjuvant radiotherapy with early salvage radiotherapy at the time of a confirmed PSA recurrence, being conducted locally in Australia, raised doubt about routine referral for radiotherapy. Alongside clinician level barriers, variation in engagement with, and selective presentation of cases to, the MDT were identified as cultural and systems and processes barriers within CLICC trial sites. Patient level barriers (namely treatment preference) were excluded because research governance and ethical approvals did not permit direct patient interaction. Using the PRECEDE-PROCEED model of behaviour change (3-5) as a foundation for the CLICC conceptual program logic framework, barriers were mapped to physician- and context-focused CLICC intervention elements. These included: *predisposing factors* - provider education and printed materials; *reinforcing factors* - opinions leaders and audit and feedback; and *enabling factors* – automated systems (flagging of eligible cases by the pathologist to the MDT coordinator for addition to the MDT agenda for discussion at a MDT meeting).

The CLICC intervention was rolled out across nine participating sites using a stepped wedge cluster randomised design as per the trial protocol (6)

(Chapter Five). At the end of the active intervention phase the CLICC process evaluation (Chapter Six) was conducted to aid interpretation of outcomes and identify mechanisms of provider and organisational change, which were assessed using three domains: (i) *implementation:* whether the intervention was implemented as intended; (ii) *participation* and *response:* why the intervention did or did not result in evidence-based care; and (iii) *context:* why was or was not the intervention implemented or sustained across implementation sites. Results of the CLICC process evaluation demonstrated that CLICC elements could be implemented with fidelity. Within the CLICC conceptual program logic model, the hypothesised *enabling* factor, namely flagging of eligible cases by the pathologist to the MDT coordinator for addition to the MDT agenda for discussion at a MDT meeting, was considered by participants to be the most essential and sustainable element in achieving desired practice change. The automatic nature of the MDT flagging process, requiring no action on the part of the urologist, was noted as a key facilitator in the uptake of the process. Several contextual factors, most prominently insufficient resourcing to support flagging of patients through public pathology services, adversely affected implementation of the MDT flagging process with the result that private patients were significantly more likely to be flagged by pathology for discussion than public patients.

It is of note, that while participants integrated and adopted the MDT flagging process into routine practice, which resulted in a significant increase in the secondary outcome of discussion of the patient at a MDT meeting within 4 months after prostatectomy, they expressed uncertainty as to whether increased discussion would translate into an increase in the primary outcome of referral to radiotherapy or RAVES within 4 months after prostatectomy. Analyses of patient level data collected through medical record review, presented in Chapter Seven, indicate that this perception was correct and, after adjustment for potential confounders, referral was not significantly

different between the intervention and control groups. Thirty per cent of patients in the control group were referred to radiotherapy or RAVES within 4 months after prostatectomy compared with 32% in the intervention group. For intervention patients who were discussed at a MDT meeting, the MDT recommendation was referral to radiotherapy or RAVES for 58% but this did not translate to an increase in the primary outcome because less than half of these patients were actually referred to radiation oncology by the consulting urologist within 4 months after surgery. One possible solution to address this lack of referral could be the implementation of a direct care pathway to radiotherapy for those with a MDT recommendation for referral, for example, through a letter of MDT recommendation sent to the patients' general practitioner or directly to the radiation oncology unit for follow-up.

Where documented, the most commonly cited reason for non-referral of the subset of patients with a MDT recommendation for referral was a low or undetectable PSA (<0.1ng/ml). This is fundamentally the group of patients that should be referred to radiation oncology for discussion of adjuvant radiotherapy, in line with the evidence-based clinical practice recommendation, and lack of referral can be considered indicative of a continued preference for early salvage radiotherapy at the time of a confirmed PSA rise. This is consistent with the results of the CLICC process evaluation (Chapter Six). It is also consistent with the results of CLICC participant surveys, conducted to assess change in knowledge and attitudinal outcomes (Chapter 8), which found no significant difference in treatment preferences, knowledge, attitudes or beliefs between baseline and post-intervention surveys. In combination, these results suggest that the *predisposing* CLICC elements (provider education and printed materials) were not effective in addressing clinician level barriers associated with knowledge, attitudes, perceptions and norms.

A common denominator across Chapters Six and Seven reporting knowledge and attitudinal outcomes for CLICC participants and Chapters Three and Nine reporting the same outcomes for the wider Australian urological community was the continued influence of the RAVES trial on the persisting belief that there is insufficient evidence to support adherence to the guideline recommendation. Lack of definitive results from the RAVES trial was repeatedly used as justification for non-referral to radiation oncology for discussion of adjuvant radiotherapy in surveys and interviews. Of note, however, as reported in Chapter Seven, there was no significant change in referral to the RAVES trial, which closed to accrual during the course of the CLICC study due to a combination of a low event rate and poor recruitment. The low rate of referral to RAVES suggests that the trial was used by some as a way to opt out rather than a genuine alternative referral option that would generate new evidence.

It was not possible to make formal statistical comparisons of knowledge and attitudinal changes between CLICC participant baseline and post-intervention surveys and changes between the 2012 and 2015 USANZ surveys. This is because, although CLICC participants were excluded from the 2015 USANZ survey, some may have completed the 2012 USANZ, which was conducted prior to recruitment to the CLICC implementation trial. To comply with ethical approvals, both USANZ surveys were anonymous unless respondents voluntarily provided identifying information. Without linking identifiers it was not possible to retrospectively exclude CLICC participants from the 2012 USANZ sample. Analyses including individuals who participated in both CLICC and USANZ surveys would result in standard errors and p-values that are too low, potentially producing falsely significant results. The results of the follow-up survey of urologist members of USANZ (Chapter Nine) do, however, shed light on external factors and broader attitudinal changes within the wider

urological community that may have lessened the effects of the CLICC intervention in a more stable environment. While there was no significant change in agreement with the clinical practice recommendation for adjuvant radiotherapy for locally advanced disease between baseline and post-intervention among CLICC participants, there was significantly less agreement with the recommendation in the wider urological community in 2015 than in 2012. There was a small but not significant increase in the proportion of CLICC participants who indicated a preference for adjuvant radiotherapy for a hypothetical clinical case between baseline and post-intervention surveys. For the same hypothetical clinical case there was a significant decrease in the proportion that indicated a preference for adjuvant radiotherapy between the 2012 and 2015 USANZ surveys. Even after adjusting for the different time periods between the 2012 and 2015 USANZ surveys (on average 30 months) and baseline and post-intervention CLICC participant surveys (on average 10 months) there is still a difference in point estimates (USANZ respondents were on average -0.6 points *less* favourable towards adjuvant radiotherapy over 10 months; CLICC respondents were on average 0.2 points *more* favourable towards adjuvants radiotherapy over 10 months). There was significantly less agreement that the recommendation is consistent with the opinions of respected clinical colleagues between both the CLICC baseline and post-intervention surveys and the USANZ 2012 and 2015 surveys. This implies that external peer influence served to reinforce the normative behaviour of watchful waiting over the evidence-based clinical practice recommendation for immediate referral to radiotherapy for discussion of adjuvant radiotherapy and this was not sufficiently addressed by the CLICC opinion leader element. This is perhaps not surprising given that only three of the nine Clinical Leaders perceived their role as one of an opinion leader to actively influence and promote participating urologist behaviour change. Further, given the lack of heterogeneity between the nine participating CLICC trial sites and generally

low referral patterns within the cohort, it is also possible that the provision of audit feedback data may have counter intuitively reinforced the status quo and provided justification to maintain current referral practices that were perceived to be in alignment with those of colleagues both within and across sites.

There was some perception amongst CLICC participants, in both the CLICC process evaluation and participant surveys, that referral to radiation oncology for discussion of adjuvant radiotherapy would result in commencement of radiotherapy in the majority of instances. However, data from medical record review show that overall 9% of patients commenced radiotherapy within this six months of surgery. This figure is identical to recently published data from the Victorian Prostate Cancer Registry.(7) Within the subset of patients who were referred to a radiation oncologist only a little over half commenced radiotherapy within 6 months of prostatectomy despite more than 90% attending an initial consultation. This demonstrates that radiation oncologists do not follow the clinical practice recommendation for adjuvant radiotherapy for locally advanced prostate cancer uniformly for all patients. This lends weight to the view expressed through the CLICC process evaluation and participant and USANZ surveys that the clinical practice recommendation is not nuanced enough and does not take account of other factors such as the patient's postoperative recovery, continence, potency and treatment preference. These factors aside, patients who are referred to a radiation oncologist to discuss the risks and benefits of adjuvant radiotherapy are arguably better able to make a fully-informed decision about what they consider to be the most appropriate treatment for them.

The results of the studies included in this thesis indicate that, while implemented with fidelity and adopted and integrated into routine practice, the CLICC elements did not result in provider behaviour and knowledge and

attitudinal changes, as hypothesised through the CLICC conceptual program logic framework, across the nine trial sites as a whole. However, the effect of the intervention on referral was significantly modified by site with evidence that the intervention worked better in some sites than others. Specifically, the intervention appeared to work best in four of the nine sites (Sites 1, 4, 7 and 8), each with similar increases in referral rates. While there was a significant, more than threefold, increase in the secondary outcome of discussion of patients at a MDT meeting within 4 months of prostatectomy this did not translate to an increase in the primary outcome of referral to radiotherapy or RAVES within 4 months after prostatectomy. The CLICC trial did not have sufficient power to detect site level intervention effects due to small sample sizes associated with low caseload at some sites, however, the four sites that had the highest proportional increases in referral to radiotherapy or RAVES within 4 months after prostatectomy (Sites 1, 4, 7 and 8) were amongst the 5 sites with the highest proportional increases in patients discussed at a MDT meeting. This is consistent with the hypothesis that introducing new systems or processes, tailored to identified barriers, can enable desired behaviour change if they are integrated and adopted into routine clinical practice as designed. Further research is necessary to explore the reasons for heterogeneity of CLICC intervention effectiveness between sites, and the determinants of effectiveness, to contribute to wider knowledge about how to make this type of intervention transferable across settings.(8, 9) A strength of the studies within this thesis was the use of mixed methods to assess knowledge, attitudinal and process outcomes alongside clinician behavioural outcomes from independent medical record review, which will enable further exploration of whether there is a causative relationship between them.

It must be acknowledged that there are more than 60 theories, models and frameworks relevant to the dissemination and implementation of research into practice (10, 11). These incorporate a variety of constructs from social

psychology, organisational behaviour theories and socio-technical systems theory (12), and basing the CLICC conceptual program logic framework any one of these may have yielded different results. However, there is a recognised need to build upon and advance established theories and frameworks through empirical testing to increase their validity and utility for future implementation efforts.(9) The eight phases of the PRECEDE-PROCEED model of behaviour change guided each step in the development of the CLICC implementation trial, from social assessment of the need to improve health related quality of life for men with locally advanced prostate cancer, through tailoring of the intervention, and beyond implementation to provide a structured framework for the CLICC process evaluation to assess the extent to which elements were able to overcome barriers as hypothesised.(13) While the CLICC intervention was not as successful as hypothesised, this is in line with results of the 2015 update of the Cochrane systematic review of the effectiveness of tailored interventions to overcome determinants of practice (14), which concluded that while tailored interventions can be effective, their effect is variable and tends to be small to moderate. The review challenged the cost-effectiveness of tailored interventions compared with other interventions given their variable effect but through the CLICC process evaluation it emerged that the most tailored aspect of CLICC, namely MDT flagging, was the most effective element. This would suggest that a non-tailored, single or multi-faceted, intervention incorporating more generic elements such as provider education, clinical champions, or audit and feedback would have been less effective.

A limitation of the CLICC implementation trial was the lack of community or consumer engagement due to ethical restrictions. There is potential for future research to examine whether a patient-oriented intervention can effect change on clinical practice. A recent editorial (15) proposed that poor uptake of adjuvant radiotherapy is due to a “failure of marketing-based medicine”.

The introduction of patient-centred tools such as decision aids or the targeted dissemination of small media such as a consumer version of the clinical practice guideline offers the opportunity to convey evidence directly to patients, at the appropriate point in the care pathway, to determine whether they might make a different assessment of the best-available evidence in terms of potential risks and benefits and arrive at a different treatment decision than one made on their behalf by their care provider.

More broadly, the results of the CLICC implementation trial highlight several general issues in relation to clinical practice guideline implementation:

(i) Guidelines need to be *implementable* and this starts during the guideline development process.(16, 17) Ensuring that target end users are represented on guideline review committees or working parties will help overcome issues relating to the perceived lack of applicability or veracity that were evident in the CLICC implementation trial. Continued disagreement with the recommendation for adjuvant radiotherapy was the most persistent clinician level barrier to achieving desired practice change and this may have been mitigated by greater representation of the target clinical group to inform more acceptable or persuasive communication of the recommendation. Further, involving end users early in the guideline development process can help to achieve engagement that can be leveraged to champion subsequent implementation of clinical practice recommendations and reinforce desired changes. Gaps in knowledge can be overcome by producing multiple abbreviated versions of guidelines for different end users. For clinicians this could include, shortened versions that focus on treatment algorithms (nomograms in the current context) and clinical pathways to add the degree of nuance considered lacking

from the guideline recommendation for adjuvant radiotherapy and enable better identification of patients that will benefit. As noted above, patients also need to be aware of recommended care through consumer versions of guidelines so that they are better able to make fully-informed decisions and request information about available treatment options if this is not offered.

(ii) Implementation of clinical practice guideline recommendations needs to be *timely*. By its very nature an implementation trial is a long protracted endeavour. Including the development phase, ethical and governance approval phase for nine separate trial sites, the active intervention phase, and patient follow-up, the CLICC implementation trial took nearly five years to complete. During this period, as can be seen from the 2012 and 2015 USANZ surveys, the external environment was changing, and forces outside the CLICC implementation trial were creating momentum away from the direction of desired behaviour change even though there was no new published evidence to precipitate this change in attitude. The CLICC implementation trial was designed to test the effectiveness of different implementation strategies through a randomised controlled trial design but other clinical practice guidelines can be implemented through rapid cycle quality improvement initiatives taking on board the lessons learned from CLICC.

(iii) Clinicians are not necessarily able to accurately assess their own practice without access to data. For example, it emerged through the CLICC process evaluation that many participants perceived all high-risk cases were already being discussed at the MDT but in actuality less that 20% of patients were discussed pre-intervention. As one Clinical Leader noted, *"the most important thing is the measurement against desirable patterns of care – you can't manage*

what you can't measure so the ability to provide us with data which drives patterns of care positively is the main contribution CLICC has made". There is a need for ongoing provision of data to ensure clinical practice is consistent with current evidence-based best practice. While acknowledging that the medical record review component of the CLICC implementation trial was time and labour intensive there is scope to provide ongoing feedback data through centralised cancer (or other specialty) registries to enable clinicians to better monitor their own practice.

In conclusion, this thesis found some evidence that the CLICC intervention resulted in desired practice change. Although there was no statistically significant difference in the primary outcome of referral to radiotherapy or RAVES within 4 months after prostatectomy, self-reported treatment preferences for, and attitudes towards, adjuvant radiotherapy remained stable amongst CLICC participants despite a shift in momentum away from adjuvant radiotherapy in the wider urological community (albeit without any evidence to precipitate this change in attitude). The introduction of a new process for flagging patients eligible patients by the pathologist to the MDT coordinator for addition to the MDT agenda for discussion at the MDT meeting achieved a significant increase in the secondary outcome of discussion of patients at a MDT meeting within 4 months of surgery. This suggests that implementation strategies that *enable* clinician behaviour change are more effective than those designed to *predispose* or *reinforce* desired behaviours.

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Clinician-Led Improvement in Cancer Care (CLICC): Complementing Evidence-Based Medicine with Evidence-Based Implementation

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A thesis submitted in fulfilment of the requirements for the degree of
Doctor of Philosophy in the School of Public Health,
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VOLUME II

Appendices

2016

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Appendix I

Detailed description of systematic review methodology

Supplementary File 1 – Detailed description of systematic review methodology

Overall Approach

This systematic review was conducted in accordance with the PRISMA approach to ensure the transparent and complete reporting of our sensitive searching, systematic screening and independent quality assessment [1]. The concepts and overarching methods for systematic reviews [2] have been adapted to be applicable for a mixed methods systematic review [3, 4].

Eligibility – inclusion and exclusion criteria

Articles were eligible for inclusion in this review if:

i) The primary focus of the paper was on clinical networks in any healthcare setting (e.g. acute, primary, community, vertical integration)

ii) The networks corresponded with the category of network that would be included - that is a managed or non-managed clinical network

iii) The paper reported an outcome related to improvement of quality of care or patient outcomes (based on objective measures)

Excluded were:

i) Abstracts and titles with the term 'clinical network' that were not referring to actual clinical networks (e.g. clinical network guidelines, simulation studies for proposed networks, protocol papers detailing study plans of networks, information technology or infrastructure networks)

ii) Research networks

iii) Clinical trial networks

iv) Clinical guideline networks

v) Integrated service delivery networks (sometimes called regional networks or networked hospitals, Health Management Organisations and managed care organisations in the United States)

vi) Articles that used clinical networks as vehicles for samples for studies

vii) Articles that were not published in peer review journals (e.g. conference proceedings)

Identification and selection of publications

Initial search (1996-2010)

Authors BB and MH conducted the initial literature search with the assistance of a librarian/information scientist. Figure 1 (in the main text of the article) outlines the search process. We searched Medline, Embase and CINAHL to locate all research publications for the period 1996 to 2010 that focused on clinical networks. None of these databases have subject terms (i.e. MESH terms for Medline) that cover the concept of clinical networks so the search terms were developed based on 58 papers that were obtained through an initial search using the term 'clinical networks' and iterative searching. Box 1 contains the search terms used, restricted to the English language, with a year of publication between 1996 and 2010.

After duplicates were removed (N=57), researchers screened abstract titles (N=843) for inclusion. Abstracts with titles that had: a) the terms 'clinical network/s'; clinical specialty network (e.g. cancer network); or the word 'network'; and b) were referring to a clinical network, were included (N=151). In the case where a judgement could not be made on the basis of the abstract then the authors reviewed the whole publication to make a judgement on whether it should be included in the review.

Box 1 – Search terms used to identify articles for this systematic review

EMBASE

Query 1 *National Health Service/ or *public relations/ or *Integrated Health Care System/ or *managed care/ or exp *cooperation/ or exp *patient care/ or exp *health care quality/ or exp *disease management/ or *health care management/ or exp Health Care System/

Query 2 ((regional adj2 **network***) or (national adj2 **network***) or clinical **network***).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm

Query 3 Combine queries 1 and 2

Query 4 Limit 3 to (english language and yr="1996 - 2008")

MEDLINE

Query 1 *state medicine/ or *interinstitutional relations/ or *delivery of health care integrated/ or *managed care programs/ or *cooperative behavior/ or exp patient care management/ or exp "Quality of Health Care"/

Query 2 ((regional adj2 network*) or (national adj2 network*) or clinical network*).mp.

Query 3 Combine queries 1 and 2

Query 4 Limit 3 to (english language and yr="1996 - 2008")

CINAHL

Query 1 mm National Health Programs or mm Interinstitutional Relations or mm Health Care Delivery, Integrated or mm Managed Care Programs or mm Cooperative Behavior or mm Patient Care+ or mm Quality of Health Care+ or mm Disease Management or mm Health Care Delivery+

Query 2 ((regional adj2 network*) or (national adj2 network*) or clinical network*).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, nm

Query 3 Limit 2 to (english language and yr="1996 - 2008")

Two authors (MH, BB) independently reviewed the identified abstracts for eligibility and cross-checked their classifications. There was 96% agreement between the authors' initial

codes (145/151) and after discussion there was 100% agreement on whether the abstract should be included (n=89).

After excluding abstracts for which the full text was unavailable (n=28) and including publications identified through screening of reference lists of included articles (n=3), two authors (MH, BB) independently reviewed these full text articles (n=64) and cross-checked their classifications to confirm whether the publication should be included in the analysis based on the criterion of whether the study was focused on a mandatory or non-mandatory clinical network. There was 94% agreement between reviewers (60/64) and, following discussion, 23 articles were excluded. The remaining 41 eligible papers were coded into empirical (n=20) and commentary contributions (n=21). Empirical studies were defined as original research and presented new data - either qualitative or quantitative. The commentary pieces were excluded. As a further quality assurance measure, a third author (CP) assessed the eligibility of the 20 empirical studies against the above criteria. This resulted in three further exclusions with reasons.

The remaining 17 empirical studies were included regardless of country, number of networks studied, clinical focus of the networks, study design or outcomes assessed in relation to the networks.

Updated search (2011-2014)

Following the steps outlined above, two authors (BB, CP) performed an updated literature search for the period covering 1 January 2011 to 30 September 2014 (PubMed and CINAHL were searched to update the search from 1 January 2013 to 30 September 2014). A separate search using the search term “clinical network” was also performed given the more frequent

use of this term in recent years. The search procedure is outlined in Figure 2. Following the same procedure as the initial search, 2,035 titles were screened, duplicates removed and assessed for eligibility, with 95 abstracts remaining. Based on the inclusion and exclusion criteria above and excluding commentary articles, we excluded 44 abstracts, leaving 51 eligible abstracts. Both authors independently reviewed 50 full-text publications (one full-text was unavailable) to determine whether they should be included in the review. Forty-three articles were excluded, as they did not meet the eligibility criteria. Queries were resolved by consultation with a third author (MH). After discussion, there was 100% agreement between the three authors on which articles met the eligibility criteria for inclusion. Reference lists of the included papers and relevant commentary papers were reviewed for inclusion of additional eligible articles, but none meeting our criteria were found. The updated search yielded an additional five papers to be included in this review.

With 17 articles from the initial search and 5 from the updated search, a total of 13 qualitative and 9 quantitative studies were included over our search period from 1996 to 30 September 2014.

Quality and assessment of risk bias

The risk of bias and quality assessment of the quantitative studies and qualitative studies were assessed separately [2, 5].

Quantitative Studies

The quantitative study designs were assessed on the basis of whether they would meet the study design acceptable for a Cochrane Effective Practice and Organisation of Care Group (EPOC) review with those being: a) patient or cluster randomised control trials; b) non-

randomised cluster control trials; c) controlled before and after studies; and d) interrupted time series [6, 7]. Given the lack of high quality study designs found in the included articles, study designs were coded into the followed grades of evidence used previously for a communities of practice review [8]:

1. Experimental
2. Quasi-experimental studies (controlled trials, time series, controlled before and after designs)
3. Observational designs (before and after studies, cross-sectional studies).

The assessment of the quality of the methods and reporting drew on elements of EPOC and the Agency for Healthcare Research and Quality [6, 9]:

- Was the study free from selective outcome reporting? (yes/no/unclear)
- For comparative studies, was the control/comparison group used equivalent to the intervention group? (yes/no) (where appropriate)
- For non-comparative studies, were the cases representative (i.e. all eligible cases over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital, clinic or group, or an appropriate sample of those cases)? [10] (yes/no) (where appropriate)
- Was there a clear description of the exposure or intervention? (yes/no)
- Was the study adequately protected against contamination? (yes/no/unclear) (where appropriate)
- Statistical analysis – were the methods appropriate and was reporting adequate? (yes/no)
- Was there a declaration of funding or sponsorship? (yes/no)
- Was the study free from other risks of bias? (yes/no)

The studies were grouped into three categories on the basis of quality of methods and reporting [11]:

- High quality – design and conduct of study address risk of bias, appropriate measurement of outcomes, appropriate statistical and analytical methods, low drop-out rates, adequate reporting;
- Moderate quality – do not meet all criteria for a rating of good quality but no flaw is likely to cause major bias, some missing information;
- Low quality – significant biases including inappropriate design, conduct, analysis or reporting, large amounts of missing information, discrepancies in reporting.

Two authors (BB, CP) independently assessed each quantitative study against the criteria above. There was 50% agreement (5/10 articles) and through discussion there was 90% agreement (9/10 articles) with final ratings given to 8 articles (see Table 1). A third author (MH) resolved one instance where there was disagreement and two instances where additional input was sought. The authors agreed that observational articles would not be given a "high" quality rating even when bias was minimised in the study due to the inherent flaws of an observational study design. At this stage, one article in question was deemed to be ineligible and excluded from this review. There was 100% agreement on the quality assessment rating of the nine included articles between the three authors.

Qualitative Studies

There is lack of consensus about how to assess risk of bias for qualitative studies [12]. For this review we considered that assessing the validity of the methods and quality of the reporting was the most appropriate approach to take [13, 14]. To do this, we used nine criteria

to assess the quality of qualitative studies recently developed by Harden and colleagues [4] and two criteria on the extent to which the 'participant voice' [15] was elucidated using a definition suggested by Mays and Pope [13] (see Box 2).

Box 2 - Criteria used to assess the quality of the qualitative studies.

Quality of reporting [4]

1. Were the aims and objectives clearly reported?
2. Was there an adequate description of the context in which the research was carried out?
3. Was there an adequate description of the network and the methods by which the sample was identified and recruited?
4. Was there an adequate description of the methods used to collect data?
5. Was there an adequate description of the methods used to analyse data?

Use of strategies to increase reliability and validity [4]

6. Were there attempts to establish the reliability of the data collection tools (for example, by use of interview topic guides)?
7. Were there attempts to establish the validity of the data collection tools (for example, with pilot interviews)?
8. Were there attempts to establish the reliability of the data analysis methods (for example, by use of independent coders)?
9. Were there attempts to establish the validity of data analysis methods (for example, by searching for negative cases)?

Quality of the application of the methods [13]

10. The extent to which qualitative studies are grounded in and reflect study participants' perspective and experiences (as evidenced by the use of supporting quotes)
11. Whether the studies produce also rich or 'thick' descriptions of the investigation and explanatory insights rather than 'thin' descriptions or flat summaries of the findings.

We grouped these studies into three categories on the basis of quality in accordance with the approach used by Harden and colleagues [4] and the Cochrane qualitative research methods group [16]. Arbitrary cut offs were selected as:

- High quality – those meeting 8 or more criteria
- Medium quality – those meeting between 5 and 7 criteria
- Low quality – those meeting fewer than five criteria

Data extraction and synthesis

Given the lack of high quality evidence from randomised controlled trial data, we adopted a pragmatic approach of examining all available evidence from primary observational studies, and assessing study quality within this lower level of the evidence hierarchy. Studies were first categorised as either qualitative or quantitative. Quantitative papers were then further categorised according to the focus of the study linked to the review objectives into two categories:

1. Improving quality of care: These papers examined whether clinical networks were successful in improving the delivery of health care.
2. Improving patient outcomes: These papers examined whether reorganisation into clinical networks or interventions implemented by networks were effective in improving patient outcomes.

Qualitative methods were used to thematically analyse and synthesise textual data extracted from the qualitative studies [17]. Two authors (BB and CP) independently identified the focus of the qualitative papers and categorised them into four themes. As several papers could have been classified under more than one theme, articles were categorised on the basis of the most prominent theme. The four themes were:

1. Features and outcomes of effective networks: These papers examined what features of a network enabled it to be successful, and what successful networks have achieved.
2. Network implementation: These articles described the process of implementing a clinical network and the key lessons learned from the implementation process.
3. Organisational structure: These articles looked at how networks were structured and how its structure impacted the way the network worked (namely, the network's ability to achieve its desired outcomes).
4. Organisational learning and knowledge: These articles examined the organisational learning and education role of clinical networks.

Due to the heterogeneity of the included studies, data were extracted directly into a data extraction table. Information was extracted on: i) country; ii) description of network studied; iii) description of the sample and size in terms of networks and participants; iv) study aim; v) intervention (quantitative studies); vi) design; vii) data collection method; viii) outcomes assessed; ix) results. One author (BB) extracted all the information from the initial search on the basis of what was available in the publications and a second (CP) checked all the extracted information. There was majority agreement between the reviewers on the data extracted and queries were resolved through consensus. For the updated search, two authors (BB, CP) extracted information from the articles and agreed on the data extracted through consensus. The main findings of the quantitative and qualitative studies were first examined separately, and then integrated to identify recurrent themes and findings to enable conclusions to be drawn.

Due to the heterogeneity of the included quantitative studies and their outcomes, results were reported narratively. Key outcomes demonstrating the effectiveness of clinical networks were

reported. Qualitative methods were used to synthesise textual data extracted from the qualitative studies. Results from the quantitative narrative analysis were then integrated with the qualitative synthesis in the discussion to identify recurrent themes and findings to enable conclusions to be drawn. Details on the findings of each of the included articles can be found in Additional File 2.

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Appendix II

Detailed findings of articles included in the systematic review

Additional File 2 – Detailed findings of articles included in the systematic review

Quantitative Articles

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
▪ **Improving Quality of Care**					
Gale et al 2012	UK	Managed clinical network for neonatal services	*Before reorganisation:* from report of the Confidential Enquiry into Stillbirths and Death in Infancy (CESDI) Project 27/28, data from 1 Sep 1998 to 30 Aug 2000. Data was from England, Wales and Northern Ireland and was not disaggregated. *After reorganisation:* from National Neonatal Research Database held by the Neonatal Data Analysis Unit, data from 1 Jan 2009 to 31 Dec 2010.	**Aim** To assess the impact of reorganisation of neonatal specialist care services in England following the formation of managed clinical networks, specifically the impact on access to specialist care for pre-term births **Intervention** National reorganisation of neonatal services in England into managed clinical neonatal networks **Design** Population-wide observational comparison of outcomes before and after the establishment of managed clinical neonatal networks. **Method** • Analysis of data on live births born at 27-28 weeks' gestation held by the Neonatal Data Analysis Unit and CESDI Project 27/28 **Indicators** • Proportion of babies born at hospitals providing the highest volume of neonatal	▪ The proportion of babies delivered at 27-28 weeks' gestation in hospitals with the highest specialist care activity increased significantly from 18% (England, Wales and Northern Ireland) to 49% (England only) (risk difference 31%, 95% CI: 28 to 33; odds ratio 4.30, 3.83 to 4.82; P<0.001), indicating success of the networks in increasing high risk transfers ▪ The proportion of babies undergoing acute and late postnatal transfer in England increased significantly from 7% to 12% and 18% to 22%, respectively ($\chi 2$ P<0.001) ▪ No difference in proportion of transferred twins/triplets (33% vs 29%, odds ratio 0.86, 95% CI: 0.50 to 1.46; P=0.57) ▪ Survival in England increased from 88% to 94% (risk difference 5.6% (95% CI: 4.2 to 7.0); odds ratio 2.00 (95% CI: 1.67 to 2.40); P<0.001) ▪ However given over half of the study population were not delivered at a centre providing the highest volume of neonatal intensive care activity, poor adherence to the guidelines of the National Audit Office and National Institute for Health and Clinical Excellence is ongoing, underlining the limitations of a major reorganisation of one aspect of service provision rather than the entire pathway of care.

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			This data was from England only.	specialist care • Proportion of acute transfer and/or late transfer • Proportion of babies in multiple births separated by transfer	
Greene et al 2009	UK	Tayside Diabetes Managed Clinical Network	13,527 patients with diabetes in the region treated by 72 general practices and 2 district hospitals. 36 in-depth interviews with a purposive sample of people with high and low commitment to managed clinical networks: Network core management group (n=9); GPs (n=3); Hospital professionals (n=8); patients (n=4); patient representatives and Trust managers (n=5)	**Aim** To evaluate the form and impact of quality improvement (QI) strategies used by the Tayside Diabetes Managed Clinical Network between 1998 and 2005 **Intervention** Progressive implementation of multiple quality improvement strategies including; guideline development and dissemination; education; clinical audit, feedback and benchmarking; encouragement of multidisciplinary team working; task redesign; and care pathway redesign **Design** ▪ Retrospective observational mixed-methods evaluation **Method** ▪ Analysis of network documents (annual reports, planning documents, minutes of network meetings), observation of meetings and qualitative semi-structured interviews with multidisciplinary team	▪ Simple process indicators such as measuring glycated haemoglobin, blood pressure and cholesterol rapidly improved, while there was slow continuous improvement for complex processes that required more intensive professional education or redesign of care pathways such as assessment of foot vascular and neurological status and retinal screening. ▪ Improvements were greater for type 2 than type 1 diabetes. ▪ Between 2002 and 2006, there was a 13% (95%CI: 11.6% to 14.1%; $p<0.001$) fall in the proportion of newly diagnosed patients with type 2 diabetes attending the hospital in the previous 15 months. However the number of patients treated in hospital remained unchanged due to rising prevalence. ▪ Network organisation and leadership with a clear vision for care were important facilitators in delivering QI in particular, achieving widespread clinical engagement through persuasion and appeal to shared professional values by clinical leaders. ▪ Information technology played a supportive role but was not perceived to deliver QI by itself.

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				members and patients ▪ Analysis of impact of QI strategies using data extracted from the regional diabetes register at two time points – 1/1/1998 and 1/1/2005 **Indicators** ▪ 17 indicators of clinical processes and outcomes for patients with type 1 and type 2 diabetes (e.g. blood pressure measured, foot neurological status assessed, mean glycated haemoglobin %) ▪ Shifting care for uncomplicated type 2 diabetes into primary care, measured by rates of hospital referral for newly diagnosed patients	
Hamilton et al 2005	Scotland	Managed clinical network for cardiac services	N = 202 myocardial infarction patients < 76 years old admitted between 1st July 2000 and 30th June 2002 (97 prior to launch of the network) and 105 after launch of the network) in Dumfries and Galloway, South West	**Aim** To investigate the setup and operation of a managed care network for cardiac services, and assess its impact on quality of patient care and resource implications **Intervention** Establishment of a managed clinical network for cardiac services in a predominantly rural area in South West Scotland **Design** Quasi-experimental study design (interrupted time series) - Single case study using process evaluation and observational	▪ The network brought clinicians, patients and managers together to redesign services. ▪ There was statistically significant improvement in 2 out of 16 clinical care indicators: immediate aspirin administration (Regression coefficient= -35.9; p=0.037) & pain to needle times (Regression coefficient= -1.207; p=0.051) ▪ There was non-significant improvement in 9 other indicators. ▪ Changes were not noticeable until after a 2 year start-up period ▪ No improvement in 5 indicators. ▪ Set-up costs of the MCN were £52,615 during its pilot year. A further £50,000 was allocated for administrative support and time of the clinical lead following the MCN's launch. These costs are underestimates due to the difficulty in obtaining

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			Scotland	before and after comparison **Method** ▪ Document Reviews ▪ Interviews with two patients and a random sample of 12 health service personnel ▪ Analysis of routinely collected clinical data **Indicators** ▪ Process evaluation of network setup – how was the network set up, how did it operate, what did it do? – clinical leadership, scepticism & lack of support, collaboration, communication, quality, equity ▪ Outcome evaluation of network impact – impact on 16 quality of patient care indices, including percentage of patients receiving: immediate aspirin, thrombolysis, discharge medication, cardiac rehabilitation, secondary prevention at 6 months post MI ▪ Economic evaluation of cost of setup and operation of network – what were the resource implications of the network?	data. ▪ No significant difference in hospital cost of care (£2,055 before and £2,053 after launch of MCN), length of stay or resource use. ▪ An energetic lead clinician and change in structure of the network from a flat internal structure to mainly hierarchical was crucial to the stability and acceptability of the network, leading to its successful implementation.
McCullough et al 2014	Scotland	Scottish Sarcoma Managed Clinical	158 patients identified	**Aim** To determine whether the	▪ Prior to establishment of the network more patients were referred directly to the sarcoma

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		Network (SSMCN)	through a database of all patients with histopathology reports presenting with sarcomas of the trunk or extremity in Grampian between 1991 and 2009 (79 before establishment of the network, 79 after; the network was established in 2004). An additional 144 records (48% of all records) were unavailable due to medical record destruction; most of these were from the before period.	establishment of the Scottish Sarcoma Network improved the quality of diagnosis, treatment and care of sarcoma patients **Intervention** Establishment of the Sarcoma Managed Clinical Network. Key interventions included facilitating national multidisciplinary discussion of all sarcoma cases, registering case details and provision of care by a multidisciplinary team. **Design** Retrospective observational comparison before and after the establishment of the sarcoma clinical network **Method** • Cohort analysis of patient records pre- and post-establishment of the network using administrative datasets and medical records **Indicators** ▪ Referral to specialised sarcoma services ▪ Time to specialist review, ▪ Preoperative magnetic resonance imaging scanning ▪ Proportion of patients undergoing investigation with MRI scan prior to excision of sarcoma ▪ Proportion of patients undergoing appropriate	service by GPs, while subsequently greater numbers presented from other hospital specialists with referral numbers peaking in 2005 and 2006 following the initiation of the network. ▪ More patients were seen by more specialities after establishment of the network. ▪ Time interval from receipt of a referral to initial assessment by the service improved from a median of 19.5 days to 10 days after the SSN was established (p=0.016). However the interval between initial GP consultation and initial assessment by service increased from 35 to 41 days (p=0.57). ▪ Patients undergoing investigation with a magnetic resonance imaging (MRI) scan prior to excision of the sarcoma, increased from 67% to 86% after the establishment of the network (p = .0009) ▪ There was an increase in the number of patients undergoing appropriate biopsy from 57% to 79% (p=0.006). ▪ Data were available on the adequacy of surgical margins in 69 patients in each group. Resection margins were grouped into complete and incomplete margins. Prior to the network, 33 (48%) patients had documented complete resection and 36 (52%) were documented as incomplete. Post network this has increased to 56 (81%) complete margins and 13 (19%) (p <0.001).

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
				biopsy ▪ Complete margins achieved at surgical resection	
Ray-Coquard et al 2002	France	Regional cancer network of hospitals	**Experimental group – patients at 4 hospitals (private and public)** **Control group – patients at 3 hospitals (private and public)** **Breast Cancer** Women with newly referred localised breast cancer. Experimental Group: 1994 N = 282 1996 N = 346 Control Group: 1994 N = 194 1996 N = 172 **Colon Cancer** All new patients with colon cancer. Experimental Group -: 1994 N = 95	**Aim** To assess the compliance of medical practice with clinical practice guidelines in hospitals in a region with a regional cancer network and a matched region without a network at two time points. **Intervention** Implementation of clinical practice guidelines (CPGs) through a regional clinical network **Design** Controlled before and after study with hospitals in a matched control region **Method** ▪ Analysis of institutional medical records from patients pre- and post-implementation of clinical practice guidelines **Indicators** ▪ The number of overall treatment sequences judged to conform with clinical practice guidelines or to be evidence-based ▪ For breast cancer procedures the overall treatment sequence included: initial examination; surgery; chemotherapy; radiotherapy;	▪ Compliance with guidelines for the overall treatment sequence was significantly higher in 1996 (36%; 95%CI: 30-42) than in 1994 (12%; 95%CI: 8-16) in the experimental group for breast cancer ($p<0.001$). ▪ Compliance with guidelines for the overall treatment sequence was significantly higher in 1996 (46%; 95%CI: 30-54) than in 1994 (14%; 95%CI: 7-21) in the experimental group for colon cancer ($p<0.001$). ▪ There was no change in the compliance rate in the control group for both cancers: ▪ The number of medical decisions that conformed to clinical practice guidelines or judged to be based on scientific evidence was significantly higher in the experimental groups after the intervention. There was no significant change in the control groups. ▪ Breast cancer: 62% (95%CI: 54-64) in 1996 vs 47% (95%CI: 41-53) in 1994 ($p<0.001$) ▪ Colon cancer: 86% (95%CI: 80-92) in 1996 vs 74% (95%CI: 65-82) in 1994 ($p<0.001$)

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
			1996 N = 94 Control Group: 1994 N = 89 1996 N = 118	hormonal therapy and follow-up ▪ For colon cancer procedures the overall treatment sequence included: initial examination; surgery; chemotherapy and follow-up	
Ray-Coquard et al 2005	France	Regional cancer network of hospitals	All new patients with colon cancer and breast cancer at two audit points. **Experimental group – 4 hospitals (private and public)** **Control group – 3 hospitals (private and public)** **Colon Cancer** Experimental group 1996 N = 177 1999 N = 200 Control group 1996 N = 118 1999 N = 100 **Breast cancer** Experimental	**Aim** To evaluate the persistence of conformity to clinical practice guideline (CPG) recommendations in a cancer network through an audit of medical practice records **Intervention** Implementation of CPG through a clinical network initiated in 1995 **Design** Quasi-experimental study design - Controlled transversal study in experimental (cancer network) and control (no cancer network) groups **Method** ▪ Analysis of institutional medical records at two audit points **Indicators** • The number of 825 assessable overall treatment sequences judged to conform with clinical practice guideline recommendations or to be evidence based • The overall treatment	• Amongst breast cancer patients, compliance of medical decisions with CPG recommendations in the experimental group was similar for both periods (40%; 95%CI: 35-45 in 1996 vs 36%; 95%CI: 31-41 in 1999; p=0.25). Compliance was also the same in the control group (7% in 1996 vs 4% in 1999; p=0.99). Of note, the stratified analysis showed that only cancer centres maintained their initial compliance for surgical procedures (>85% and 75% in the experimental and control groups, respectively) whereas compliance rates decreased to less than 70% in all other institutions. • For breast cancer patients, the proportion of medical decisions that were consistent with CPG or based on scientific evidence remained at the same level between 1996 (50%; 95%CI: 45-55) and 1999 (44%; 95%CI: 39-49) (p=0.01). In the control group, these results were 8% in 1996 (95%CI: 4-12) vs 10% (95%CI: 6-14) (p=0.58). • Amongst colon cancer patients, compliance of medical decisions with CPG recommendations in the experimental group increased between 1996 (56%; 95%CI: 49-63) and 1999 (73%; 95%CI: 67-79) (p=0.003). Compliance was also the same in the control group (7% in 1996 vs 4% in 1999; p=0.99). Compliance was also higher in the control group (38%; 95%CI: 30-48 in 1996 vs

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
			group 1996 N = 444 1999 N = 381 Control group 1996 N = 172 1999 N = 204	sequence included decisions for each type of procedure individually (surgery, radiotherapy, chemotherapy, hormone therapy, initial examination, and follow-up)	67%; 95%CI: 58-76 in 1999; p<0.001). Stratified analyses showed that the compliance rate of the overall treatment sequence was higher in 1999 than in 1996 for any stage of disease in the experimental group, but only for the metastatic stage in the control group (and not for the localised group, p=0.11). • For colon cancer patients, the proportion of medical decisions that were consistent with CPG or based on scientific evidence remained at the same level between 1996 (83%; 95%CI: 76-89) and 1999 (75%; 95%CI: 69-81) (p=0.49). In the control group, compliance increased from 59% in 1996 (95%CI: 50-67) to 68% (95%CI: 59-77) (p=0.01). • The authors concluded that in this network, clinical practice guidelines were able to produce sustained improvements in adherence to medical practice over time compared with a control region.
Spence & Henderson-Smart 2011	Australia	Australian and New Zealand Neonatal Network	All neonatal nurses, midwives, neonatologists, junior medical staff, allied health and families providing care for newborn infants in 23 tertiary institutions with a neonatal intensive care	**Aim** To establish a process incorporating a team approach for using evidence to support practice change and prove its effectiveness in closing the evidence practice gap for newborn pain **Intervention** The implementation model used a clinical network with state facilitators, local champions and project teams. Interventions included: ▪ Resource documents distributed to each	• Statistically significant increase in the percentage of attending staff aware of an available clinical practice guideline for management of newborn pain (61% to 86%; p=0.000) • 21% improvement in the number of infants receiving sucrose for procedural pain (p<0.005). • Use of pain assessment tool increased from 14% to 22%, although was still under-utilised. • 56% (13/23) of units introduced the use of a pain assessment tool into practice. • Distribution of information resulted in an increase in family awareness that their infant can experience pain and strategies to manage the pain (19% to 57%, p=0.000). The proportion of families that received any form of printed

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
			unit, one special care unit and special care nurseries in 9 district hospitals across 8 Australian states participated in the project. Neonates of all gestational ages and post-natal ages who were in-patients in each unit during the audits were included as part of a quality improvement project.	participating unit ▪ Educational workshops on critical appraisal ▪ Audit and feedback at baseline and after 18 months ▪ Point of care reminders ▪ Posters and parent information brochures ▪ Clinical practice guideline **Design** Observational before-and-after study. **Methods** ▪ Surveys of clinical practices ▪ Prospective collection of data from participating units at baseline and 18 months after commencement of the project ▪ Audit of the use of a pain assessment tool for ventilated neonates 3 months prior to the project and 2 years after commencement ▪ Audits with families of infants **Indicators** ▪ Use of sucrose or breastfeeding for procedural pain ▪ Use of pain assessment tool for ventilated neonates ▪ Parents awareness of their infant's pain	information doubled from 8% to 17%. • Some targets were not met during the two year study period but a process for sustainability was established through the network to allow that to occur in the future
▪ **Improving patient outcomes**					
McClellan et al 1999	US	End Stage Renal Disease (ESRD)	Within each ESRD network,	**Aim** To assess the association between	▪ At baseline there was substantial variation between networks in URR, with mean age,

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		Networks	each year between 1994 and 1997, an annual random sample was selected of Medicare beneficiaries aged 18 and over receiving haemodialysis in the fourth quarter of 1993 – 1996. Network specific interventions were conducted with a 10% sample of treatment centres in each of the18 ESRD Networks	quality improvement interventions and change in haemodialysis adequacy using network specific interventions **Intervention** Network specific interventions included education on quality improvement, workshops, on-site assistance, distribution of an algorithm for assessing dialysis adequacy and distribution of clinical practice guidelines. National intervention reports were generated, comparing URRs by network, distribution of guidelines and patient education. **Design** Evaluation of a population-based, prospective quality improvement intervention. **Method** • Completion of a network-specific activities survey to ascertain interventions undertaken by each network, and an annual patient-level survey (completed by staff at each dialysis facility) to inform calculation of URRs. • Analysis of haemodialysis adequacy before and after national and network-specific quality improvements interventions **Indicators**	proportions of patients who were male or black, and distribution of causes of ESRD. ▪ Mean URR increased from 63% in 1993 to 67% in 1996 ($p<0.001$). ▪ The proportion of under-dialysed patients decreased from 56.6% in 1993 to 31.7% in 1996 ($p<0.0001$). ▪ Prolonged supervision in selected facilities was associated with an increased rate of improvement in URR from 62.1% at baseline to 67.7% after the intervention ($p<0.001$).

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
				• Network-specific Urea reduction ratios (URRs)	
Tideman et al 2014	Australia	Integrated cardiac support network (Integrated Cardiovascular Clinical Network – ICCNet)	29,623 independent contiguous episodes of MI identified through hospital administrative data and statewide death records from 1 July 2001 to 30 June 2010 in rural and metropolitan hospitals in South Australia, representing all independent contiguous cases of MI in South Australia during that time period.	**Aim** • To evaluate the impact of the regionalised Integrated Cardiovascular Clinical Network (ICCNet) on 30-day mortality among patients with acute myocardial infarction (MI) presenting to hospitals in a rural setting. **Intervention** Three key design features of the network: • Standardised risk stratification and evidence-based treatment protocols • Point-of-care testing for whole-blood troponin T levels with central quality control • A designated on-call consultant cardiologist to ensure response within 10 minutes and facilitation of transfer to metropolitan hospitals **Design** Retrospective state-wide observational comparison of outcomes before and after the establishment of a regionalised integrated Cardiovascular clinical network **Method** • Analysis of routinely	• The mean predicted 30-day mortality was lower among rural patients compared with metropolitan patients, while actual mortality rates were higher (30-day mortality: rural, 705/5630 [12.52%] v metropolitan, 2140/23 993 [8.92%]; adjusted odds ratio [OR], 1.46; 95% CI, 1.33–1.60; $P<$ 0.001). • Overall, annual mortality rates declined over the 9 years (per year, $OR_{risk\text{-}adj}$ 0.97 [95% CI, 0.95–0.99]; $P < 0.001$). However, these declines were greater in rural areas (interaction between year and rural location, $P = 0.04$). In 2001, the adjusted OR for patients presenting in rural areas was 1.69 (95% CI, 1.40–2.04; $P < 0.001$), but by 2010 this was no longer significant. • Among rural hospitals, 30-day mortality was lower among patients presenting to hospitals integrated into the clinical network compared with those not in the network (OR=0.78; P=0.007). • After adjustment for temporal improvement in MI outcome, baseline comorbidities and MI characteristics, availability of immediate cardiac support (i.e. presentation to an ICCNet hospital) was associated with a 22% relative odds reduction in 30-day mortality (OR, 0.78; 95% CI, 0.65–0.93; $P=$ 0.007). • A strong association between network support and transfer of patients to metropolitan hospitals was observed (before ICCNet, 1102/2419 [45.56%] v after ICCNet, 2100/3211 [65.4%]; $P<$ 0.001). Increased transfers were associated with a lower total length of stay compared with

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Primary Results
				collected data for patients with a diagnosis of myocardial infarction pre- and post-implementation of the network, comparing rural network hospitals with rural non-network hospitals and metropolitan hospitals. **Indicators** • Risk-adjusted 30-day mortality • Rate of transfer of rural patients to metropolitan hospitals • Proportion of patients receiving angiography	admissions before implementation of the network. • Rates of angiography increased among rural patients, but remained lower than metro patients. The difference between rural and metro patients diminished over the time period. • Increasing co-morbidities were associated with a lower likelihood of transfer among rural patients. Patients presenting to rural hospitals within the network were more likely to be transferred to a metro hospital than patients presenting to rural hospitals outside the network (OR=2.23; P<0.001) and were associated with a reduction in mortality across all degrees of comorbid risk.

Qualitative Articles

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
▪ **Features and outcomes of effective networks**					
Ahgren & Axelsson. 2007	Sweden	'Chains of care' (managed clinical networks) for patients having the same illness or symptom	6 chains of care networks – 3 selected to be successful 3 selected to be unsuccessful in developing chains of care in 4 counties.	**Aim** To identify the factors and their relative importance that may be important for the development of chains of care **Design** Cross-sectional embedded multiple-case study **Method** Semi-structured group and individual interviews and studies of documents **Indicators** *Success of network:* Extent of functional integration that included clinical, administrative as well as financial integration within the chain of care. *Explanatory factors were:* ▪ Development focus ▪ Development opportunities ▪ Organisational structure ▪ Organisational culture Each sub-unit of analysis had several indicators.	▪ Success of networks was based on the extent of their functional integration ▪ It was important that the focus of the development was compatible with the culture of the organisations ▪ 3 networks were considered to be unsuccessful based on their lack of functional integration ▪ The three major determinants of successful networks were: professional dedication of the staff within the networks; legitimacy of the network; confidence of the staff and organisations involved. ▪ Networks initiated locally by dedicated professionals, physicians in particular, are more likely to have a successful outcome
Baker & Wright 2006	UK	Managed clinical network for paediatric liver services	93 practitioners, patients, families of patients, drug company representatives	**Aim** To address the special problems arising from tension between need for centralisation of skills and advantages of decentralisation of care	▪ The requirements of patients and families overlapped with the ideals of professionals ▪ Results of the three sessions agreed broadly on the elements essential to the creation of a successful clinical network ▪ Key elements included patient education, open

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			and NHS managers	**Design/Method** Appreciative enquiry sessions held in 3 locations: Crieff, Birmingham & London **Indicators** ▪ Learning ▪ Roles and relationships ▪ Share-care and liver disease at home ▪ Access to services/first interaction ▪ Standards, protocol and safety	and inclusive communication, customer care, a clear care pathway, and national protocols, guides and standards ▪ The vision for the MCN was partner relationships, respect for autonomy, personal autonomy, information and service access, least possible disruption of normal life with flexibility according to personal needs and patient centredness ▪ Features of a successful network were identified as: ▪ Care as close to home as possible ▪ Open and inclusive communication ▪ A clear care pathway ▪ Better customer care including interactions with a key worker/coordinator
Cunningham et al 2012	Australia	Advisory clinical networks – two networks for musculoskeletal health in two states in Australia (New South Wales and Western Australia)	36 interviews with key informants (network managers, network members and stakeholders including representatives from Departments of Health and clinical and non-governmental organisations)	**Aim** To describe the features and roles of clinical networks and identify factors relating to clinical network effectiveness and sustainability, and to explore achievements of the networks. **Design** Longitudinal comparative case study **Methods** Semi-structured in-depth interviews to ascertain perceptions of network members and stakeholders regarding key factors relating to clinical network effectiveness and sustainability conducted between March-August 2011 • 19 of 92 core members in	• Interviewees perceived a network to be successful: ▪ At the community level if there was greater consultation, greater agreement and acceptance of network recommendations, greater implementation of Models of Care, improving practice patient care and measureable improvement in patient outcomes; ▪ At the network level if the network was able to get together measured by growth in network membership, broad stakeholder representation, and contribution of the network manager and network leadership; ▪ At the member level if there is member participation and responsiveness in the network, member contribution to the network, and success in embedding practice changes in the member's own hospital/clinic. ▪ Network manager and leadership were perceived

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				NSW interviewed • 17 of 34 core members in WA interviewed **Indicators** • Measures of effectiveness at the community, network and member level at the short, medium and long term • Key achievements of each network	as being critical for the success of the networks. ▪ Both networks used a distributive leadership model, and a structure of establishing key working groups led by expert members of the network. ▪ Stakeholders noted the role of networks in identifying gaps between current practice and evidence-based practice; directing care into more evidence-based practices and improve professional/patient interface; collaboration across health sites; effective communication with and inclusion of a broad range of stakeholders; engaging clinicians and enabling them to contribute to policy. ▪ Challenges included funding and a disconnection between network recommendations and implementation especially if the network did not have the authority for implementation.
Hogard & Ellis 2010	UK	Managed clinical network for personality disorder (PD)	All members of staff involved in the MCN	**Aim** To evaluate how the network had performed in its purpose to establish a better coordinated service for patients with PD and what changes or refinements might be required **Design** Evaluation Trident methodology **Method** Evaluation of outcomes, processes and multiple stakeholder perspectives over a 2 year period including: interviews, focus groups, telephone interviews, questionnaires, documentation analysis and NHS data sets. Processes were further	▪ On the basis of the audit, staff in the network could be described as in a partnership in that they shared values and objectives. However such commitments in principle do not guarantee clinical effectiveness. ▪ Positives of the network reported included being able to provide a holistic service to users including provision of a nonmedical assessment and formulation and ultimately encouraging better engagement with clients. The wide range of services linking into the network was also commended. ▪ Negatives of the network reported included a lack of funding and resources leading to limited capacity to coordinate care for a large number of clients, the speed with which the network was able to process referrals, and poor communication. Tension in relationships between

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
				assessed using the following standardised dedicated measures: A partnership audit tool (PAT); a care programme approach audit tool (CPA) and the PD self-capabilities framework self-audit tool (PDCF). **Indicators:** ▪ *Outcomes*- Focus on 2 key outcomes relating to effectiveness of treatment provided: reduction in frequency of crises; reduction in inappropriate service use ▪ *Process* – 5 main focuses: organisational and functional structure; service user pathway; partnership; care planning approach (CPA); staff development needs ▪ *Stakeholder interviews* – explored five core themes: 1. Attitude prior to joining the network; 2. Attitude changes as a result of joining the network; 3. The impact of MCNs; 4. Working relationships; and 5. The value added by the PD MCN	network staff and referrers were also reported, with participants noting a need to improve working relationships and transfer of knowledge. ▪ Record keeping for assessment and clinical assessment was at an early stage and there was a need for a more systematic use of assessment instruments and data management instruments ▪ The service did not keep appropriate information that could be used to measure outcomes and tools to measure crisis were being used inconsistently by network staff. There were challenges in capturing whether there was an impact for service users and a lack of evidence regarding clinical outcomes. ▪ Much of what was reported in this evaluation relied on anecdotal data, due to a lack of formal evidence. ▪ While the network had achieved its objectives to establish new operational structures it was unclear whether it had maintained or improved clinical services. ▪ Stakeholder interviews indicated that prior to joining the MCN a number of staff had previously viewed PD in a negative light. Many staff reported that their attitude towards PD had not changed since joining the network but a number did explain that their knowledge and experience had increased significantly. ▪ Staff highlighted the benefits of working as part of a MCN which was viewed as a way to provide an efficient and informed service. ▪ Working relationships within the MCN were viewed positively on the whole, despite some tensions between network staff and the referrers. ▪ The MCN was considered by staff to have added value by raising the profile of PD and helping to

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					share skills and knowledge across a number of agencies and services. ▪ However the benefits of the MCN "remain theoretical rather than proven".
McInnes et al 2012	Australia	Voluntary collegial clinical networks in New South Wales, Australia established by the NSW Agency for Clinical Innovation	27 interviews with network drivers especially network managers (9), network participants (6), senior health service managers in a clinical operations or clinical governance role at a hospital (4), and senior policy-makers (8).	**Aim** To identify key stakeholders' views on the conditions required to establish successful and effective clinical networks and what they identify as outcomes of successful clinical networks. **Design** Comparative case study **Methods** A purposive maximum variation sampling approach was used to recruit the four types of participants. 27 individual semi-structured face-to-face interviews were conducted. Sample size was determined by saturation of themes. **Indicators** • Factors necessary for effective networks • Outcomes indicating whether clinical networks are effective	▪ Factors necessary for networks to be effective included: ▪ Building relationships within and with external networks and a strong commitment to the networks ▪ A bottom-up approach to integration, preferably locally-initiated but with formalisation of the networks ▪ Supportive policy environments and links with state health agencies and local health services ▪ Strong leadership, including passionate clinical leaders, was necessary for effective structure, organisation and governance ▪ A strategic, feasible evidence-based work plan with measureable milestones and that was valuable to participants ▪ Adequate resources including a dedicated network manager and technological resources ▪ The ability to implement changes in practice or service delivery to address gaps in current practice, that are relevant to members, feasible and measureable ▪ Features of ineffective networks included: ▪ Lack of funding and resources ▪ Tension between network members ▪ Poor communication ▪ Poor record keeping making it difficult to assess impact ▪ Poor teamwork and working relationships ▪ Lack of inclusion of certain populations

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
					▪ The following outcomes of successful clinical networks were identified: ▪ Better working relationships and greater interdisciplinary collaboration in patient care and development of research projects ▪ Open and transparent partnerships with external stakeholders such as the health department and greater mutual understanding of perspectives ▪ More effective clinical services reflected by improving patient journeys, clear care pathways, provision of holistic services, standardising care, reducing variation in care, reducing costs and monitoring quality ▪ Implementation and wide-scale spread of network initiatives and impact on practice ▪ Growth of the network
▪ **Network Implementation**					
Fleury et al 2002	Canada	Mental health integrated service network	N = 143 staff and administrators at all levels of service intervention, clients of self-help groups and outpatient clinics and relatives and friends of the mentally ill selected using an intentional sampling strategy and interviewed in	**Aim** To examine the process of implementing regional planning and the influence of contextual, structural, cultural and dynamic factors on forming networks **Design** Case study and multi-dimensional analytic model **Method** • Interviews • Review of primary sources (e.g. minutes, correspondence, administrative documents and policies) • Review of secondary sources	▪ The study found that regional planning involving stakeholders was not sufficient for implementing mental health care networks integration as it did not create a genuine reconfiguration of services ▪ Successful implementation was inhibited by several factors including: ▪ the large number of professionals involved in different services, ▪ ambivalence towards network priorities when and if opposed to organisational priorities and rigidity of established practices, ▪ centrality rather than dispersion of power, ▪ the lack of recognition of legitimacy and expertise of planners, ▪ irreconcilable visions of system structuring, ▪ the lack of clinical, function and professional integration, ▪ hospitals maintained a centralised position in

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
			six time periods from Winter 1995 to Summer 1997	(e.g. mental health, organisational theory, network literature) **Indicators** The framework focused on three lines of analysis: • Context for implementing the regional planning procedure • Determinants of implementing and impact of regional planning such as problem-setting, network direction setting and structuring • The dynamic of developing regional planning	the networks that allowed them to hoard resources. ▪ The study reinforced that reform can only be implemented with the approval and genuine participation of the professionals directly involved the field
Tolson et al 2005[9]	Scotland	Managed clinical network (Palliative Care), linking primary, secondary and tertiary care	1 network sample in study 3 older men, their families, the doctors and nurses providing care, along with 13 members of the network management group	**Aim** ▪ To evaluate, refine and inform the ongoing development of the MCN. ▪ To reflect of the merits and challenges of a realistic evaluation design in establishing a new palliative care MCN to implement a care guideline for pain management in a primary care setting. **Design** A "realistic evaluation design". A qualitative pilot study evaluating guideline implementation at three separate points (6, 11, and 15 months) during the implementation of managed	▪ Progress in establishing the network was much slower than expected and was hindered by: inexperience in change management and unfamiliarity with leading practice development projects and supporting practitioner learning. ▪ Co-ordination, leadership and strategic support (particularly professional buy-in) in change-management were critical to success. ▪ There was a consistent trend of an increasing recognition over time about the pivotal role of practitioners in the development of the network. ▪ Professional outcomes centred on improved team working and enhanced communication, increased knowledge, greater satisfaction, reflective practice and increased commitment to evidence-based care. ▪ In terms of patient outcomes, there was accumulating evidence of better pain management and symptom control, and increased

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
				clinical network. **Method** Findings from qualitative interviews and patient-level clinical data comprised case studies of patient-centred experiences of care. These case studies, along with semi-structured interviews with health-care professionals informed the evaluation, reviewed and refined by the network executive. **Indicators** Relationships between: ▪ Context ▪ Mechanisms ▪ Outcomes	knowledge through better patient education. ▪ The amount of time and input demanded of the coordinator role was high and increased with wider reach of the network. ▪ The length of time and effort required to achieve buy-in into the network is high. This often involves a "values reconciliation" phase where members examine and compare their own/team values and practices to those of the network. ▪ Networks can only be effective if the appropriate (often numerous) steps are taken and the context is favourable (e.g. clinicians are receptive to audit and feedback).
Touati et al 2006[8]	Canada	Managed clinical network (cancer)	5 hospitals offering oncological services in the Quebec region	**Aim** To determine the extent of clinical leadership as a means for transforming health care in an oncological services network **Design** Longitudinal qualitative case study using process analysis to examine how the networks influenced change **Method** Data collected from 1999-2003 included: ▪ Non-participant observation of 50 administrative meetings relating to governance of change ▪ 65 semi-structured interviews with network promoters	▪ Inter-professional and inter-organisational trust developed in all hospitals. However the level of commitment by physicians and professionals to the implementation of the network varied. ▪ All of the hospitals attempted to stabilise oncology teams and felt that they benefited from administrative support to set up clinical teams. ▪ In varying degrees all hospitals implemented measures to foster cooperation between professionals. Interdisciplinary team meetings were being held in 4 out of 5 hospitals but oncologists did not participate in all hospitals. ▪ In 4 out of 5 hospitals, most respondents shared the philosophy and vision promoted by the governance of the network with regard to: response to all of the individual's needs; coordinated care; standardisation of clinical practices; and patient-centered care. ▪ Clinical leadership is effective in implementing

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
				including clinician leaders, professionals from multidisciplinary teams, hospital managers ▪ Document analysis (e.g. protocols, budget statements) **Indicators** ▪ Origins of change ▪ Facets of integration: - normative - functional - clinical	change but is limited. Contextual variables, the nature of the changes emphasized (those consistent with the actors' values and interests) fostered change. ▪ Positive change is more likely to be achieved by a 'constellation of clinical, administrative and political leaders' at different levels of the health care system. ▪ To enhance the coordination of care, coordination committees were set up to jointly formalise processes involving nursing care case-management. Longstanding collaboration facilitated the implementation of these committees. ▪ The study highlights the complexity of health services integration processes which demand considerable time, resources and initiatives at different levels of the health system.
▪ **Organisational Structure**					
Addicott R 2008	UK	Managed clinical network for cancer services	117 professionals from 5 cancer networks in London	**Aim** To explore the changing model of governance in the UK, particularly the increasing focus on networks and the role of the network Board **Design** Comparative case study **Method** ▪ Semi-structured interviews with nurses, clinicians, managers and policy makers ▪ Document analysis ▪ Observation at meetings **Indicators** ▪ Network structure ▪ Purpose of the network	▪ Cancer network management teams and Boards had limited strategic influence as networks were constrained by a continued emphasis on centralised performance management and structural reconfiguration ▪ Success of decision making was dependent on seniority of representation on the network Board. In only 1 out 5 networks the Board had high representation from extremely senior representatives and this Board had a noteworthy impact on strategic decision making. ▪ Both the network management teams and Board only had minimal decision-making influence within a prevailing centralised bureaucratic structure. Although the espoused logic of the network was to decentralise decision making to a local level, power and budgetary responsibilities

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
				▪ Network Management Team approach to networking ▪ Characteristics of the Board ▪ Approach to organisational change	ultimately remained centralised. Network Boards have had limited scope for strategic decision making. ▪ The key finding is that the managed network model was not powerful enough to deinstitutionalise the prevailing governance discourse of performance management and centralised accountability.
Addicott R & Ferlie E 2007	UK	Managed clinical network for cancer services	117 professionals from 5 cancer networks in London	**Aim** To explore and theorise the nature of power relations within a network model of governance **Design** Comparative case study **Method** ▪ Semi-structured interviews with nurses, clinicians, managers and policy makers ▪ Document analysis ▪ Observation at meetings **Indicators** 3 tracers of power relationships: ▪ Centralisation of specialist services ▪ Budget/resource allocation ▪ Education and training activities	▪ The 5 networks were structured in similar ways due to the national policy agenda. ▪ Network Management Teams had no statutory influence or performance management mechanism and had to rely on interpersonal skills to influence cooperation. A lack of these skills frequently resulted in inability to generate meaningful changes or control the delivery of services. ▪ Decision making was dominated by medical staff in all 5 networks. ▪ During localised decision-making and implementation of policy less dominant medical professionals presented barriers in an attempt to exert influence. ▪ These cases demonstrated that the internal divisions in the medical profession, with active power and influence unevenly distributed in favour of those in the cancer centre while less powerful medical professionals were then forced into defensive mode to resist decisions that had been made.
Addicott R, McGivern G & Ferlie E 2007	UK	Managed clinical network for cancer services	117 professionals from 5 cancer networks in London	**Aim** To explore how stakeholders involved in the delivery of cancer services in the UK adopted or adapted managed clinical networks as a novel managerial	▪ The knowledge sharing purpose of networks was distorted by top-down structural reorganisation demands of central government resulting in superficial bottom-up adoption of the networks models and a lack of focus on process or strategic issues.

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
				technique for sharing best practice and knowledge **Design** Comparative case study **Method** ▪ Semi-structured interviews with nurses, clinicians, managers and policy makers ▪ Document analysis ▪ Observation at meetings **Indicators** 3 tracers of knowledge management: ▪ Centralisation of specialist services ▪ Budget/resource allocation ▪ Education and training activities (an indicator for knowledge management activity)	▪ The centralisation process was feared by clinicians and negatively impacted on alternative educational and knowledge sharing activities. ▪ In 4 out of 5 networks there was frequent resistance to making decisions and implementing changes. ▪ One network demonstrated greater network-wide investment in education and training activities. This was largely due to a strong, well-perceived Network Management Team which began to develop an educational strategy across the network. ▪ Overall, networks had little impact on organisational processes. The majority of networks had a limited focus on educational and training activities, and broader issues surrounding organisational change. ▪ One network was an outlier. An open and facilitative approach to managing networks was more successful. The network was more successful in building on pre-existing relationships that were evident prior to establishment of the networks. Those involved in managing and leading the network were successful in considering the needs of the local context during the process of implementing the network.
▪ **Organisational Learning and Knowledge**					
Addicott et al 2006	UK	Managed clinical network for cancer services	117 professionals from 5 cancer networks in London	**Aim** To explore whether the knowledge management function of managed clinical networks was realised in practice **Design** Observational, cross-sectional organisational process study	▪ There was little evidence of change in practice within 4 out of 5 networks. This was considered to be a result of interorganisational competition following from structural reconfiguration, an emphasis on achieving targets and conformance with protocols and persistent interprofessional boundaries. ▪ In 1 out of 5 networks there was cohesion within

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
				Method ▪ Semi-structured interviews with nurses, clinicians, managers and policy makers ▪ Document analysis ▪ Observation at meetings **Indicators** Network impact on: ▪ structural reconfiguration ▪ budgetary allocation ▪ educational and training activity	the network and the structural reconfiguration process resulted in significant changes in practice. ▪ In this 'successful' network, there was more evidence of learning, training, knowledge sharing, and education. This was thought to be due in part to the network being well and supportively managed, facilitating engagement, having a detailed understanding of cancer services, a localised appreciation for the dynamics of the organisations involved, and good pre-existing relationships between members of the network prior to commencement. ▪ Lack of success in the other four networks was perceived as being due to limited time and resources, lack of enthusiasm from network members, and increased competition for resources within each network. Respondents from cancer centres were more positive about the learning aspects of the networks than representatives from peripheral units. Some thought that learning would become a greater priority when structural reconfigurations were underway or complete.
Burnett et al 2005	UK	Managed clinical networks (MCNs)	9 interviewees from Scottish MCN priority areas: cancer, coronary heart disease, stroke and mental health and a representative from local health community co-	**Aim** To explore the extent to which the information culture and practices within MCNs and whether they are able to deliver improved care **Design/Method** Qualitative information and knowledge needs analysis comparing responses from MCN respondents with those from a previous study of staff working in a more traditional environment	▪ Evidence-based practice was a requirement within the Scottish Health Service in general and within the MCN in particular, noting the importance of being able to access information. ▪ Individuals working within the MCN perceived that information and knowledge had an impact on service delivery and demonstrated a greater ability to reflect on the value of knowledge and information in their roles ▪ Information and communication technologies (and in particular the e-Library) was widely recognised as an important for access to health

Reference	Country	Type of Network	Sample	Study Aim, Design, Method and Indicators	Results
			operative; respondents represented a range of roles including specialist nurses, lead clinicians, planning and implementation managers.	**Method** • Semi-structured in-depth interviews; approximately 1 hour in duration. **Indicators** • How MCN staff used knowledge in their roles, requirements of the knowledge base and problems with knowledge provision; • Role of information in supporting evidence based practice • Perceptions of the e-Library • Education and training • IT support • Barriers to the use of information	care knowledge and MCN respondents reported a greater need for and confidence in information literacy. ▪ MCN respondents also considered colleagues an important source of information with emphasis on the inter-disciplinary and cross-boundary aspects of MCNs facilitating knowledge transfer. ▪ Healthcare professionals in MCNs discussed information facilitating communication with patients and including patients as a part of the "knowledge network". ▪ The MCN group demonstrated an ability to reflect on the value of information and knowledge in their roles. They saw information and knowledge as having an impact on service delivery. They also recognised that it is vital to have easy and timely access to the information and knowledge they require to operate as effectively and efficiently as possible.

Appendix III

PRISMA 2009 Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	**43**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	**43-44**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	**44-46**
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**46**
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	**N/A**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	**49**
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**49**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**Appendix I**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**49-52, Appendix I**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**52, Appendix II**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**Appendix I**
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**51, Appendix I**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	**N/A**
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	**N/A**

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**N/A**
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	**N/A**
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**Fig. 2.1&2.2, Appendix I**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**52, Appendix II**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	**Table 2.2, 2.4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	**52-68, Table 2.3, 2.5, Appendix II**
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	**N/A**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	**N/A**
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	**N/A**
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	**68-74**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	**72-73**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**74**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	**xvii**

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097.

Appendix IV
Survey of urologist members of the Urological Society of Australia and New Zealand (USANZ)

saxinstitute

NHMRC Partnership Grant 1011474

Improving care for men with locally advanced prostate cancer

Survey of Urologists

THE UNIVERSITY OF SYDNEY

Prostate Cancer Foundation of Australia

ACI NSW Agency for Clinical Innovation

Cancer Council

Background

There is currently much debate over the most appropriate treatment for high-risk prostate cancer. In particular, there are controversies in post-prostatectomy radiotherapy.

This survey aims to assess the current views and practice of urologists relating to adjuvant radiotherapy for men with locally advanced prostate cancer following radical prostatectomy. You have been selected to participate in the study as a member of the Urological Society of Australia and New Zealand (USANZ).

The survey forms part of a wider study funded by the National Health and Medical Research Council (NHMRC) and the Prostate Cancer Foundation of Australia (PCFA) with the research being undertaken in partnership with The Sax Institute, University of Sydney, Cancer Council NSW and the NSW Agency for Clinical Innovation (ACI).

Participation in this survey is entirely voluntary. Submitting a completed survey is an indication of your consent to participate in the study. All aspects of the study, including the results, will be strictly confidential. Your responses will be anonymous and aggregated with those of other respondents in all reports relating to this study.

If you would like further information about the study and how your responses will be used, please read the Participant Information Sheet.

Section 1 – Clinical Uncertainty

1.1 For each scenario, we are interested in your ***current level of certainty*** about which treatment option is better. Please rate your certainty by circling the number that best reflects your view. If you are completely undecided between the two options, please circle '0'. If, however, you consider one treatment option to be superior, for whatever reason, please indicate how strongly you hold this view by circling the appropriate number on the scale.

Case 1

A 64 year old man, previously well, presented with a pre-op PSA of 12.2. Patient had radical prostatectomy 10 weeks ago. Pathology results show a Gleason 3+4=7 carcinoma with extracapsular extension and positive margins near apex over a 2mm front. Seminal vesicle and lymph nodes were clear. Post radical prostatectomy he has good urinary control. Post-op PSA 0.01. No return of erections.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

Case 2

A 58 year old man had a nerve sparing radical prostatectomy 3 months ago for a low volume Gleason 3+4=7 carcinoma (20% high grade) with 0.2mm extracapsular extension in left peripheral zone but clear surgical margins. No perineural or lymphovascular invasion. Seminal vesicles clear. 0/12 nodes involved. Post-op PSA <0.01. Some dribbling on straining but pad free. Partial erections but inadequate for intercourse.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

Case 3

A 62 year old man had a non nerve sparing prostatectomy for a clinical T3 prostate cancer with pre-op PSA of 14. Histopathology demonstrates a widespread Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension and involvement of base of right seminal vesicle. Multiple sites of positive surgical margins. Post-op PSA 0.04. No lymph node involvement. Good urinary function and no erections.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

1.2 Thinking about **your understanding of the current literature and evidence** for treatment of prostate cancer, please rate the extent to which you agree or disagree with each statement by ticking ONE option:

a. Immediate external irradiation after radical prostatectomy improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 prostate cancer who are at high risk of progression.

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

b. Relapse after local therapy is defined by prostate-specific antigen (PSA) values >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir PSA after radiation therapy (RT).

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

c. All high risk patients should have multidisciplinary input and be referred by their urologist to a radiation oncologist *before* treatment to ensure informed decision making based on discussion of the relative advantages and disadvantages of adjuvant radiotherapy or watchful waiting.

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

d. There are no data from randomised controlled trials to define the benefits of salvage radiation versus adjuvant therapy or salvage radiation versus systemic therapy (either at time of PSA rise or at time of radiographic progression).

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

Section 2 – Clinical Practice Guidelines

In this section we are interested in your opinions about clinical practice guidelines in general.

2.1 Do you use any clinical guidelines in your practice? Yes / No

2.1a How many clinical guidelines do you use in your practice? 1-5 / 6-10 / 11 -15 / >15

2.2 On the scale provided please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box.

In general, clinical guidelines:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
Are good educational tools						
Are a convenient source of advice						
Are intended to improve quality by standardising care						
Improve patient outcomes						
Are intended to cut costs						
Interfere with my professional autonomy						
Are oversimplified 'cookbook' medicine						
Are too rigid to apply and adapt to individual patients						
Limit my ability to apply clinical judgement						
Are based on an unbiased synthesis of robust scientific evidence						
Are not readily accessible when I want to refer to them						
Provide contradictory advice						

In 2010, Australia Cancer Network and Cancer Council Australia in conjunction with the Prostate Cancer Foundation of Australia and Andrology Australia published the Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer.

2.3 Are you aware of this guideline? Yes / No

2.3a How did you find out about it?

☐ Direct mail	☐ Urology Association	☐ Journal
☐ Internet search	☐ Patient	☐ Colleague
☐ Hospital department/administration		☐ Other

A Grade B recommendation in the guideline states "patients with extracapsular extension, seminal vesicle involvement or positive surgical margins receive post-operative external beam radiation therapy within four months of surgery".

In the next section we are interested in your opinions about <u>this specific clinical guideline recommendation</u>.

2.4 Following radical prostatectomy who do you believe is the person best placed to decide on the most appropriate post-operative treatment option? Please select ONE option:

☐ The urological surgeon is best placed to decide

☐ The radiation oncologist is best placed to decide

☐ The medical oncologist is best placed to decide

☐ The MDT is best placed to decide

☐ The patient is best placed to decide

2.5 Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiotherapy within four months of surgery, please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
The recommendation is based on a valid interpretation of the underpinning evidence						
The side-effects of adjuvant radiotherapy for patients with locally advanced prostate cancer outweigh the benefits						
There are other recommendations for the appropriate management of this patient population that conflict with this one						
Following this recommendation will lead to improved patient outcomes						
If I follow this recommendation my patients may experience unnecessary discomfort						
I support post-operative external beam radiation therapy for patients but not within four months of surgery						
If I don't follow this recommendation I may be liable for malpractice						
This recommendation is consistent with my clinical experience with this patient group						
This recommendation is consistent with the opinions of my respected clinical colleagues						
This recommendation does not reflect evidence that is emerging on this topic						
This recommendation should only be followed within fully informed decision making by the patient						

There are 3 randomised controlled trials (ARO, EORTC, SWOG) comparing adjuvant radiotherapy versus observation post radical prostatectomy in patients with extracapsular extension, seminal vesicle involvement and/or positive surgical resection margins. Two of these trials were conducted in Europe and one in the US.

2.6 Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiation therapy within four months of surgery:

a. How many randomised controlled trials do you think are necessary to provide an acceptable level of evidence to support this recommendation? 1 / 2-3 / 4-5 / >5

b. How many years follow up of patients would be necessary to convince you of the benefits of adjuvant radiotherapy? <1 yr / 2-3yrs / 4-5 yrs / 6-8 yrs / 9-10 yrs / >10yrs

c. When considering evidence from randomised controlled trials to do you think it is necessary to have local, Australian data? Yes / No

d. Randomised trials have demonstrated a range of survival effects following adjuvant radiotherapy for this patient group. Thinking about the current evidence, what is the minimum survival benefit you consider acceptable for you to follow this recommendation? Please complete **ONE OPTION**.

Days	Months	Years

e. What do you consider to be the maximum proportion of men who suffer from rectal damage or develop faecal incontinence as a result of radiotherapy for this treatment to be unacceptable? Please **place an X on the scale** below.

0% **100%**

2.7 Do you have any comments on adjuvant radiotherapy following radical prostatectomy?

Section 3 – Innovation

3.1 Which best describes your feelings about trying new procedures in your practice? (Circle ONE)

1. I experiment with new procedures
2. I prefer to wait until others have tried new procedures
3. I prefer to wait until new procedures have been established for a while
4. I only try new procedures when regulations require them

3.2 Thinking about your current clinical practice, on the scale provided please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
Clinical experience is the only form of valid knowledge in decision-making						
I am comfortable recommending contentious treatments or procedures if I am confident of the evidence behind them						
I discuss all treatment options with my patients to allow them to make an informed decision						
I sometimes forget to discuss guideline recommendations with patients						
I would like guidance as to how to apply recommendations to specific patients						
I am confident in applying recommendations for individual patients in my practice						
I would like guidance about how to provide information on the pros/cons of radiotherapy without overburdening patients						

Section 4 – Other Factors

4. Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiation therapy within four months of surgery, please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
This recommendation takes into consideration the needs and preferences of patients						
Routinely referring patients to radiation oncology will increase costs						
Other urologists will be critical of me if I routinely refer these patients to radiation oncology						
This guideline is likely to be followed by most of my colleagues						
It would be easy to incorporate this new process into practice in my clinical setting if I wanted to						

Section 5 – Readiness for change

5. Thinking about your clinical practice, on the scale provided please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box.

Urology leaders in my organisation:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
Believe that current practice patterns can be improved						
Encourage and support changes in practice patterns to improve patient care						
Are willing to try new protocols						
Work cooperatively with senior leadership/clinical management to make appropriate changes						

Section 6 – About You

6.1 Gender: Male / Female

6.2 Age group: 20-30 / 31-40 / 41-50 / 51-60 / >60

6.3 Which type of practice do you have? (Circle ONE option for your major appointment):

VMO/Consultant
Salaried University Academic
Staff Specialist
Registrar/Junior Medical Officer
Other (please specify) _____

6.4 How many years have you been a practicing Urologist?

0-5 / 6-10 / 11-15 / 16–20 / 21–25 / 26-30 / >30

6.5 Do you perform Radical Prostatectomy? Yes / No

6.5a Approximately how many new patients diagnosed with prostate cancer do you care for in a **TYPICAL MONTH?** _____patients

6.5b Approximately what percentage of your practice is comprised of prostate cancer patients? _____ %

6.5c What percentage of your patients are in **ACTIVE TREATMENT** for prostate cancer (as opposed to routine surveillance or follow up)? _____ %

6.6 Which of the following best describes the location in which you practice? (Circle ONE option only):

Capital city
Other major urban area
Rural
Remote
Other

6.7 In which setting do you treat the MAJORITY of prostate cancer patients: (Circle ONE option only):

Teaching hospital
Public, non-teaching hospital
Private hospital

THANK YOU FOR YOUR TIME

Appendix V

Intervention tracking forms

CLIC

Clinician-Led Improvement in Cancer Care

Urologist name: _____ Hospital: _____ Date consented: _____

Opinion Leaders	Date received	Method of delivery (e.g. MDT meeting, V/C, email, phone)	Data source (e.g. MDT attendance record, Post-intervention follow up checklist, interviews)	Minimum requirement met? (Y/N)
CLICC Video				
Discussion with Clinical Leader				
Discussion with Urology Network Co-Chair				

Printed Materials	Date received	Method of delivery (e.g. MDT meeting, email, post)	Data source (e.g. MDT attendance record / Post-intervention follow up checklist / survey	Minimum requirement met? (Y/N)
Urologist Resource				
Full Clinical Practice Guideline				
Supporting papers				

Audit & Feedback					
	Date Sent	**Attended MDT meeting** (Y/N – date)	**Individual report viewed** (Y/N)	**Data source** (e.g. MDT agenda, minutes, EzyMsg report, interviews)	**Minimum requirement met?** (Y/N)
Feedback report 1 – Baseline individual					
Feedback report 2 – Baseline aggregate					
Feedback report 3 – 6 months individual					
Feedback report 4 – End of study					

Systems & Processes						
	Date first implemented	**Number of MDT meetings with flagged cases**	**Date ceased** (if applicable)	**Additional information**	**Data source** (e.g. Pathology, MDT agendas & minutes, MDT flagging data collection forms)	**Minimum requirement met?** (Y/N)
MDT flagging						

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Evaluation			
	Date sent	Completed survey/interview? (Y/N)	Date completed/received
First survey			
Second survey			
Third (last) survey			
End-of-study interview			

Minimum requirement for intervention element to be considered "received"?	
	Minimum requirement
Opinion leader	One option required: Watched CLICC video, OR Had discussion with Clinical Leader, OR Had discussion with Urology Network Co-Chair
Printed Materials	Received CLICC printed resource (required) Optional (but not sufficient): Received Full Clinical Practice Guideline AND/OR Received Supporting papers
Audit & Feedback	Required: Sent all feedback reports since agreement to participate
MDT flagging	Required: MDT flagging implemented since agreement to participate

Appendix VI

Participant information statement and consent forms

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Clinician-Led Improvement in Cancer Care

Improving care for men with locally advanced prostate cancer

UROLOGIST INFORMATION STATEMENT

Introduction

You are invited to participate in this study as a Urologist who performs Radical Prostatectomy in one of the hospitals participating in this research that is part of the NSW Agency for Clinical Innovation Urology Network in NSW hospitals. This study aims to develop and trial an intervention, to implement the Australian Cancer Network's Clinical Practice Guidelines for the Management of Locally Advanced and Metastatic Prostate Cancer. Specifically, the study aims to increase fully informed decision making in patients with high risk prostate cancer following radical prostatectomy.

This study is being conducted by the Sax Institute, led by A/Prof Mary Haines, in partnership with the University of Sydney, Cancer Council NSW and the NSW Agency for Clinical Innovation (ACI). A full list of investigators is provided below. This study has been funded by the National Health and Medical Research Council (NHMRC) and the Prostate Cancer Foundation of Australia (PCFA). The study is registered with the Australia New Zealand Clinical Trials Registry: ACTRN12611001251910.

Study Procedures

Consent

If you agree to participate in this study, you will be asked to sign the Urologist Consent Form.

Questionnaire

You will then be asked to complete a short questionnaire (5-10mins) relating to your current knowledge and attitudes towards adjuvant radiotherapy for patients with high-risk prostate cancer after radical prostatectomy. This survey will be repeated 6 months after the intervention session and at the end of the study.

Interactive Education Session

You will participate in a short (10-15 minute) interactive education session. At this session you will be provided with printed materials and a summary of the evidence underlying the guideline recommendation including a video presentation. You will have the opportunity to discuss any concerns.

Medical Audit

You will be asked to allow a research assistant to attend your practice at a convenient time to perform an audit of medical records of some of your prostate cancer cases. The research assistant will collect re-identifiable (ie coded) data from medical records of prostate cancer cases who have undergone a radical prostatectomy during the study period and meet the criteria of 'high-risk' following surgery.

Feedback

After the interactive education session you will be provided with a quarterly performance report describing the number of prostate cancer cases referred to radiation oncology at the individual, hospital, regional and state level, obtained through the post-intervention medical audit, via email or SMS depending on your preferred method of communication. This report will also include information on the number of prostate cancer cases at high-risk discussed at MDT meetings. An aggregated quarterly feedback report will additionally be provided by the Clinical Leader at an MDT meeting.

Automatic Case Flagging at MDT Meetings

You will be asked to provide consent for the names of all patients who are subject to a histopathological examination of a radical prostatectomy specimen for prostate cancer and who have extracapusular extension, positive surgical margins or seminal vesicle invasion to be submitted to the urology MDT for discussion.

Interview

At the end of the study you will be invited to participate in an audiotaped telephone interview (10-15 minutes) where you will receive feedback on results and have the opportunity to discuss reasons why changes occurred and why the intervention did or did not result in greater referral.

Risks

It is not expected that you will be exposed to any risks by taking part in this study.

Benefits

While we intend that this research study furthers medical knowledge and may improve treatment of men with locally advanced prostate cancer in the future, it may not be of direct benefit to you.

Costs

Participation in this study will not cost you anything, nor will you be paid.

Voluntary Participation

Participation in this study is entirely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your relationship with the researcher(s) or the Sax Institute, Prostate Cancer Foundation of Australia, University of Sydney, Cancer Council NSW or the NSW Agency for Clinical Innovation now or in the future.

Confidentiality

All the information collected from you for the study will be treated confidentially, and only the researchers named below will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants and individual medical records will not be identifiable in such a presentation or publication.

Further Information

If you would like to know more at any stage, please feel free to contact Bea Brown, study Research Fellow, on (02) 9188 9540 or bea.brown@saxinstitute.org.au.

Ethics Approval and Complaints

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number [X12-0388].

The conduct of this study at Royal North Shore Hospital has been authorised by the Northern Sydney Local Health District. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer on telephone number 02 9926 4560 and quote SSA/13/HAWKE/234 or protocol number 1307-229M.

Investigators and Affiliations

- Mrs Jane Bois, Sax Institute
- Dr Andrew Brooks, NSW Agency for Clinical Innovation and Westmead Hospital
- Mrs Bea Brown, Sax Institute and University of Sydney
- A/Prof Mary Haines, Sax institute and University of Sydney
- A/Prof Andrew Kneebone, Northern Clinical School, University of Sydney
- Prof Dianne O'Connell, Cancer Council NSW
- Dr David Smith, Cancer Council NSW
- Prof Jane Young, The University of Sydney

This information sheet is for you to keep.

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Improving care for men with locally advanced prostate cancer

UROLOGIST CONSENT FORM 06-03

I, ... *[name]*

of ..... *[hospital]*

have read and understood the Information for Urologists on the above-named research

study and have discussed the study with.....

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or potential side effect and of their implications as far as they are currently known by the researchers.

I understand that a research assistant will attend my office to collect specific re-identifiable (ie coded) information from the medical records of some of my prostate cancer cases (public and private), and I agree to this.

I provide consent for the names of all my patients (public and private) who are subject to a histopathological examination of a radical prostatectomy specimen for prostate cancer and who have extracapusular extension, positive surgical margins or seminal vesicle invasion to be submitted to the urology MDT for discussion.

I understand that the end of study interview will be audio taped and I agree to this.

I freely choose to participate in this study and understand that I can withdraw at any time.

I understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME: .....

SIGNATURE: .....

DATE: .....

MOBILE PHONE NO.: ..... **FAX NO.:** .....

EMAIL ADDRESS: .....

CONTACT DETAILS FOR ACCESS TO PATIENT RECORDS:

.....

.....

I PREFER TO BE CONTACTED VIA THE FOLLOWING METHOD FOR THE PURPOSES OF AUDIT AND FEEDBACK:

☐ Email ☐ Mobile phone ☐ Mail/letter ☐ Other (please specify): .....

PUBLIC PATHOLOGIST TO CONTACT FOR MDT CASE FLAGGING:.....

PRIVATE PATHOLOGIST TO CONTACT FOR MDT CASE FLAGGING:.....

Appendix VII

Clinical Leader and participating urologist interview schedules

NHMRC Partnership Project APP 1011474: Improving Care for Men with Locally Advanced Prostate Cancer

Australia New Zealand Clinical Trials Registry: ACTRN12611001251910.

Phase 2: Identify mechanisms of provider and organisational change

Clinical Leaders Interview Guide

saxinstitute

Contents

Scope of this document

This is a protocol for the post-intervention interview with Urologist Clinical Leaders involved in the CLICC study. The interview forms part of a mixed methods study to identify the mechanisms of provider and organisational change. The interview will additionally explore factors that hindered or facilitated the implementation of the CLICC study.

Procedure for data collection

Interview invitations and arrangements

The research team will contact Urologist Clinical Leaders either by telephone or email to request a convenient time to conduct the post intervention interview. This interview is included in the Clinical Leaders Terms of Reference. The interview will be conducted face-to-face in consulting rooms or by teleconference.

Outline of the Interview Guide; verbal instructions and prompts for interviewer

Introduction

(outline of verbal instructions for the meeting)

- *Introduce all of the people attending the meeting, with reference to their role in the study.*
- *Thank the Urologist Clinical Leaders for their involvement in the CLICC study.*
- *Outline the "agenda" for the meeting, in which they will be given some feedback on on their hospital and asked to think about why changes may/may not have happened.*
- *Talk them through the hospital specific report which will provide feedback obtained through the medical audit of patient records and document review.*
- *Explain that we are going to be asking the same questions of all of Urologist Clinical Leaders involved in the study to identify common themes and determine which intervention components were successful in overcoming which barriers and facilitated provider and organisation change. We will also explore any reasons why the intervention may not have worked or had limited success and areas for improvement.*
- ***This interview will be recorded and transcribed after the meeting.***

Interview Guide

Role and work in the CLICC study

- *What did you understand to be your role as a Clinical Leader in the CLICC study?*
- *Could you describe the work you undertook as a Clinical Leader for the CLICC study?*
- *Did you feel sufficiently informed about what you were expected to do?*
- *Could you describe any factors that hindered or facilitated your role in the project?*
- *As a Clinical Leader do you feel that you were able to interact with Urologists in your hospital and offer guidance and support?*

Factors facilitating or hindering the work or the project in general

- Do you think the CLICC study was successful in your hospital?
- *Were there factors that hindered or facilitated the implementation of the project?*
- *What conditions do you see as critical to the project's success/lack of success?*
- *What specific features of the CLICC study led to the desired effects?*
    - *Printed materials,*
    - *MDT video,*
    - *Feedback reports [presented at MDT meetings, individual reports]*
    - *MDT flagging of high-risk cases*
- *How important were the MDT coordinator and pathologist in facilitating the study?*
- *Did discussion of cases at the MDT meeting change your referral patterns or those of your colleagues? [In what way?]*
- *Has the study affected relationships with your colleagues?* [urologists and others]

Relevance/benefits for the participants

- *What are the main issues the project can contribute to in the care of high-risk men following radical prostatectomy?*
- *Have there been any wider changes in the pattern of care for these men for you personally, within your hospital or more generally?*
- *Why were these changes made?*

Expectations concerning the project and its effects

- *What do you think are the main benefits of this project?*
- *Do you have any concerns regarding the implementation of the project?*
- *Do you think that urologists at your site or elsewhere were gaming numbers?*
- *Will you continue any CLICC elements at your hospital?*
- *Is there anything else that you would like to elaborate on or share regarding the CLICC study?*

NHMRC Partnership Project APP 1011474: Improving Care for Men with Locally Advanced Prostate Cancer

Australia New Zealand Clinical Trials Registry: ACTRN12611001251910.

Phase 2: Identify mechanisms of provider and organisational change

Urologist Interview Guide

saxinstitute

Table of Contents

Scope of this document

This is a protocol for the post-intervention interview with the Urologists involved in the CLICC study. The interview forms part of a mixed methods study to identify the mechanisms of provider and organisational change. The interview will additionally explore factors that hindered or facilitated the implementation of the CLICC study.

Procedure for data collection

Interview invitations and arrangements

The research team will liaise with the Urologist to arrange a convenient time to conduct the post intervention interview by telephone. Participation in the interview is included in the Participant Information Statement for Urologists.

Outline of the Interview; verbal instructions and prompts for interviewer

- ***Welcome***: *"Thank you for participating in this interview. As a Urologist participant in this study, your point of view is important to us. We know that you are very busy and we greatly appreciate your contribution to this project. Participation in this interview is entirely voluntary and you are free to end the interview at any time."*

- ***Purpose:*** **"**The purpose of this interview is determine your views about the Clinician-Led Improvement in Cancer Care (CLICC) study that was roled out in your hospital during the period [date] to [date]. We are going to be asking the same questions of all of Urologists involved in the study to identify common themes and determine which intervention components were successful in overcoming which barriers and facilitated provider and organisation change. We will also explore any reasons why the intervention may not have worked or had limited success and areas for improvement".

- ***Recording:*** *This interview will be recorded and transcribed after the meeting.*

- Do you have any questions?"

- *Outline the "**agenda**" for the meeting, in which they will be given some feedback on on their hospital and asked to think about why changes may/may not have happened.*

- ***Feedback:*** *Talk them through the hospital specific report which will provide feedback obtained through the medical audit of patient records and document review.*

Question Guide

Role and work in the CLICC study

[PROMPT] The CLICC study at your hospital comprised the following elements: [printed materials, MDT video, support from Clinical Leaders, feedback reports presented at MDT meetings, individual feedback reports, MDT flagging of high-risk cases]

- *Could you tell me which components of CLICC you experienced?*

Information, facilitation

- *Did you feel sufficiently informed about what the study was hoping to achieve?*
- *The Clinical Leader at your hospital was [name]. Do you think he was supportive of CLICC? Did you have sufficient interaction with him about the study?*

Factors facilitating or hindering the work or the project in general

- *Do you think the CLICC study was successful in your hospital?*
- *What conditions do you see as critical to the project's success/lack of success?*
- *What specific features of the project do you think were most helpful?*
    - *Printed materials*
    - *MDT video*
    - *Support from Clinical Leaders*
    - *Feedback reports [presented at MDT meetings, individual feedback reports]*
    - *MDT flagging of high-risk cases*
- *Has the study affected MDT decision-making?*
- *Has the study affected relationships with your colleagues?* [urologists and others]
- *Do you have any concerns regarding the implementation of the project?*

Relevance/benefits for the participants

- *To what extent did CLICC lead to changes to your care for men at high-risk following prostatectomy? [What are the major differences in the care of these patients? Why did you make these changes?]*
- *Have there been any wider changes in the pattern of care for these men for you personally, within your hospital or more generally? [Why were these changes made?]*
- *What are the main issues CLICC can contribute to in the care of high-risk men following radical prostatectomy?*

Expectations concerning the project and its effects

- *What do you think are the main benefits of this project?*
- *Is there anything else that you would like to elaborate on or share regarding the CLICC study?*

Appendix VIII

CLICC printed resource

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Clinician-Led Improvement in Cancer Care

ADJUVANT RADIOTHERAPY FOLLOWING PROSTATECTOMY IN HIGH-RISK PATIENTS: **SUPPORTING INFORMED DECISION-MAKING**

Informed decision-making about the use of adjuvant/ salvage radiotherapy can be supported by:

- **Discussion with patients before surgery** about the possibility of adverse features being detected through pathological examination of the prostate specimen - these features do not reflect the quality of surgery.
- **Referral to a radiation oncologist** to discuss what radiation treatment would involve at the patient's local radiotherapy unit.

Referral should not mean the patient will receive radiotherapy but will allow thoughtful discussion of possible short- and long-term side effects of radiotherapy as well as the potential benefits of preventing recurrence. The decision to administer radiotherapy should be made by the patient and the multidisciplinary team with full consideration of the patient's history, values, preferences, quality of life and functional status.[1]

PATIENT PERSPECTIVES

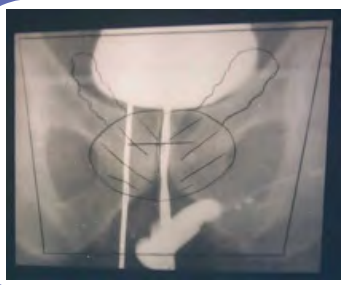
Studies from the US, UK, Canada and Europe consistently show that patients with advanced cancer are generally willing to undergo aggressive treatment and endure significant toxicity for a smaller benefit than their health providers indicated they would if in the same situation. [2-5]

Focus groups with NSW consumer representatives revealed that patients want the following information to make a decision about their treatment:

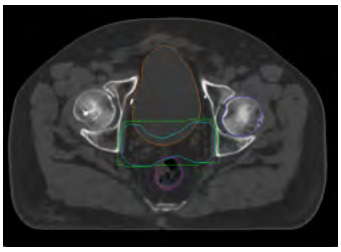
- Who will be involved in the treatment process to optimise long-term outcomes.
- The risk of short or long-term recurrence after initial treatment and management options if this occurs.
- The benefits and potential side effects of secondary treatment options.

CURRENT RADIOTHERAPY TECHNIQUES

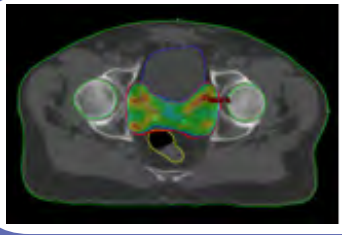
Morbidity after radiation treatment is intimately linked to the volume of normal tissue treated. Decisions regarding dose should be made by the treating physician who has full knowledge of the patient's functional status, history and toxicity tolerance.[1]



In Conventional "2D" External Beam Radiotherapy (EBRT), radiation borders are determined by bone anatomy seen on a plain X-Ray. This uncertainty results in large volumes of radiation and unnecessary irradation of surrounding organs such as the hips, rectum, bladder and small bowel. 2D EBRT was the technique of radiotherapy used in the EORTC and SWOG trials.



The current minimum standard is 3-Dimensional Conformal Radiotherapy (3D-CRT), which allows more precise delivery to the target organ as the contours of the treated area are based on CT anatomy rather than a plain X-Ray. The full dose (green line) covers the CT determined volume but cannot be precisely shaped, consequently causing additional normal tissue to be unnecessarily irradiated.



Many centres now have capacity to deliver Intensity Modulated Radiation Therapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) which can achieve tightly conformal dose distributions with the use of non-uniform radiation beams delivered by multileaf collimators, which are constantly reshaped many times during treatment.

1. Thompson et al. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. J Urol 190: 441-449, 2013. **2.** Kuchuk et al. Patient perceptions about potential side effects and benefits from chemotherapy agents (abstract 6595). J Clin Oncol 31(15S), 2013. **3.** Matsuyama et al. Why do patients choose chemotherapy near the end of life? A review of the perspectives of those facing death from cancer. J Clin Oncol 24(21): 3490-3496, 2006. **4.** Silverstri et al. Preferences for chemotherapy in patients with advanced non-small cell lung cancer: Descriptive study based on scripted reviews. BMJ 317:771-775, 1998. **5.** Elkin et al. Treatment decision-making preferences in older patients with metastatic colorectal cancer (abstract 8519). J Clin Oncol 24(18S):472s, 2006.

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ADJUVANT RADIOTHERAPY FOLLOWING PROSTATECTOMY IN HIGH-RISK PATIENTS: THE EVIDENCE

The Australian Cancer Network *Clinical Practice Guidelines*[6] recommend: *'Patients with extracapsular extension, seminal vesicle involvement or positive surgical margins should receive post-operative external beam radiation therapy within four months of surgery... The role of active surveillance and early salvage radiotherapy has not been defined.'*

American Urological Association guidelines[7] similarly recommend that *'physicians should offer adjuvant radiotherapy to patients with adverse pathologic findings at prostatectomy'.*

Data from three large randomised controlled trials (RCTs) involving over 1,800 men with locally advanced prostate cancer (EORTC[8], SWOG[9] and ARO[10]) and a number of retrospective studies demonstrate that **adjuvant radiotherapy significantly reduces the risk of biochemical recurrence**.

BENEFITS OF ADJUVANT RADIOTHERAPY (ART)

RCT	Biochemical Progression Free Survival		Local Recurrence		Clinical Progression Free Survival		Overall Survival	
	RP + ART	RP only	RP + ART	RP only	RP + ART	RP only	RP + ART	RP only
EORTC[8]	61%	38%	8.4%	17.3%*	70.3%*	64.8%	76.9%^	80.7%^
SWOG[9]	65%	36%	8%	22%	70%	49%	74%	66%
ARO[10]	61%	40%	NR	NR	NR	NR	NR	NR

Follow-up time periods: 10-years for all EORTC data; 10 years for all SWOG data except overall survival which was at 12-years; 5-years for all ARO data.

NR = Not reported RP = Radical Prostatectomy *Result was borderline significant ^Not statistically significant, p=0.05

TOXICITIES

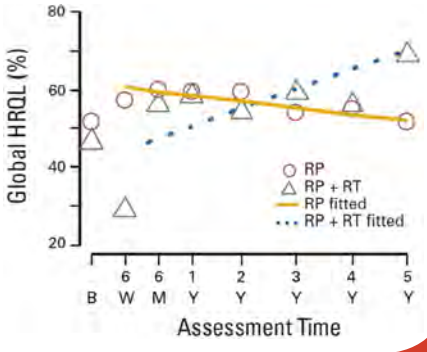
EORTC[8] and SWOG[9] used Conventional External Beam Radiotherapy (EBRT) which has been replaced with more sophisticated radiotherapy techniques. In SWOG[9], at 10-year follow-up, urethral stricture (17.8% vs 9.5%) and proctitis (3.3% vs 0%) were more common in the RP+ART arm. EORTC[8] reported no significant difference (p=0.05) in severe (Grade 3 or more) late toxicity (RP+ART 4.2% vs RP 2.6%).

The current minimum standard is 3-Dimensional Conformal Radiotherapy (3D-CRT). Toxicity data for ARO[10], the only RCT to use 3D-CRT, are reported below.

			RP + ART	RP only
ACUTE	Gastrointestinal	Rectal Grade 2	12%	NR
		Rectal Grade 3	0%	NR
	Genitourinary	Bladder Grade 3	3%	NR
LATE	Gastrointestinal	Rectal Grade 2	1.4%	0%
	Genitourinary	All Grade 2	2.0%	0%
		All Grade 3	0.7%	0%
		Urethral Stricture	1.4%	0.6%

QUALITY OF LIFE

In the SWOG[9] randomised trial, quality of life by 5 years after treatment was significantly better in the RP+ART arm.



ADJUVANT VS SALVAGE RADIOTHERAPY

The use of ART may involve irradiation of some patients who never would have had recurrent cancer. Observational studies report outcomes from 48 ART arms (n=4,043) and 137 salvage radiotherapy (SRT) arms (n=13,549). ART arms generally report lower rates of biochemical and metastatic recurrence than SRT arms.[7] There are currently no RCT data comparing ART with SRT. This is the focus of ongoing trials (RAVES, RADICALS).

RCT data presented above compare ART with observation only post-prostatectomy.

6. Australian Cancer Network 2010 *Clinical Guidelines for the Management of Men with Locally Advanced and Metastatic Prostate Cancer* **7.** American Urological Association 2013 *Adjuvant and salvage radiotherapy after prostatectomy guidelines* **8.** EORTC Trial 22911 (Van der Kwast TH, *et al. J Clin Oncol* 25(7): 4178-4186, 2007 and Bolla M, *et al. Lancet 380: 2018-2027,* 2012) **9.** SWOG S8794 (Thompson IM Jr *et al. JAMA* 296(19): 2329-2335, 2006 and Thompson IM Jr *et al. J Urol* 181: 956-962, 2009) **10.** ARO Trial 96–02/AUP AP 09/95 (Wiegel T *et al. J Clin Oncol* 27(18): 2924-2930, 2009)

Appendix IX

Feedback report templates

Clinician-Led Improvement in Cancer Care

[DATE]

Dear [NAME]

Thank you for your ongoing support and input into the CLICC study.

Please find below your initial feedback report, which provides individual, site and study level baseline data. This report complements the data presented at the [SITE} Hospital Urology MDT meeting on [DATE].

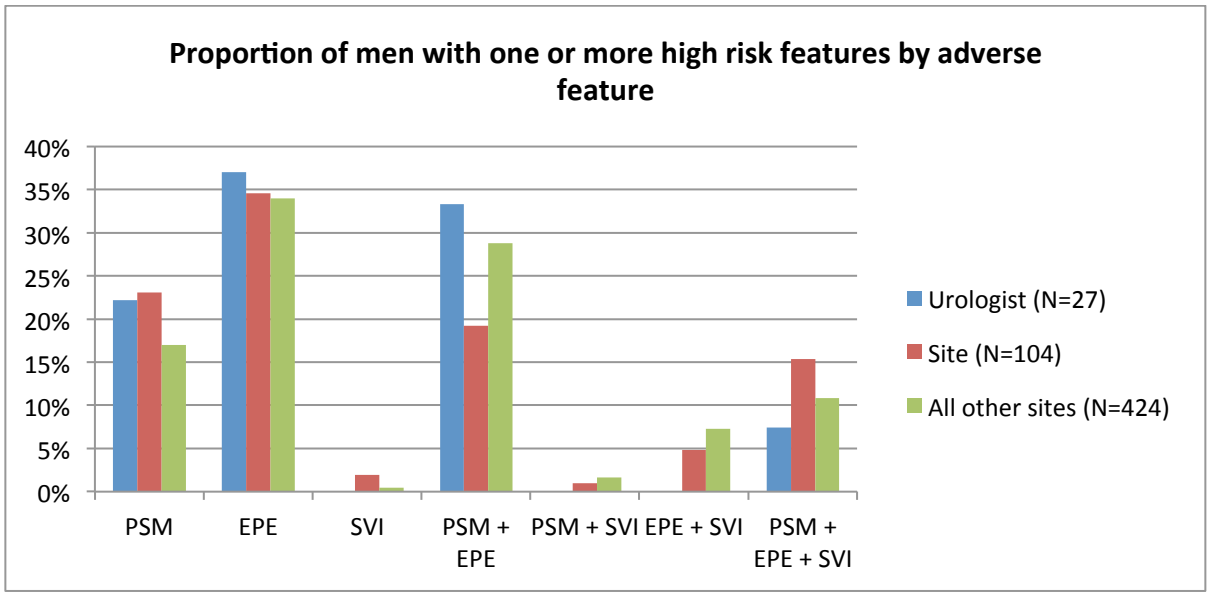
NOTES:

1. Data collection is ongoing. Figures are based on data available at the time this report was produced and are subject to change following further review of medical records.

	Urologist	Site (N=)	Study aggregate*
Prostatectomies performed 1 January 2013 – [DATE]	50	216	873
Men with one or more high risk features (PSM/EPE/SVI) post prostatectomy**	27 (54%)	104 (48%)	424 (49%)
Referrals to Radiotherapy - men with one or more high risk features	7/27 (26%)	28/104 (27%)	117/424 (28%)

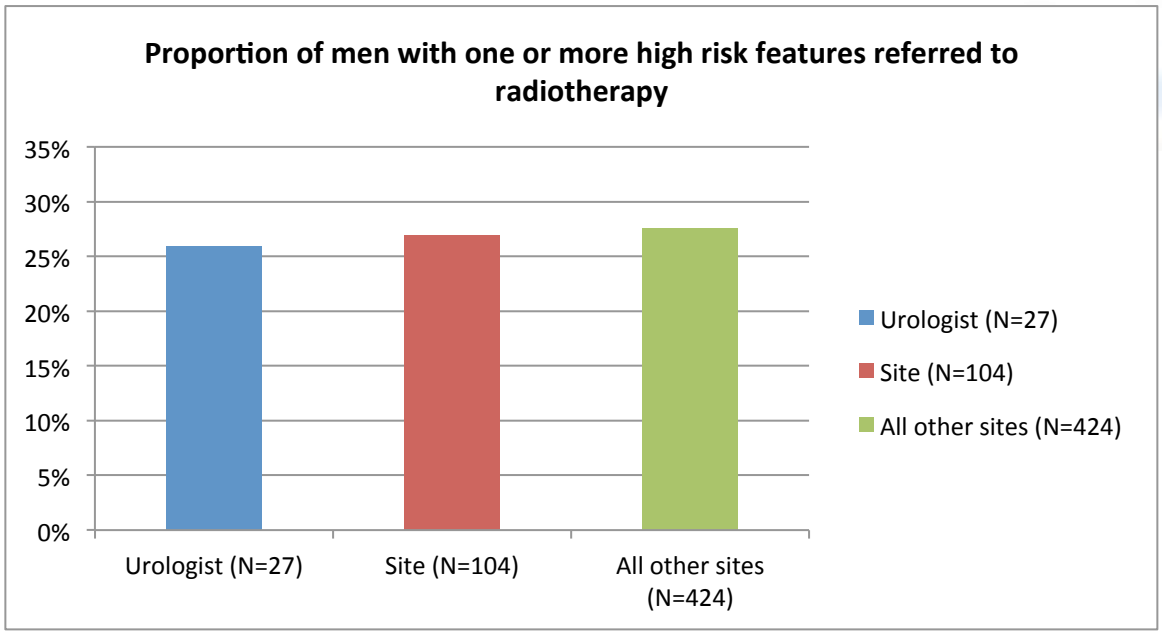
* Data collected at time of report – excluding [SITE] Hospital

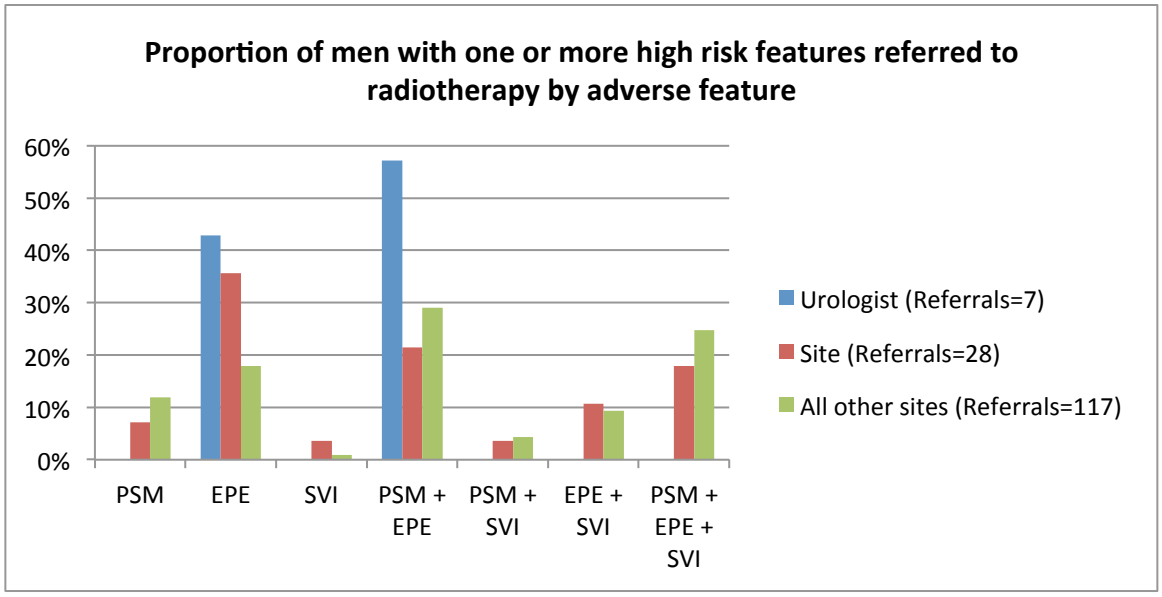
** Abbreviations: PSM – positive surgical margin, EPE – extracapsular extension, SVI – seminal vesicle invasion



Abbreviations: PSM – positive surgical margin, EPE - extracapsular extension, SVI – seminal vesicle invasion

The Sax Institute | Level 13, Building 10, 235 Jones Street ULTIMO NSW 2007 | PO Box K617 HAYMARKET NSW 1240
Website: www.saxinstitute.org.au | Direct: 02 9188 9570 | Main: 02 9188 9500 | Fax: 02 9188 9501





Abbreviations: PSM – positive surgical margin, EPE - extracapsular extension, SVI – seminal vesicle invasion

If you have any queries or would like further information please contact implementation@saxinstitute.org.au.

Kind regards,

The CLICC Team

The Sax Institute | Level 13, Building 10, 235 Jones Street ULTIMO NSW 2007 | PO Box K617 HAYMARKET NSW 1240
Website: www.saxinstitute.org.au | Direct: 02 9188 9570 | Main: 02 9188 9500 | Fax: 02 9188 9501

CLIC

Clinician-Led Improvement in Cancer Care

[DATE]

Dear [NAME],

Thank you for your ongoing support and input into the CLICC study.

This report complements the data presented at the [SITE] Hospital Urology MDT meeting on [DATE].

Note: Data collection is ongoing. Figures are based on data available at the time this report was produced and are subject to change following further review of medical records.

Table 1: MDT Flagging: Cases flagged and discussed at an MDT meeting – Post-CLICC

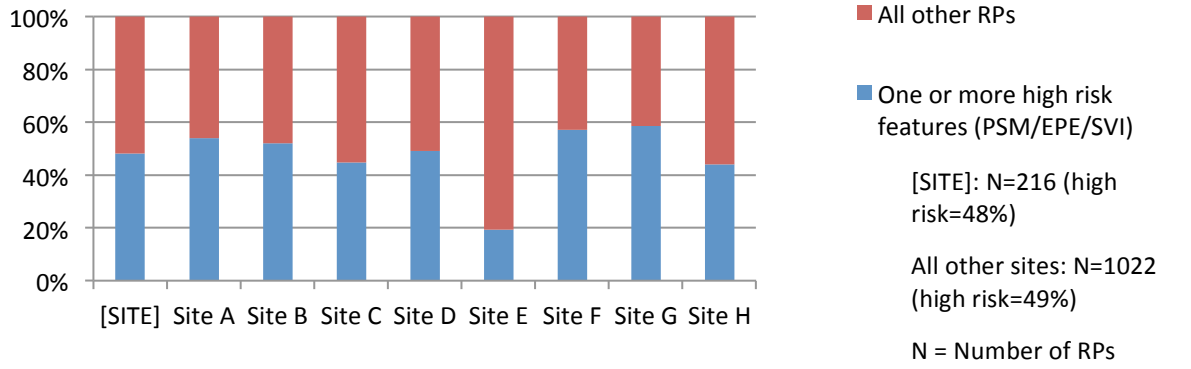
Data on MDT discussion reflects information from MDT agendas and letters of recommendation collected after the commencement of the CLICC project. Data is collected in real-time and reflects cases flagged at [SITE] Hospital from [DATE] – [DATE].

		Urologist	Site
Number of cases flagged for MDT discussion		8	20
Number of flagged cases discussed at a MDT meeting		4 (50%)	10* (50%)
MDT recommendation for cases discussed at a MDT meeting	Referral to radiation oncologist and/or discussion of radiotherapy	1 (25%)	5 (50%)
	Observation ("watch and wait")	2 (50%)	2 (20%)
	Other or unknown	1 (25%)	3 (30%)

*Discussion data missing for 10 cases; recommendation information only missing for 3 cases
Abbreviations: MDT – multidisciplinary team

Figure 1: Proportion of men with high risk features following radical prostatectomy – Pre-CLICC

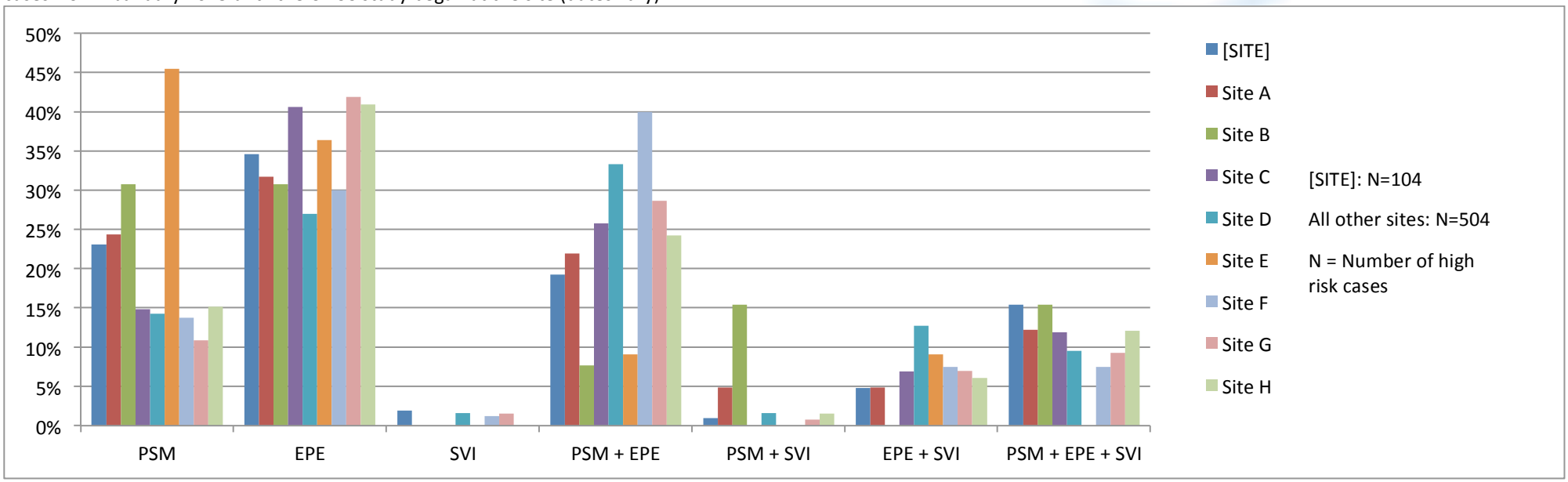
This graph shows the proportion of men who were found to have high risk features following radical prostatectomy at each site during the baseline period of the study (i.e. before the commencement of the CLICC project). Statistics are inclusive of all pre-CLICC cases from 1 January 2013 until the CLICC study began at the site (dates vary).



Abbreviations: PSM – positive surgical margin, EPE – extracapsular extension, SVI – seminal vesicle invasion, RP – radical prostatectomy

Figure 2: Proportion of men with one or more high risk features by adverse feature – Pre-CLICC

The figure shows the proportion of men who were found to have one or more high risk features upon radical prostatectomy in the baseline period (i.e. before the commencement of the CLICC project) categorised by high risk feature of the study at each site. Categories are mutually exclusive. Statistics are inclusive of all pre-CLICC cases from 1 January 2013 until the CLICC study began at the site (dates vary).



Abbreviations: PSM – positive surgical margin, EPE - extracapsular extension, SVI – seminal vesicle invasion

Figure 3: Proportion of men with high risk feature(s) referred to radiotherapy – Pre-CLICC

The figure shows the proportion of men with one or more high risk features post-radical prostatectomy in the baseline period (i.e. before the commencement of the CLICC project) who were referred to radiotherapy for consultation at each site. Statistics are inclusive of all pre-CLICC cases from 1 January 2013 until the CLICC study began at the site (dates vary).

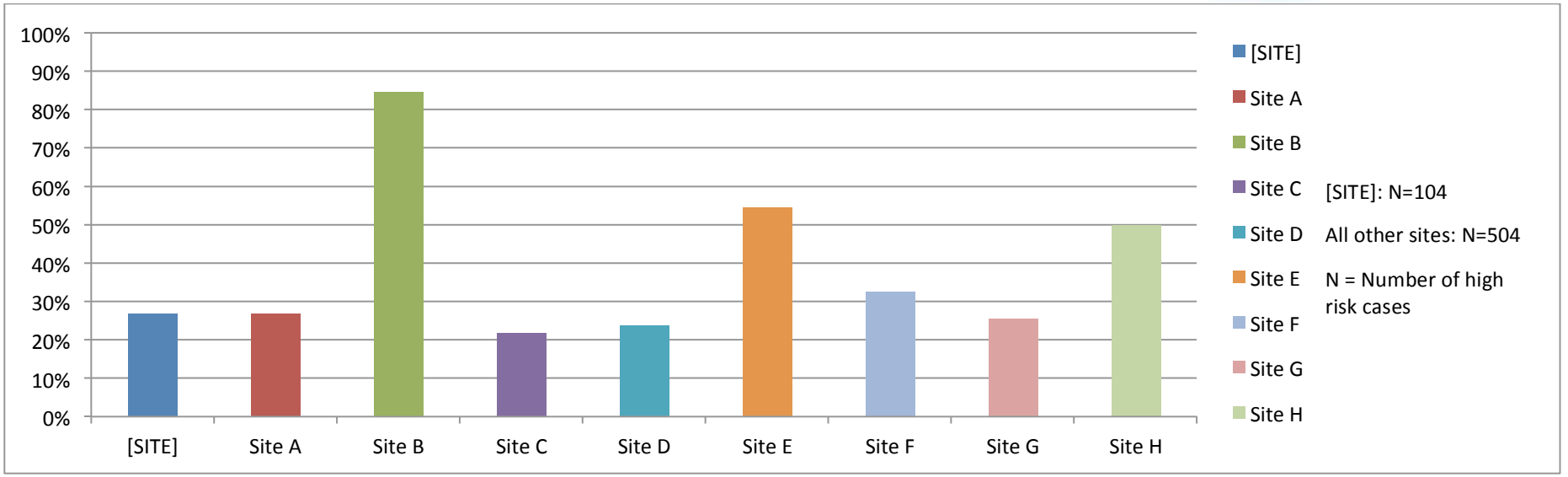


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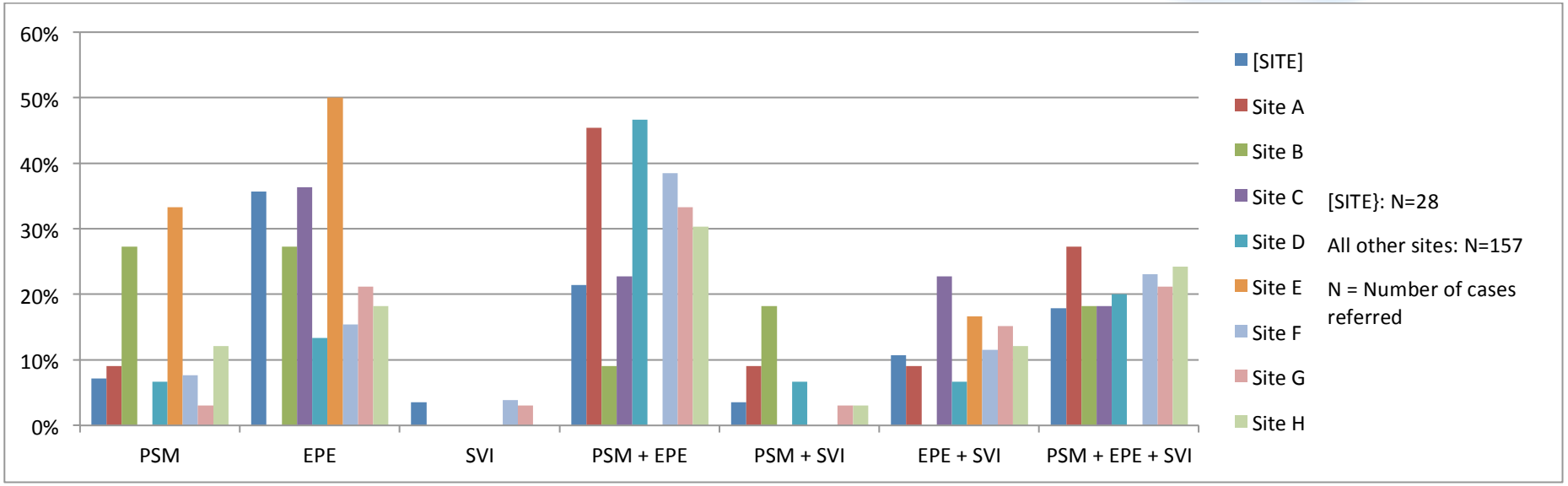
Figure 4: Proportion of men referred to radiotherapy with a specific adverse feature – Pre-CLICC

The figure shows the proportion of men referred to radiotherapy with a specific high risk feature(s) in the baseline period at each site (i.e. before the commencement of the CLICC project). E.g. at [SITE], 7% of all men referred to radiotherapy had PSM, 36% had EPE, 21% had both PSM and EPE, etc. Categories are mutually exclusive. Proportions for each site total 100%. Statistics are inclusive of all pre-CLICC cases from 1 January 2013 until the CLICC study began at the site (dates vary).



Abbreviations: PSM – positive surgical margin, EPE - extracapsular extension, SVI – seminal vesicle invasion

If you have any queries or would like further information please contact implementation@saxinstitute.org.au.

Kind regards,
The CLICC Team

Clinician-Led Improvement in Cancer Care

[DATE]

Dear [NAME],

Thank you for your ongoing support and input into the CLICC study.

Please find below your third feedback report, which compares individual, site level, and aggregate study data on your practice before and after commencement of the CLICC study. This report complements the data scheduled to be presented at the [SITE] Hospital Urology MDT meeting on [DATE].

NOTES:

1. **Referral information may not be available for patients where medical records were reviewed less than 6 months post-prostatectomy. Referral data will be verified through further record review.**
2. **Data collection is ongoing. Figures are based on data collected from patient medical records at the time this report was produced and are subject to change following further record review.**
3. **Time periods for [SITE]:**
    - **Pre-CLICC: 1 January 2013 – [DATE]**
    - **Post-CLICC: [DATE] onwards**
      (RPs for the month of [Month, Year] are excluded as this was when CLICC commenced at [SITE] and is considered to be a period of transition)

	Urologist		Site*		Study Aggregate**	
	Pre-CLICC	Post-CLICC	Pre-CLICC	Post-CLICC	Pre-CLICC	Post-CLICC
Number of radical prostatectomies performed	165	94	226	153	1061	N/A
Men with one or more high risk features (PSM/EPE/SVI) post prostatectomy***	73 (44%)	34 (36%)	101 (45%)	68 (44%)	508 (48%)	N/A
Referrals to Radiotherapy - men with one or more high risk features	1 (1%)	3 (9%)	14 (14%)	11 (16%)	158 (31%)	N/A

* Participating [SITE] urologists (N=X) ** Data collected at time of report – excluding [SITE]. Statistics are inclusive of all pre-CLICC cases (dates vary for each site). Data for the post-CLICC period were not available for all other participating sites at the time of this report. These data will be provided in your final feedback report.
*** Abbreviations: PSM – positive surgical margin, EPE – extracapsular extension, SVI – seminal vesicle invasion

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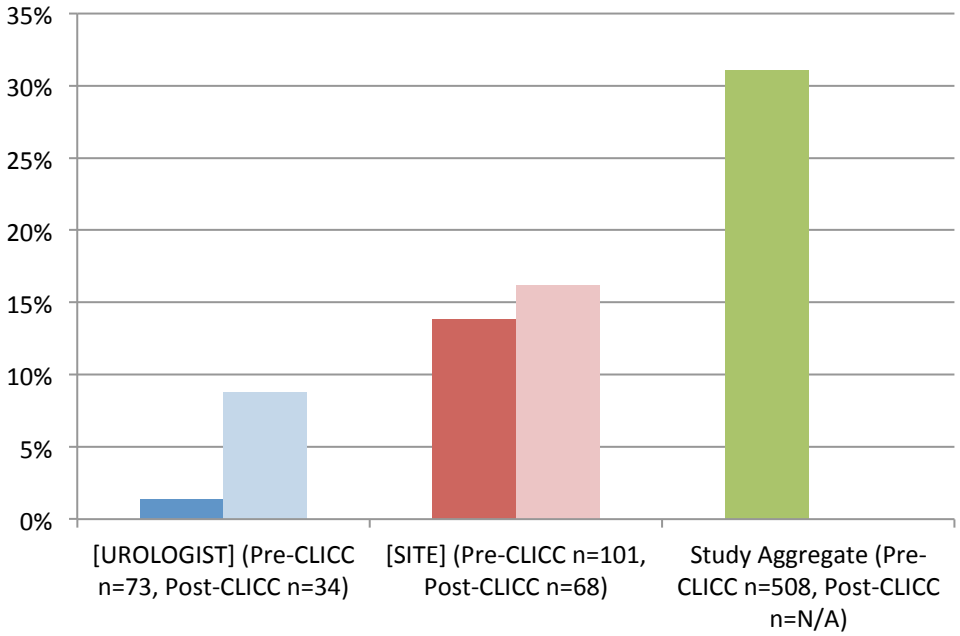
Proportion of men with one or more high risk features referred to radiotherapy



MDT case flagging: Numbers of high risk cases flagged and discussed at an MDT meeting and MDT recommendations

		Urologist	Site
Number of cases flagged for MDT discussion		22	46
Number of flagged cases discussed at an MDT meeting		18 (82%)	33 (72%)
MDT recommendation for cases discussed at an MDT meeting	Referral to radiation oncologist and/or discussion of radiotherapy	15 (83%)	25 (76%)
	Observation ("watch and wait")	3 (17%)	7 (21%)
	Other or unknown	0 (0%)	1 (3%)

Note: Data on MDT discussion reflects information provided by MDT Coordinators and is collected on an ongoing basis. Figures include all patients flagged from [DATE] to [DATE]. Data have not been provided for some flagged cases. Figures are subject to change following further record review.

Abbreviations: MDT – multidisciplinary team

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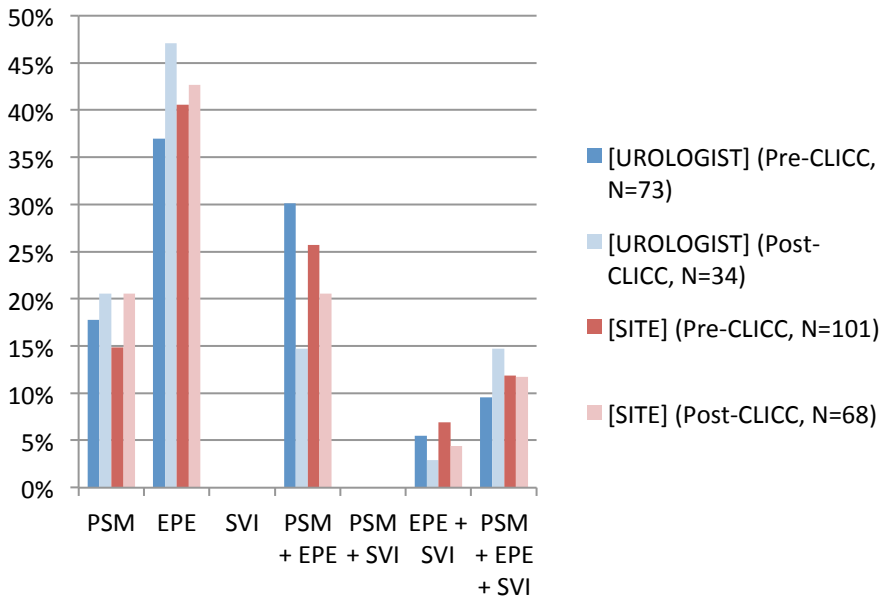
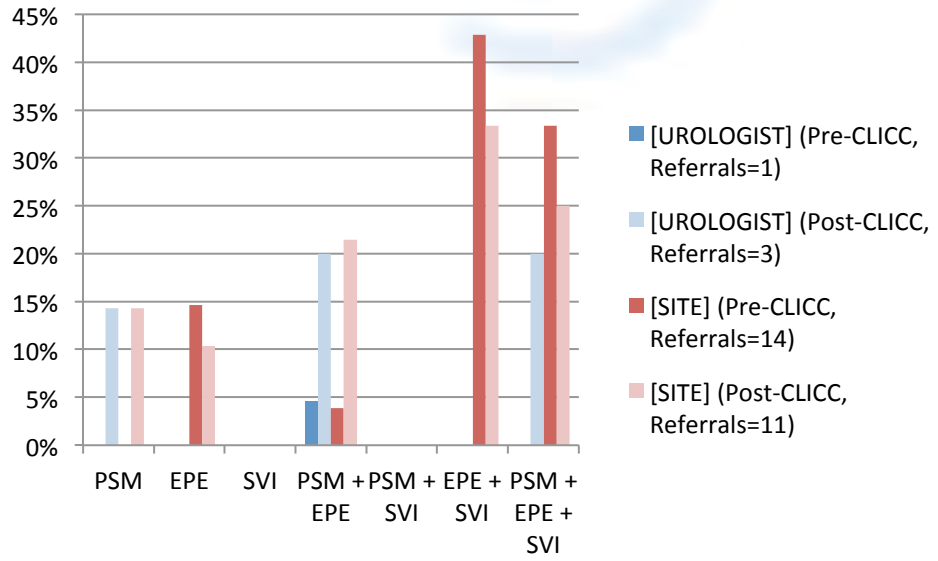
Proportion of cases with specified adverse feature(s) - pre-CLICC vs post-CLICC



Proportion of cases within each adverse feature(s) category referred to radiotherapy - pre-CLICC vs post-CLICC



Abbreviations: PSM – positive surgical margin, EPE - extracapsular extension, SVI – seminal vesicle invasion

The first figure shows the proportion of high risk cases by adverse feature(s) (e.g. in the pre-CLICC period, 15% of patients identified as high risk at [SITE] (red bar) had PSM only; 26% had PSM and EPE, etc.). The second figure shows the proportion of men within each specific adverse feature category referred to radiotherapy (e.g. in the pre-CLICC period, 0% of patients with PSM only at [SITE] (red bar absent) were referred; 4% of patients with PSM and EPE were referred, etc.).

If you have any queries or would like further information please contact implementation@saxinstitute.org.au.

Kind regards,
The CLICC Team

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[DATE]

Dear [NAME],

Thank you for your ongoing support and input into the CLICC study.

This report complements the data presented at the [SITE] Hospital Urology MDT meeting on [DATE].

Note: Data collection is ongoing. Figures are based on data available at the time this report was produced and are subject to change following further review of medical records.

Table 1: MDT Flagging: Cases flagged and discussed at an MDT meeting – Post-CLICC

Data on MDT discussion reflects information collected after the commencement of the CLICC project from pathology, MDT notes in medical records and information provided by the MDT coordinator. Data is collected in real-time and reflects cases flagged at [SITE] Hospital from [DATE] – [DATE].

		Urologist	Site	All Other Sites
Number of cases flagged for MDT discussion		48	85	225
Number of flagged cases discussed at a MDT meeting		**17 (35%)**	**36 (42%)**	**193 (86%)**
Number of flagged cases to be represented when PSA available*		14 (29%)	16 (19%)	N/A
Number of flagged cases with no information on whether they were discussed**		17 (35%)	32 (38%)	21 (9%)
MDT recommendation for cases discussed at a MDT meeting	Referral to radiation oncologist and/or discussion of radiotherapy	16 (94%)	30 (83.3%)	109 (56.5%)
	Observation ("watch and wait")	1 (6%)	3 (8.3%)	37 (19.2%)
	Other or unknown***	0 (0%)	3 (8.3%)	47 (24.3%)

*No evidence of further MDT discussion

**No evidence of MDT discussion in MDT records

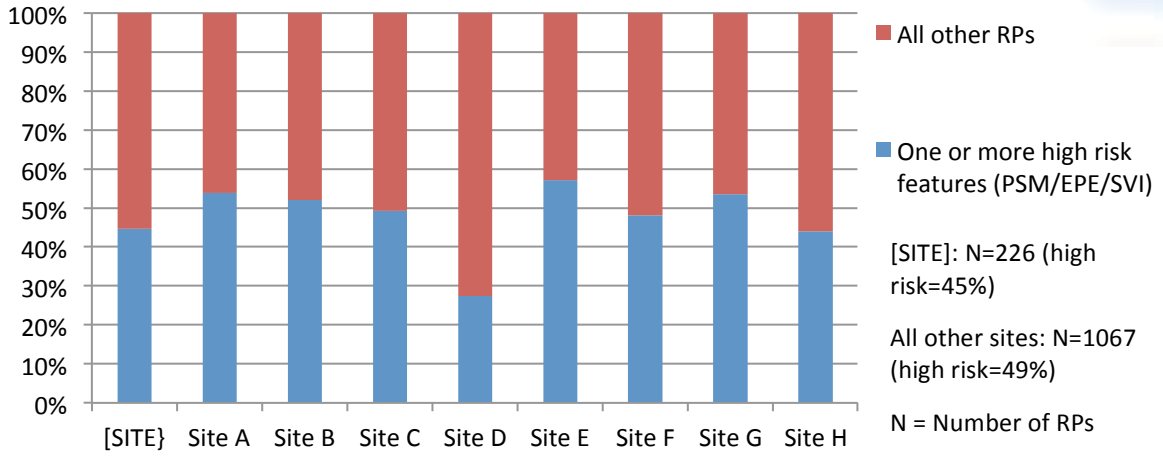
***No recommendation recorded in MDT records

Abbreviations: MDT – multidisciplinary team

Clinician-Led Improvement in Cancer Care

Figure 1: Proportion of men with high risk features following radical prostatectomy – Pre-CLICC

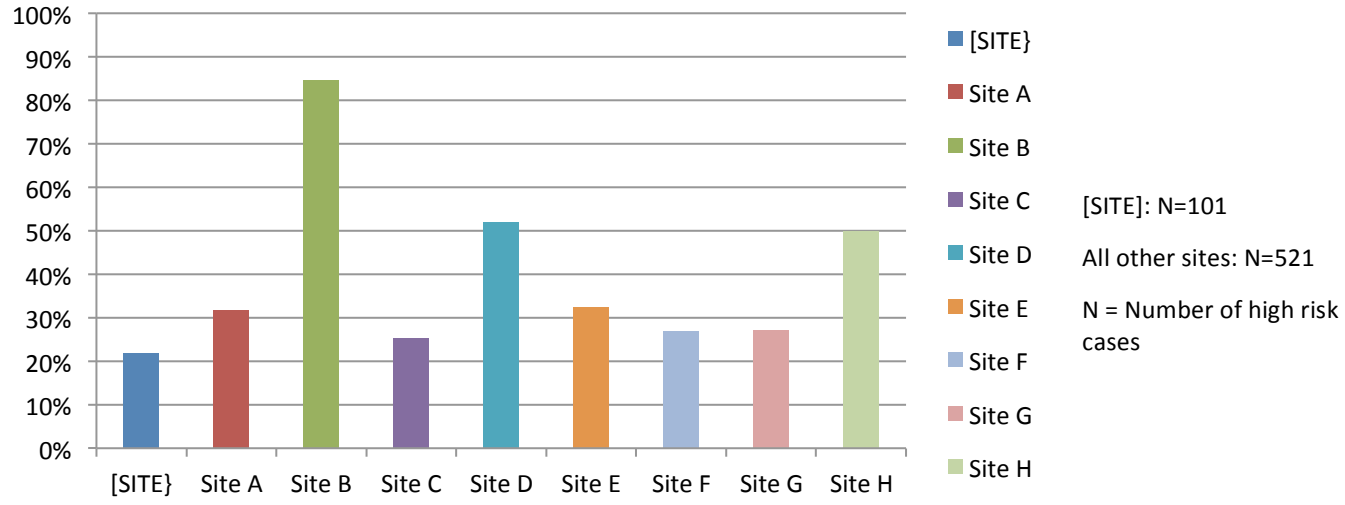
This graph shows the proportion of men who were found to have high risk features following radical prostatectomy at each site during the baseline period of the study (i.e. before the commencement of the CLICC project). Statistics are inclusive of all pre-CLICC cases from 1 January 2013 until the CLICC study began at the site (dates vary).



Abbreviations: PSM – positive surgical margin, EPE – extracapsular extension, SVI – seminal vesicle invasion, RP – radical prostatectomy

Figure 2: Proportion of men with high risk feature(s) referred to radiotherapy – Pre-CLICC

The figure shows the proportion of men with one or more high risk features post-radical prostatectomy in the baseline period (i.e. before the commencement of the CLICC project) who were referred to radiotherapy for consultation at each site. Statistics are inclusive of all pre-CLICC cases from 1 January 2013 until the CLICC study began at the site (dates vary).



If you have any queries or would like further information please contact implementation@saxinstitute.org.au.

Kind regards,

The CLICC Team

Appendix X

Clinical data collection forms

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Improving Evidence Based Care for Men with Locally Advanced Prostate Cancer

Prostate Cancer Case Data Collection Form

To be completed separately from clinical data collection form.

Patient Details

Date of Birth _____/_____/_____ (DD/MM/YYYY) Medical Records No. _____

First Name _____ Middle Name _____

Last Name _____

Address _____

_____

_____

Postcode: _____ State: _____

Doctor Details

Name of Doctor who performed RP _____

Hospital at which RP was performed _____

Name of Registrar (if present) _____

Name of Doctor managing post-surgical care (if different from above)_____

Report completed by: _____

Date report completed: _____/_____/_____ (DD/MM/YYYY)

Location: _____

Study ID Number: _____

Clinical Data Collection Form

Date Report Completed: _____(DD/MM/YYYY) Study ID Number: _____

Hospital: _____ Urologist: _____

Surgery Details

Extracapsular extension?	Positive surgical margins?	Seminal vesicle invasion?	Regional lymph node involvement at diagnosis or after surgery?
Yes / No / Unsure	Yes / No / Unsure	Yes / No / Unsure	Yes / No / Unsure

2. What was the patient's disease stage at post surgery pathology?
   Stage: _____
   Nodes: _____
   Metastasis: _____

3. Date of surgery: ____ / ____ / _____ (DD/MM/YYYY)

4. What was the surgical procedure? (Tick all that apply)
   - ☐ Laparoscopic RP
   - ☐ Retropubic RP
   - ☐ Robotic RP

5. Identified as high risk by the pathologist?
   - ☐ Yes
   - ☐ No
   - ☐ Unsure

6. What was the patient's Gleason score at post surgery pathology?
   Primary _____ Secondary _____
   Tertiary _____ Total _____
   - ☐ Gleason not assessed

7. Were there any surgical complications?
   - ☐ No
   - ☐ Yes. If yes, please specify: _____

8. Length of stay for surgery
   Date admitted ____ / ____ / ___ (DD/MM/YYYY)
   Date separated ____ / ____ / ___ (DD/MM/YYYY)

Patient Details

9. Date of Birth: _____ /_____ (MM/YYYY)

10. Postcode: _____

11. Private health insurance?
    - ☐ Private health insurance
    - ☐ Dept of Veterans' Affairs white or gold card
    - ☐ Health care concession card
    - ☐ None of these

12. Country of birth:
    - ☐ Australia
    - ☐ Another country (specify): _____

13. Existing co-morbidities:
    - ☐ None
    - ☐ Diabetes
    - ☐ Renal disease
    - ☐ Cardiovascular disease
    - ☐ Liver disease
    - ☐ COPD/Respiratory disease
    - ☐ Other (specify) _____

Diagnosis Details

14. Date of diagnosis: ____ / ____ / ___ (DD/MM/YYYY)

15. What was the patient's Gleason Score at diagnosis?
    Primary _____ Secondary _____
    Tertiary _____ Total _____
    - ☐ Gleason not assessed

16. Date and result of the last PSA test done before diagnosis (prior to hormonal therapy if received)
    Date____ / ____ / ____ PSA_____ng/mL
    - ☐ Unknown
    - ☐ Not done before diagnosis

Study ID Number: _____

Pre Prostatectomy Consult

17. Patient referred to radiation oncologist prior to prostatectomy?
- ☐ Yes i) Referred by urologist
  ii) Referred by GP
  iii) Other
  Please specify: _____
- ☐ No
- ☐ Unsure

18. Consultation with radiation oncologist prior to prostatectomy?
- ☐ Yes

  Date of consult: ___ /___ /_____ (DD/MM/YYYY)

  Radiation Oncologist

  _____

  Radiation Oncology Unit

  _____

- ☐ No

19. Decided to have radiotherapy?
- ☐ Yes
- ☐ No - no reason given
- ☐ No - reason given (specify):_____

_____

_____

Post Prostatectomy Consult

20. Date of post surgery consults with urologist:

____ / ____ / _____ (DD/MM/YYYY)

____ / ____ / _____ (DD/MM/YYYY)

____ / ____ / _____ (DD/MM/YYYY)

21. Date and result of PSA tests done since surgery

____ / ____ / _____ (DD/MM/YYYY) PSA _____ ng/ml

____ / ____ / _____ (DD/MM/YYYY) PSA _____ ng/ml

____ / ____ / _____ (DD/MM/YYYY) PSA _____ ng/ml

- ☐ Unknown

22. Urologist referred patient to radiation oncologist for consideration of adjuvant radiotherapy?
- ☐ Yes

  Date Referred: ___ /___ /_____ (DD/MM/YYYY)

  Radiation Oncologist

  _____

  Radiation Oncology Unit

  _____

- ☐ No
- ☐ Unsure

23. Urologist referred to radiotherapy as
- ☐ Adjuvant
- ☐ Salvage
- ☐ Other (specify): _____

_____

24. Urologists' reasons given for not referring to radiation oncologist for adjuvant therapy?
- ☐ No
- ☐ Yes (specify) _____

_____

_____

25. Did the patient have Hormone Therapy?
- ☐ Yes ☐ No

26. What was the course of Hormone Therapy?
- ☐ Continuous
- ☐ Intermittent

Date Started ____ /____ /_____ (DD/MM/YYYY)

Date Finished ____ /____ /_____ (DD/MM/YYYY)

Study ID Number: _____

Radiotherapy

27. Consultation with radiation oncologist, post prostatectomy?
☐ Yes ☐ No

28. Date of initial consult with radiation oncologist:

____ / ____ / _____ (DD/MM/YYYY)

29. Radiation oncologist referred to radiotherapy as
☐ Adjuvant
☐ Salvage
☐ Other (specify): _____

_____

30. Received radiotherapy post prostatectomy?
☐ Yes
☐ No – no reason given
☐ No – reason given (specify) _____

_____

31. Hospital location of radiotherapy?

_____

32. Radiotherapy

Date Started: ____ /____ /_____ (DD/MM/YYYY)

Finished: ____ /____ /_____ (DD/MM/YYYY)

Total dose:_____GY

No. of fractions: _____

MDT

33. Is there evidence that the patient was referred to a MDT?
☐ No
☐ Yes i) Noted by Clinician ☐
ii) Letter from MDT ☐
iii) Other ☐
Please specify: _____

34. Which MDT was the patient referred to?

_____

Date of MDT ____ / ____ / _____ (DD/MM/YYYY)

MDT Recommendation _____

_____

_____

_____

_____

Raves

35. Patient was referred for enrolment in RAVES trial?
☐ Yes ☐ No ☐ Unsure

36. Date of enrolment in RAVES:

____ /____ /_____ (DD/MM/YYYY)

37. Clinician's reasons given for not referring to RAVES trial?
☐ No
☐ Yes (specify) _____

_____

_____

38. Radiation oncologist's reasons given for not referring to RAVES trial?
☐ No
☐ Yes (specify) _____

_____

_____

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Improving evidence based care for men with locally advanced prostate cancer

Prostate Cancer Case Eligibility Form

Hospital: _____ Urologist: _____

All men receiving radical prostatectomy during period ____ / ____ / _____ to ____ / ____ / _____ (DD/MM/YYYY)

Medical Record Number	Date of RP	T3a extra capsular extension Y/N/U	Positive surgical margins Y/N/U	T3b seminal vesicle invasion Y/N/U	Post RP PSA level (ng/ml)	Identified as high risk by pathologist? Y/N/U	Eligible Y/N/U	Notes

Y=Yes N= No U= Unsure

Appendix XI

CLICC Clinical Leader and urologist participant surveys

CLIC

Clinician-Led Improvement in Cancer Care

NHMRC Parternship Project 1011474

Clinician Led Improvements in Cancer Care (CLICC)

Australia New Zealand Clinical Trials Registry: ACTRN12611001251910

Survey of Urologist Participants

Baseline

Background

There is currently much debate over the most appropriate treatment for high-risk prostate cancer. In particular, there are controversies in post-prostatectomy radiotherapy.

This survey aims to assess the current views and practice of urologists relating to adjuvant radiotherapy for men with locally advanced prostate cancer following radical prostatectomy.

The survey forms part of a wider study funded by the National Health and Medical Research Council (NHMRC) and the Prostate Cancer Foundation of Australia (PCFA) with the research being undertaken in partnership with The Sax Institute, University of Sydney, Cancer Council NSW and the NSW Agency for Clinical Innovation (ACI). Australia New Zealand Clinical Trials Registry: ACTRN12611001251910.

You have been selected to participate as a urologist who performs radical prostatectomy in one of the 9 NSW hospitals taking part in the study.

Participation in this survey is entirely voluntary. Submitting a completed survey is an indication of your consent to participate in the study. All aspects of the study, including the results, will be strictly confidential. Your responses will be anonymous and aggregated with those of other respondents in all reports relating to this study.

If you would like further information about the study and how your responses will be used, please read the participant information sheet provided.

1. For each scenario, we are interested in your ***current level of certainty*** about which treatment option is better. Please rate your certainty by circling the number that best reflects your view. If you are completely undecided between the two options, please circle '0'. If, however, you consider one treatment option to be superior, for whatever reason, please indicate how strongly you hold this view by circling the appropriate number on the scale.

Case 1

A 64 year old man, previously well, presented with a pre-op PSA of 12.2. Patient had radical prostatectomy 10 weeks ago. Pathology results show a Gleason 3+4=7 carcinoma with extracapsular extension and positive margins near apex over a 2mm front. Seminal vesicle and lymph nodes were clear. Post radical prostatectomy he has good urinary control. Post-op PSA 0.01. No return of erections.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

Case 2

A 58 year old man had a nerve sparing radical prostatectomy 3 months ago for a low volume Gleason 3+4=7 carcinoma (20% high grade) with 0.2mm extracapsular extension in left peripheral zone but clear surgical margins. No perineural or lymphovascular invasion. Seminal vesicles clear. 0/12 nodes involved. Post-op PSA <0.01. Some dribbling on straining but pad free. Partial erections but inadequate for intercourse.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

Case 3

A 62 year old man had a non nerve sparing prostatectomy for a clinical T3 prostate cancer with pre-op PSA of 14. Histopathology demonstrates a widespread Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension and involvement of base of right seminal vesicle. Multiple sites of positive surgical margins. Post-op PSA 0.04. No lymph node involvement. Good urinary function and no erections.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

2. Thinking about **your understanding of the current literature and evidence** for treatment of prostate cancer, please rate the extent to which you agree or disagree with each statement by ticking ONE option:

a. Immediate external irradiation after radical prostatectomy improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 prostate cancer who are at high risk of progression.

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

b. Relapse after local therapy is defined by prostate-specific antigen (PSA) values >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir PSA after radiation therapy (RT).

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

c. All high risk patients should have multidisciplinary input and be referred by their urologist to a radiation oncologist before treatment to ensure informed decision making based on discussion of the relative advantages and disadvantages of adjuvant radiotherapy or watchful waiting.

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

d. There are no data from randomised controlled trials to define the benefits of salvage radiation versus adjuvant therapy or salvage radiation versus systemic therapy (either at time of PSA rise or at time of radiographic progression).

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

3. Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiotherapy within four months of surgery, please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
The recommendation is based on a valid interpretation of the underpinning evidence						
The side-effects of adjuvant radiotherapy for patients with locally advanced prostate cancer outweigh the benefits						
There are other recommendations for the appropriate management of this patient population that conflict with this one						
Following this recommendation will lead to improved patient outcomes						
If I follow this recommendation my patients may experience unnecessary discomfort						
I support post-operative external beam radiation therapy for patients but not within four months of surgery						
If I don't follow this recommendation I may be liable for malpractice						
This recommendation is consistent with my clinical experience with this patient group						
This recommendation is consistent with the opinions of my respected clinical colleagues						
This recommendation does not reflect evidence that is emerging on this topic						
This recommendation should only be followed within fully informed decision making by the patient						

4. Following radical prostatectomy who do you believe is the person best placed to decide on the most appropriate post-operative treatment option? Please select ONE option:

- ☐ The urological surgeon is best placed to decide
- ☐ The radiation oncologist is best placed to decide
- ☐ The medical oncologist is best placed to decide
- ☐ The MDT is best placed to decide
- ☐ The patient is best placed to decide

5. Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiation therapy within four months of surgery:

a. Randomised trials have demonstrated a range of survival effects following adjuvant radiotherapy for this patient group. Thinking about the current evidence, what is the minimum survival benefit you consider acceptable for you to follow this recommendation? Please complete **ONE OPTION**.

☐☐☐ Days	☐☐☐ Months	☐☐☐ Years

b. What do you consider to be the maximum proportion of men who suffer from rectal damage or develop faecal incontinence as a result of radiotherapy for this treatment to be unacceptable? Please **place an X on the scale** below.

|_____|

0% **100%**

c. Do you have any comments on adjuvant radiotherapy following radical prostatectomy?

6.1 Gender: Male / Female

6.2 Age group: 20-30 / 31-40 / 41-50 / 51-60 / >60

6.3 Which type of practice do you have? (Circle ONE option for your major appointment):

VMO/Consultant
Salaried University Academic
Staff Specialist
Registrar/Junior Medical Officer
Other (please specify) _____

6.4 How many years have you been a practicing Urologist?

0-5 / 6-10 / 11-15 / 16–20 / 21–25 / 26-30 / >30

6.5 Do you perform Radical Prostatectomy? Yes / No

6.5a Approximately how many new patients diagnosed with prostate cancer do you care for in a **TYPICAL MONTH?** _____patients

6.5b Approximately what percentage of your practice is comprised of prostate cancer patients? _____ %

6.5c What percentage of your patients are in **ACTIVE TREATMENT** for prostate cancer (as opposed to routine surveillance or follow up)? _____ %

6.6 Which of the following best describes the location in which you practice? (Circle ONE option only):

Capital city
Other major urban area
Rural
Remote
Other

6.7 In which setting do you treat the MAJORITY of prostate cancer patients: (Circle ONE option only):

Teaching hospital
Public, non-teaching hospital
Private hospital

THANK YOU FOR YOUR TIME

CLIC

Clinician-Led Improvement in Cancer Care

NHMRC Parternship Project 1011474

Clinician Led Improvements in Cancer Care (CLICC)

Australia New Zealand Clinical Trials Registry: ACTRN12611001251910

Survey of Urologist Participants

End of Study

Background

There is currently much debate over the most appropriate treatment for high-risk prostate cancer. In particular, there are controversies in post-prostatectomy radiotherapy.

This survey aims to assess the current views and practice of urologists relating to adjuvant radiotherapy for men with locally advanced prostate cancer following radical prostatectomy.

The survey forms part of a wider study funded by the National Health and Medical Research Council (NHMRC) and the Prostate Cancer Foundation of Australia (PCFA) with the research being undertaken in partnership with The Sax Institute, University of Sydney, Cancer Council NSW and the NSW Agency for Clinical Innovation (ACI). Australia New Zealand Clinical Trials Registry: ACTRN12611001251910.

You have been selected to participate as a urologist who performs radical prostatectomy in one of the 9 NSW hospitals taking part in the study.

Participation in this survey is entirely voluntary. Submitting a completed survey is an indication of your consent to participate in the study. All aspects of the study, including the results, will be strictly confidential. Your responses will be anonymous and aggregated with those of other respondents in all reports relating to this study.

If you would like further information about the study and how your responses will be used, please read the participant information sheet provided.

1. For each scenario, we are interested in your ***current level of certainty*** about which treatment option is better. Please rate your certainty by circling the number that best reflects your view. If you are completely undecided between the two options, please circle '0'. If, however, you consider one treatment option to be superior, for whatever reason, please indicate how strongly you hold this view by circling the appropriate number on the scale.

Case 1

A 64 year old man, previously well, presented with a pre-op PSA of 12.2. Patient had radical prostatectomy 10 weeks ago. Pathology results show a Gleason 3+4=7 carcinoma with extracapsular extension and positive margins near apex over a 2mm front. Seminal vesicle and lymph nodes were clear. Post radical prostatectomy he has good urinary control. Post-op PSA 0.01. No return of erections.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

Case 2

A 58 year old man had a nerve sparing radical prostatectomy 3 months ago for a low volume Gleason 3+4=7 carcinoma (20% high grade) with 0.2mm extracapsular extension in left peripheral zone but clear surgical margins. No perineural or lymphovascular invasion. Seminal vesicles clear. 0/12 nodes involved. Post-op PSA <0.01. Some dribbling on straining but pad free. Partial erections but inadequate for intercourse.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

Case 3

A 62 year old man had a non nerve sparing prostatectomy for a clinical T3 prostate cancer with pre-op PSA of 14. Histopathology demonstrates a widespread Gleason 4+4=8 carcinoma with multifocal sites of extracapsular extension and involvement of base of right seminal vesicle. Multiple sites of positive surgical margins. Post-op PSA 0.04. No lymph node involvement. Good urinary function and no erections.

Watchful waiting is preferable					Undecided					Adjuvant radiotherapy is preferable
5	4	3	2	1	0	1	2	3	4	5

2. Thinking about **your understanding of the current literature and evidence** for treatment of prostate cancer, please rate the extent to which you agree or disagree with each statement by ticking ONE option:

a. Immediate external irradiation after radical prostatectomy improves biochemical progression-free survival and local control in patients with positive surgical margins or pT3 prostate cancer who are at high risk of progression.

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

b. Relapse after local therapy is defined by prostate-specific antigen (PSA) values >0.2 ng/ml following radical prostatectomy (RP) and >2 ng/ml above the nadir PSA after radiation therapy (RT).

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

c. All high risk patients should have multidisciplinary input and be referred by their urologist to a radiation oncologist before treatment to ensure informed decision making based on discussion of the relative advantages and disadvantages of adjuvant radiotherapy or watchful waiting.

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

d. There are no data from randomised controlled trials to define the benefits of salvage radiation versus adjuvant therapy or salvage radiation versus systemic therapy (either at time of PSA rise or at time of radiographic progression).

Strongly disagree	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Don't know**
☐	☐	☐	☐	☐

3. Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiotherapy within four months of surgery, please rate the extent to which you agree or disagree with each statement by placing an **X** in **ONE** box:

	strongly disagree	disagree	neither agree nor disagree	agree	strongly agree	Don't know
The recommendation is based on a valid interpretation of the underpinning evidence						
The side-effects of adjuvant radiotherapy for patients with locally advanced prostate cancer outweigh the benefits						
There are other recommendations for the appropriate management of this patient population that conflict with this one						
Following this recommendation will lead to improved patient outcomes						
If I follow this recommendation my patients may experience unnecessary discomfort						
I support post-operative external beam radiation therapy for patients but not within four months of surgery						
If I don't follow this recommendation I may be liable for malpractice						
This recommendation is consistent with my clinical experience with this patient group						
This recommendation is consistent with the opinions of my respected clinical colleagues						
This recommendation does not reflect evidence that is emerging on this topic						
This recommendation should only be followed within fully informed decision making by the patient						

4. Following radical prostatectomy who do you believe is the person best placed to decide on the most appropriate post-operative treatment option? Please select ONE option:

- ☐ The urological surgeon is best placed to decide
- ☐ The radiation oncologist is best placed to decide
- ☐ The medical oncologist is best placed to decide
- ☐ The MDT is best placed to decide
- ☐ The patient is best placed to decide

5. Considering the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiation therapy within four months of surgery:

a. Randomised trials have demonstrated a range of survival effects following adjuvant radiotherapy for this patient group. Thinking about the current evidence, what is the minimum survival benefit you consider acceptable for you to follow this recommendation? Please complete **ONE OPTION**.

☐☐☐	☐☐☐	☐☐☐
Days	Months	Years

b. What do you consider to be the maximum proportion of men who suffer from rectal damage or develop faecal incontinence as a result of radiotherapy for this treatment to be unacceptable? Please **place an X on the scale** below.

|_____|

0% **100%**

c. Do you have any comments on adjuvant radiotherapy following radical prostatectomy?

THANK YOU FOR YOUR TIME

SURVEY SCORING KEY AND SUMMARY SCORE CALCULATION METHOD

Survey domains:

1. Attitudes towards clinical practice guidelines in general (USANZ hard copy survey Q2.2, CLICC participant survey Q3)
2. Attitudes towards the recommendation for patients with extracapsular extension, seminal vesicle involvement or positive surgical margins to receive post-operative external beam radiotherapy within four months of surgery (USANZ hard copy survey Q2.5, CLICC participant survey Q3)

Responses for questions in the above domains were scored as follows:

1 = strongly disagree
2 = disagree
3 = neither agree nor disagree
4 = agree
5 = strongly agree
Don't know coded as missing

A summary score was calculated from respondents' total scores on questions within each domain by summing the values for all non-missing items and dividing by the total number of items completed to assess overall attitudes and beliefs relating to clinical practice guidelines in general and towards the recommendation for adjuvant radiotherapy.

<u>General Summary Score</u>

A summary score for attitudes towards guidelines in general was calculated as the sum of scores on questions 10 – 21 inclusive.

Negatively worded items (Qs 14, 15, 16, 17, 18, 20, 21) were reverse coded around the midpoint into new variables (Q14r, Q15r, Q16r, Q17r, Q18r, Q20r, Q21r) such that:

1 = strongly agree
2 = agree
3 = neither agree nor disagree
4 = disagree
5 = strongly disagree
Don't know coded as missing

General summary score = (Q10 + Q11 + Q13 + Q14r +Q15r + Q16r + Q17r + Q18r + Q19 + Q20r + Q21r) / number of items completed.

ART Summary Score

A summary score for attitudes towards the recommendation for adjuvant radiotherapy (ART) was calculated as the sum of scores on questions 25 – 35 inclusive.

Negatively worded items (Qs 26, 27, 29, 30, 34) were reverse coded around the midpoint into new variables (Q26r, Q27r, Q29r, Q30r, Q34r) such that:

1 = strongly agree
2 = agree
3 = neither agree nor disagree
4 = disagree
5 = strongly disagree
Don't know coded as missing

ART summary score = (Q25 + Q26r + Q27r + Q28 + Q29r + Q30r + Q31 + Q32 + Q32 + Q34r + Q35) / number of items completed.

Appendix XII

Ethical and governance approvals

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
Human Research Ethics Committee
Web: http://sydney.edu.au/ethics/
Email: ro.humanethics@sydney.edu.au

Address for all correspondence:
Level 6, Jane Foss Russell Building - G02
The University of Sydney
NSW 2006 AUSTRALIA

8 February 2012

A/Prof. Mary Haines
Sax Institute
Level 8, Building 10
235 Jones Street
Ultimo NSW 2007
Email: Mary.Haines@saxinstitute.org.au

Dear A/Prof Haines

RE: NHMRC partnership grant APP1011474 – Improving evidence based case for locally advance prostate cancer (CIA: Haines) – request to confirm that ethics approval is not required for year 1 development phase (2011)

Thank you for your letter dated 5 January 2012 where you outline a revised start date of your research project due to protracted contractual negotiations and we note that you have been granted a deferred start date by the NHMRC of 1 November 2011. We note you will be required to seek ethics approval prior to commencing phases 1 and 2 of your study, and understand this will take place in July 2012.

We re-confirm that you do not require ethics approval for the development phase, as the activities undertaken are deemed to be of negligible risk according to National Statement of Ethical Conduct in Human Research (2007).

We understand that the development phase of the study will involve the following activities:

- Recruitment of staff
- Recruitment of clinicians to be involved in the study
- Designing the intervention
- Developing the data collection tools
- Preparation of an ethics submission

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Margaret Faedo
Manager, Human Ethics
On behalf of the HREC

cc: Yamini Sindoba Sandiran

Manager Human Ethics
Dr Margaret Faedo
T: +61 2 8627 8176
E: margaret.faedo@sydney.edu.au

Human Ethics Secretariat:
Ms Patricia Engelmann **T:** +61 2 8627 8172 **E:** patricia.engelmann@sydney.edu.au
Ms Karen Greer **T:** +61 2 8627 8171 **E:** karen.greer@sydney.edu.au
Ms Kala Retnam **T:** +61 2 8627 8173 **E:** kala.retnam@sydney.edu.au

ABN 15 211 513 464
CRICOS 00026A

THE UNIVERSITY OF SYDNEY

RESEARCH INTEGRITY
Human Research Ethics Committee
Web: http://sydney.edu.au/ethics/
Email: ro.humanethics@sydney.edu.au

Address for all correspondence:
Level 6, Jane Foss Russell Building - G02
The University of Sydney
NSW 2006 AUSTRALIA

Ref: [MF/KFG]

18 September 2012

A/Prof Mary Haines
The Sax Institute
School of Public Health
The University of Sydney
Email: mary.haines@saxinstitute.org.au

Dear A/Prof Haines

Thank you for your correspondence dated 12 September 2012 addressing comments made to you by the Human Research Ethics Committee (HREC).

I am pleased to inform you that with the matters now addressed your protocol entitled **"Improving evidence based care for men with locally advanced prostate cancer - Survey of Australian Urologists"** has been approved.

Details of the approval are as follows:

Protocol No.: **15222**

Approval Date: **17 September 2012**

First Annual Report Due: **30 September 2013**

Authorised Personnel: **A/Prof Mary Haines**
Prof Jane Young
Mrs Bernadette Brown
Mrs Jane Bois

Documents Approved:

Document	Version Number	Date
Information for Participants	Version 2	10 September 2012
Implied Consent Wording	Version 2	10 September 2012
Competition Entry Form	Version 1	20 August 2012
Survey of Urologists	n/a	n/a
Invitation letter from CI	Version 1	9 August 2012
Email invite to websurvey participants	Version 1	16 August 2012
Email reminder to websurvey participants	Version 1	9 August 2012

HREC approval is valid for four (4) years from the approval date stated in this letter and is granted pending the following conditions being met:

THE UNIVERSITY OF SYDNEY

Condition/s of Approval

- Continuing compliance with the National Statement on Ethical Conduct in Research Involving Humans.
- Provision of an annual report on this research to the Human Research Ethics Committee from the approval date and at the completion of the study. Failure to submit reports will result in withdrawal of ethics approval for the project.
- All serious and unexpected adverse events should be reported to the HREC within 72 hours.
- All unforeseen events that might affect continued ethical acceptability of the project should be reported to the HREC as soon as possible.
- Any changes to the protocol including changes to research personnel must be approved by the HREC by submitting a Modification Form before the research project can proceed.

Chief Investigator / Supervisor's responsibilities:

1. You must retain copies of all signed Consent Forms (if applicable) and provide these to the HREC on request.
2. It is your responsibility to provide a copy of this letter to any internal/external granting agencies if requested.

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Margaret Faedo
Manager, Human Ethics
On behalf of the HREC

cc: *Bea Brown*
bea.brown@saxinstitute.org.au

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Research Integrity
Human Research Ethics Committee

Friday, 27 March 2015

Assoc Prof Mary Haines
School of Public Health: Public Health; Sydney Medical School
Email: mary.haines@saxinstitute.org.au

Dear Mary

Your request to modify the below project submitted on 17 February 2015 was considered by the Executive of the Human Research Ethics Committee at its meeting on 17 March 2015

The Committee had no ethical objections to the modification/s and has approved the project to proceed.

Details of the approval are as follows:

Project No.:	**2012/2403**
Project Title:	**Improving evidence based care for men with locally advanced prostate cancer - Survey of Australian Urologists**
Revised Completion Date:	**30 September 2016**

Please do not hesitate to contact Research Integrity (Human Ethics) should you require further information or clarification.

Yours sincerely

Dr Fiona Gill
Chair
Executive, Human Research Ethics Committee

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
FACSIMILE: (02) 9515 7176
EMAIL: lesley.townsend@sswahs.nsw.gov.au
REFERENCE: X12-0388 & HREC/12/RPAH/584

NSW GOVERNMENT Health
Sydney
Local Health District

1 February 2013

A/Professor M Haines
PO Box K617
HAYMARKET NSW 1240

Dear Professor Haines,

Re: Protocol No X12-0388 & HREC/12/RPAH/584 - "Improving evidence based care for men with locally advanced prostate cancer – A randomised phased trial of clinical guideline implementation through a clinical network"

The Executive of the Ethics Review Committee, at its meeting of 31 January 2013, considered your correspondence of 14 January 2013. In accordance with the decision made by the Ethics Review Committee, at its meeting of 12 December 2012, ethical approval is granted.

The proposal meets the requirements of the *National Statement on Ethical Conduct in Human Research.*

This approval includes the following:

- Study Protocol (Version 1, 20 November 2012)
- Authorship Principles and Policy (Version 1, 27 November 2012)
- Clinical Leader Letter of Invitation (Version 1, 26 November 2012)
- Clinical Leaders - Terms of Reference (Version 1, 27 November 2012)
- Clinical Leader Information Statement (Master Version 2, 7 January 2013)
- Clinical Leader Consent Form (Master Version 2, 7 January 2013)
- Clinical Leader Interview Guide (Version 1, 28 November 2012)

- Urologist Letter of Invitation (Version 1, 26 November 2012)
- Urologist Information Statement (Master Version 2, 7 January 2013)
- Urologist Consent Form (Master Version 2, 7 January 2013)
- Urologist Interview Guide (Version 1, 28 November 2012)
- Survey of Urologist Participants (Version 1, 28 November 2012)
- Prostate Cancer Case Eligibility Form (Version 1, 27 November 2012)
- Prostate Cancer Case Data Collection Form (Version 1, 27 November 2012)
- Clinical Data Collection Form (Version 1, 27 November 2012)
- Nationwide Survey of Urologist Members of USANZ (Version 1, 28 September 2012)

You are asked to note the following:

- **This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.**

  On the basis of this ethics approval, authorisation may be sought to conduct this study within any NSW public health organisation and/or within any private organisation which has entered into an appropriate memorandum of understanding with the Sydney Local Health District, Sydney Local Health Network or the Sydney South West Area Health Service.

  The Committee noted that authorisation will be sought to conduct the study at the following sites:

  - [redacted]

- This approval is valid for four years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in February 2014. If recruitment is ongoing at the conclusion of the four year approval period, a full re-submission will be required. Ethics approval will continue during the re-approval process.

- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.

- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.

- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney Local Health District website.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Yours sincerely,

Lesley Townsend

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXCOR\13-01

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH DEVELOPMENT OFFICE
ROYAL PRINCE ALFRED HOSPITAL
CAMPERDOWN NSW 2050

TELEPHONE: (02) 9515 6766
FACSIMILE: (02) 9515 7176
EMAIL: lesley.townsend@sswahs.nsw.gov.au
REFERENCE: X12-0388 & HREC/12/RPAH/584
9.29/SEP13

NSW GOVERNMENT Health
Sydney
Local Health District

2 September 2013

A/Professor M Haines
The Sax Institute
PO Box K617
HAYMARKET NSW 1240

Dear Professor Haines,

Re: Protocol No X12-0388 & HREC/12/RPAH/584 - "Improving evidence based care for men with locally advanced prostate cancer – A randomised phased trial of clinical guideline implementation through a clinical network"

Thank you, on behalf of the Ethics Review Committee, for your correspondence of 5 August 2013. The following site changes were noted with thanks:

- Withdrawal of [redacted] as sites
- Inclusion of [redacted] as a site, subject to governance authorisation. Please advise the name of the Principal Investigator for the site as soon as this has been determined.

Yours sincerely,

Lesley Townsend

Lesley Townsend
Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXECOR\13-08

NSW GOVERNMENT
Health
South Eastern Sydney Local Health District
RESEARCH SUPPORT OFFICE

Room G71, East Wing
Edmund Blacket Building
Prince of Wales Hospital
Cnr High & Avoca Streets
RANDWICK NSW 2031
Tel: 02-9382 3587
Fax: 02-9382 2813

17 July 2013

[redacted]

Dear Dr [redacted]

RE: SSA Ref: **13/G/217**
HREC/AURED Ref: **HREC/12/RPAH/584**
Project title: **Improving evidence based care for men with locally advanced prostate cancer - A randomised phased trial of clinical guideline implementation through a clinical network.**

I refer to your Site Specific Assessment application for the above titled project. I am pleased to advise that on 16 July 2013 the Director of Operations granted authorisation for the above project to commence at the [redacted] Hospital.

The following conditions apply to this research project. These are additional to any conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the Research Governance Officer.

2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the Research Governance Officer.

If you have any queries relating to the above please contact the Research Support Office on 9382 3587.

Yours sincerely

Tali Leizer
Research Governance Officer

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

NSW GOVERNMENT Health
Hunter New England
Local Health District

7 August 2013

[redacted]

Dear Dr [redacted]

Re: Improving evidence based care for men with locally advanced prostate cancer – a randomised phased trial of clinical guideline implementation through a clinical network

NSW HREC Reference No: HREC/12/RPAH/584
SSA Reference No: SSA/13/HNE/300

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following sites:

- [redacted]**Hospital**

As part of the process of the governance review process for this protocol, the following documents were reviewed for use at the John Hunter Hospital site:

- For the Study Protocol (Version 1 dated 20 November 2012);
- For the Authorship Principles and Policy (Version 1 dated 27 November 2012);
- For the Clinical Leader Letter of Invitation (Version 1 dated 26 November 2012);
- For the Clinical Leaders – Terms of Reference (Version 1 dated 27 November 2012);
- For the Clinical Leader Information Statement (Master Version 2 dated 7 January 2013);
- For the Clinical Leader Consent Form (Master Version 2 dated 7 January 2013);
- For the Clinical Leader Interview Guide (Version 1 dated 28 November 2012);
- For the Urologist Letter of Invitation (Version 1 dated 26 November 2012);
- For the Urologist Information Statement (Master Version 2 dated 7 January 2013);
- For the Urologist Consent Form (Master Version 2 dated 7 January 2013);
- For the Urologist Interview Guide (Version 1 dated 28 November 2012);
- For the Survey of Urologist Participants (Version 1 dated 27 November 2012);
- For the Prostate Cancer Case Eligibility Form (Version 1 dated 27 November 2012);
- For the Prostate Cancer Case Data Collection Form (Version 1 dated 27 November 2012);
- For the Clinical Data Collection Form (Version 1 dated 27 November 2012); and
- For the Nationwide Survey of Urologist Members of USANZ (Version 1 dated 18 September 2012)

Hunter New England Research Ethics & Governance Unit
(Locked Bag No 1)
(New Lambton NSW 2305)
Telephone (02) 49214 950 Facsimile (02) 49214 818
Email: hnehrec@hnehealth.nsw.gov.au
http://www.hnehealth.nsw.gov.au/research_ethics_and_governance_unit

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to the research governance officer;
2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to the research governance officer.

Yours faithfully

Dr Nicole Gerrand
Research Governance Officer
Hunter New England Local Health District

Hunter New England Research Ethics & Governance Unit
(Locked Bag No 1)
(New Lambton NSW 2305)
Telephone (02) 49214 950 Facsimile (02) 49214 818
Email: hnehrec@hnehealth.nsw.gov.au
http://www.hnehealth.nsw.gov.au/research_ethics_and_governance_unit

NSW GOVERNMENT Health
South Eastern Sydney Local Health District

RESEARCH SUPPORT OFFICE

Room G71, East Wing
Edmund Blacket Building
Prince of Wales Hospital
Cnr High & Avoca Streets
RANDWICK NSW 2031
Tel: 02-9382 3587
Fax: 02-9382 2813

3 October 2013

[redacted]

Dear [redacted]

RE: SSA Ref: **13/G/323**
HREC/AURED Ref: **HREC/12/RPAH/584**
Project title: **Improving evidence based care for men with locally advanced prostate cancer - A randomised phased trial of clinical guideline implementation through a clinical network.**

I refer to your Site Specific Assessment application for the above titled project. I am pleased to advise that on 3 October 2013 the Director of Operations granted authorisation for the above project to commence at the [redacted] Hospital.

The following conditions apply to this research project. These are additional to any conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the lead HREC for review, are copied to the Research Governance Officer.
2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the Research Governance Officer.

If you have any queries relating to the above please contact the Research Support Office on 9382 3587.

Yours sincerely

R Smallcombe

Robert Smallcombe
Research Governance Officer

Prince of Wales Hospital
Community Health Services
Barker Street
Randwick NSW 2031

NSW GOVERNMENT | Health
Central Coast
Local Health District

17 September 2013

[redacted]

Dear Dr [redacted]

RE: **0513-021C:** Improving evidence based care for men with locally advanced prostate cancer - a randomised phased trial of clinical guideline implementation through a clinical network
Site Investigators; [redacted]
Site Contact; *TBA*

SPONSOR PROTOCOL NUMBER: *X12-0388*

I am pleased to inform you that the delegate of the Chief Executive authorised the Site Specific Assessment for the above study on behalf of Central Coast Local Health District (CCLHD).

It is noted that this approval covers the following NSW Public Health site:

- [redacted] **Hospital**

The documentation included in the approval is as follows:

1. SSA Form version AU2/B19216
2. NEAF submission code AU/1/034017
3. HREC approval letter dated 1st February 2013
4. CV for Principal Investigator – Finlay Macneil
5. Study Protocol – Version 1.0, 20th November 2012
6. Authorship Principles and Policy – Version 1, 27 November 2012
7. Clinical Leader Letter of Invitation – Version 1, 26 November 2012
8. Clinical Leaders – Terms of Reference – Version 1, 27 November 2012
9. Clinical Leader Information Statement – Master Version 2, 7 January 2013
10. Clinical Leader Consent Form – Master Version 2, 7 January 2013
11. Clinical Leader Interview Guide – Version 1, 28 November 2012
12. Urologist Letter of Invitation – Version 1, 26 November 2012
13. Urologist Information Statement – Master Version 2, 7 January 2013
14. Urologist Consent Form – Master Version 2, 7 January 2013
15. Urologist Interview Guide – Version 1, 28 November 2012
16. Survey of Urologist Participants – Version 1, 28 November 2012
17. Prostate Cancer Case Eligibility Form – Version 1, 27 November 2012
18. Prostate Cancer Case Data Collection Form – Version 1, 27 November 2012
19. Clinical Data Collection Form – Version 1, 27 November 2012
20. Nationwide Survey of Urologist Members of USANZ – Version 1, 18 September 2012
21. NHMRC Partnership-Project Agreement
22. Approved budget letter dated 16 December 2012
23. PCFA Letter of support dated 21 March 2011
24. Information summary about the project
25. Standard Budget, signed 24 July 2013

CCLHD REF NO: 0513-021C
SITE ANNUAL REPORT DUE: 31st October Annually

AURED SSA REF: SSA/13/CCLHD/24
AURED NEAF REF: HREC/12/RPAH/584
NEAF HREC EXPIRY: 12th December 2016

RESEARCH - Central Coast Local Health District
Level 1, Health Services Building
(Inside Gosford Hospital Library)
Gosford Hospital, Holden St, Gosford, NSW 2250
Tel (02) 4320 3218 Fax (02) 4320 3860

It is recommended that you consult with your Medical Defence Union to ensure that you are adequately covered for the purpose of conducting this clinical trial.

At this time, we also remind you that, in order to comply with the *Guidelines for Good Clinical Research Practice (GCRP) in Australia*, and in line with CCLHD policy, the Chief Investigator is responsible to ensure that:

1. *The approving Human Research Ethics Committee (HREC) is notified of anything that might warrant review of the ethical approval of the project, including unforeseen events that might affect the ethical acceptability of the project and that the Research Manager, CCLHD (acting as the Research Governance Officer) is then notified of the decision of the HREC.*
2. *The HREC is notified of all Serious Adverse Events (SAEs) or Serious Unexpected Suspected Adverse Reactions (SUSARs) in accordance with the Serious Adverse Event Reporting Guidelines and that the Research Manager, CCLHD is then duly notified (please note that the site should be notified at the same time as the HREC in the case of any serious adverse events occurring at a CCLHD site or where the safety of any CCLHD participants is at risk as per the NHMRC Position Statement: Monitoring and Reporting of Safety for Clinical Trials (2009): http://www.nhmrc.gov.au/_files_nhmrc/file/health_ethics/hrecs/reference/090609_nhmrc_position_statement.pdf*
3. *Proposed amendments to the research protocol or conduct of the research that may affect the ethical acceptability of the project are submitted to the HREC on an amendment form (including any relevant attachments). For multi-centre studies, the Chief Investigator should submit to the Lead HREC and then send the amendment approval letter to the investigators at each of the sites so that they can notify their Research Governance Officer (Research Manager, CCLHD).*
4. *Proposed changes to the personnel involved in the study are submitted to the HREC and/or individual site/s as required.*
5. *The HREC must be provided with an annual progress report for the study. For multi-centre studies the Chief Investigator should submit to the Lead HREC on behalf of all sites. The annual report acknowledgment from the Lead HREC should then be submitted to the Research Governance Office of all subsequent sites (Research Manager, CCLHD).*
6. *The HREC must be provided with a final report upon completion of the study. For multi-centre studies the Chief Investigator should notify the Lead HREC and the investigators at each site should notify the relevant Research Governance Officer (Research Manager, CCLHD).*
7. *The HREC must be notified, giving reasons if the project is discontinued at a site before the expected date of completion. (Please note that the site should be notified at the same time as the HREC in the case of any serious adverse events occurring at a CCLHD site or where the safety of any CCLHD participants is at risk).*

Site Authorisation remains valid until the HREC approval associated with this project expires. It is therefore noted that the Ethics approval for this project will expire on 28th January 2018. Should you require an extension you would need to negotiate this with the approving HREC. Any extensions approved by the Lead HREC would then need to be reported to the Research Governance Officer at each study site (Research Manager, CCLHD).

The CCLHD Library Services provides the following resources to support researchers:

1. Literature searches – the library staff will work with you to develop a search strategy and advise on bibliographic databases available to CCLHD staff;
2. Document delivery – where journal articles are not available in full text via CIAP or the library's other subscribed resources, library staff will obtain full text copies of journal articles from other health libraries at no charge to you; and

RESEARCH - Central Coast Local Health District
Level 1, Health Services Building
(Inside Gosford Hospital Library)
Gosford Hospital, Holden St, Gosford, NSW 2250
Tel (02) 4320 3218 Fax (02) 4320 3860

3. Managing your references – the library maintains an LHD-wide subscription to EndNote reference management software. You may request EndNote to be installed on your work computer by logging a job with the Statewide Service Desk. Disks are also available for loan from Gosford and Wyong Hospital libraries to enable you to install EndNote on your home computer and/or laptop. Library staff provide training in the use of EndNote.

For further information, please contact Gosford (4320 3370) or Wyong (4394 9022) Hospital Libraries or contact the Library Manager, Suzanne Lewis (4320 3856; slewis@nsccahs.health.nsw.gov.au).

Yours sincerely,

A. Jackson

Amanda Jackson
Research Manager
CENTRAL COAST LOCAL HEALTH DISTRICT

RESEARCH - Central Coast Local Health District
LEVEL 1, HEALTH SERVICES BUILDING
(INSIDE GOSFORD HOSPITAL LIBRARY)
GOSFORD HOSPITAL, HOLDEN ST, GOSFORD, NSW 2250
TEL (02) 4320 3218 FAX (02) 4320 3860

NSW GOVERNMENT Health
Central Coast
Local Health District

17 September 2013

[redacted]

Dear Dr [redacted],

RE: **0513-021C:** Improving evidence based care for men with locally advanced prostate cancer - a randomised phased trial of clinical guideline implementation through a clinical network
Site Investigators; [redacted]
Site Contact; *TBA*

SPONSOR PROTOCOL NUMBER: *X12-0388*

IMPORTANT NOTE:

As the authority responsible for granting site authorisation of the conduct of the above study the Central Coast Local Health District (CCLHD) is required to keep records of all agreements executed along with this trial.

It is therefore requested that copies of the following documents be returned to the Research Office once they have been executed:

- Receipt/Acknowledgment from the Therapeutic Goods Administration for the Clinical Trial Notification Form.

Yours sincerely,

A. Jackson

Amanda Jackson
Research Manager
CENTRAL COAST LOCAL HEALTH DISTRICT

RESEARCH - Central Coast Local Health District
LEVEL 1, HEALTH SERVICES BUILDING
(INSIDE GOSFORD HOSPITAL LIBRARY)
GOSFORD HOSPITAL, HOLDEN ST, GOSFORD, NSW 2250
TEL (02) 4320 3218 FAX (02) 4320 3860

NSW GOVERNMENT | Health
Mid North Coast
Local Health District

27th August 2013

[redacted]

Dear Dr [redacted]

Re: Site Research Authorisation.

HREC Reference: HREC/12/RPAH/584

SSA Reference: SSA/13/NCC/84

Project Title: Improving evidenced based care for men with locally advanced prostate cancer – A Randomised phased trial for clinical guideline implementation through a clinical network.

Protocol: Version 1 dated 20th November 2012.

Thank you for submitting an application for site authorisation of the above referenced project. I am pleased to inform you that authorisation has been granted for this project to take place at the [redacted] Hospital of the Mid North Coast Local Health District.

The following documents have been authorised for distribution at the above site:

- Clinical Leader Letter of Invitation, Version 1 dated 26th November 2013.
- Clinical Leaders – Terms of Reference, Version 1 dated 27th November 2012.
- Clinical Leader Information statement, Master Version 2 dated 7th January 2013.
- Clinical Leader Consent Form, Master 2 dated 7th January 2013.
- Clinical Leader, Interview Guide, Version 1 dated 28th November 2012.
- Urologist Letter of Invitation, Version 1 dated 26th November 2013.
- Urologist Leader Information statement, Master Version 2 dated 7th January 2013.
- Urologist Leader Consent Form, Master 2 dated 7th January 2013.
- Urologist, Interview Guide, Version 1 dated 28th November 2012.
- Survey of Urologist Participants, Version 1 dated 28th November 2012.

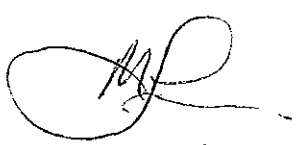
In addition I acknowledge receipt of the following documents:

- HREC approval letter dated 1st February 2013.
- Prostate cancer eligibility form, Version1 dated 27th November 2012.
- Clinical data collection form, Version 1 dated 27th November 2012.
- Protocol, Version 1 dated 20th November 2012.
- Nationwide survey of Urologist Members of USANZ, Version 1 dated 28th September 2012.
- NEAF AU/1/034017 dated 28th November 2012.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical and scientific approval:

1. Recruitment of participants can only be conducted by those Investigators listed in the Site Specific Application and who have signed the Declaration of Researchers.
2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical or scientific acceptability of the application and are submitted to the approving HREC for review must be copied to the Research Governance Officer.
3. Proposed amendment which affect the ongoing documents/materials for circulation at the site listed above, or which alter the information submitted in your application for site authorisation, must be submitted to the Research Governance Officer.
4. All Medical Practitioners are to ensure they have adequate Professional Indemnity Insurance to cover trial related activity.
5. Any trial activity in the private consulting rooms of the participating Urologists is outside the jurisdiction of this Site Specific Assessment. This authorisation is for the site of Port Macquarie Base Hospital only.
6. External researchers are to contact the Health Information Manager at PMBH to arrange a time for review of the requested medical records.

Yours Sincerely



Maureen Lawrence
Research Governance Officer
Mid North Coast Local Health District.

CC. Dr. Robert Pegram, General Manager [redacted]
Ms. Lesley McKenzie, Health Information Manager, [redacted]
Ms Kristie Weir, Senior Research Assistant, Cancer Council NSW.

NSW GOVERNMENT Health
Mid North Coast
Local Health District

23rd October 2014

[redacted]

Dear Dr [redacted]

Re: Site Research Authorisation.

HREC Reference: HREC/12/RPAH/584

SSA Reference: SSA/14/NCC/87

Project Title: Improving evidenced based care for men with locally advanced prostate cancer – A Randomised phased trial for clinical guideline implementation through a clinical network.

Protocol: Version 2 dated 10th September 2013.

Thank you for submitting an application for site authorisation of the above referenced project. I am pleased to inform you that authorisation has been granted for this project to take place at [redacted] of the Mid North Coast Local Health District.

The following documents have been authorised for distribution at the above site:

- Clinical Leader Letter of Invitation, Version 3 dated 10th February 2014
- Clinical Leaders – Terms of Reference, Version 1 dated 27th November 2012.
- Clinical Leader Information statement, Master Version 4 dated 10th February 2014.
- Clinical Leader Consent Form, Master version 5 dated 26th May 2014.
- Clinical Leader, Interview Guide, Version 1 dated 28th November 2012.
- Urologist Letter of Invitation, Version 3 dated 10th February 2014.
- Urologist Leader Information statement, Master Version 4 dated 10th February 2014.
- Urologist Consent Form, Master version 5 dated 26th May 2014.
- Urologist, Interview Guide, Version 1 dated 28th November 2012.
- Survey of Urologist Participants, Version 1 dated 28th November 2012.
- Nationwide survey of urologist members of USANZ, Version 1 dated 18th September 2012.

In addition I acknowledge receipt of the following documents:

- HREC approval letters dated 1st February 2013, 25thSeptember 2013, 26th November 2013, 13th March 2014, 17th April 2014 and 8th July 2014.
- Protocol Version 2 dated 10th September 2013.
- Prostate Cancer Case Data Collection Form, Version 3 dated May 2014.
- Prostate cancer eligibility form, Version 3 dated May 2014.

- Clinical data collection form, Version 3 dated May 2014.
- MDT Flagging Case Data Collection Form, Version 1 dated March 2014.
- MDT Data Collection Form, Version1 dated March 2014.
- NEAF AU/1/034017 dated 28th November 2012.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical and scientific approval:

1. Recruitment of participants can only be conducted by those Investigators listed in the Site Specific Application and who have signed the Declaration of Researchers.
2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical or scientific acceptability of the application and are submitted to the approving HREC for review must be copied to the Research Governance Officer.
3. Proposed amendment which affect the ongoing documents/materials for circulation at the site listed above, or which alter the information submitted in your application for site authorisation, must be submitted to the Research Governance Officer.
4. All Medical Practitioners are to ensure they have adequate Professional Indemnity Insurance to cover trial related activity.
5. Any trial activity in the private consulting rooms of the participating Urologists is outside the jurisdiction of this Site Specific Assessment. This authorisation is for the site of CHHC only.
6. External researchers are to contact the Health Information Manage, Stephanie Givney at CHHC to arrange a suitable time for review of the requested medical records.

Yours Sincerely

Maureen Lawrence
Research Governance Officer
Mid North Coast Local Health District.

CC. Dr. Sergio Diez Alvarez, DMS [redacted]
Ms. Stephanie Givney, Health Information Manager, [redacted]
Ms Cyra Patel, Senior Research Assistant, Sax Institute NSW.

Health
Northern Sydney
Local Health District

01 November 2013

[redacted]

Dear Dr [redacted]

NSLHD Local Project Number: 1307-229M
Project Title: Improving evidence based care for men with locally advanced prostate cancer - a randomised phased trial of clinical guideline implementation through a clinical network
LNR reference: HREC/12/RPAH/584
LNRSSA reference: SSA/13/HAWKE/234

Thank you for submitting an application for authorisation for a Low and Negligible Risk Research Site Specific Assessment (SSA) project. I am pleased to advise that the delegate of the Chief Executive for Northern Sydney Local Health District on 31 October 2013 has granted authorisation for the above project to commence at [redacted] Hospital

The version of the SSA reviewed by NSLHD RGO was: AU/2/74B2117

The documentation authorised to be used at this site are:

- Study Protocol. Version 1, 20 November 2012.
- Clinical Leader Letter of Invitation. Version 1, 26 November 2012.
- Clinical Leader Information Statement. Version 2, 7 January 2013.
- Clinical Leader Consent Form. Version 2, 7 January 2013.
- Clinical Leader Interview Guide. Version 1, 28 November 2012
- Urologist Letter of Invitation. Version 1, 26 November 2012.
- Urologist Information Statement. Version 2, 7 January 2013.
- Urologist Consent Form. Version 2, 7 January 2013.
- Urologist Interview Guide. Version 1, 28 November 2012.
- Survey of Urologist Participants. Version 1, 28 November 2012.
- Prostate Cancer Case Eligibility Form. Version 1, 27 November 2012.
- Prostate Cancer Case Data Collection Form. Version 1, 27 November 2012.
- Clinical Data Collection Form. Version 1, 27 November 2012.
- Nationwide Survey of Urologist Members of USANZ. Version 1, 28 September 2012.

Site authorisation will cease on the date of HREC expiry **(01/02/2017)**.

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

At this time, we also remind you that, in order to comply with the Guidelines for Good Clinical Research Practice (GCRP) in Australia, and in line with additional requirement of NSLHD, the Chief Investigator is responsible to ensure that:

1. The HREC is notified of anything that might warrant review of the ethical approval of the project, including unforeseen events that might affect the ethical acceptability of the project.

2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the HREC for review, are copied to the Research Governance Officer.

3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the Research Governance Officer.

4. The annual report acknowledgment from the Lead HREC should be submitted to the Research Governance Officer.

Standard forms and additional guidance documents are available on the Research Office Website: http://www.nslhd.health.nsw.gov.au/research.html

Yours sincerely,

Kylie Becker
Research Governance Officer
Research Office
NORTHERN SYDNEY LOCAL HEALTH DISTRICT

cc: Kristie Weir

Research Office
Kolling Building, Level 13
Royal North Shore Hospital
St Leonards NSW 2065
Tel (02) 9926 4590 Fax (02) 9926 6179

Health
South Western Sydney
Local Health District
Research and Ethics Office
Leadership · Quality · Governance
Locked Bag 7279, LIVERPOOL BC, NSW, 1871
Phone: 02 8738 8304
Facsimile: 02 8738 8310
http://www.sswahs.nsw.gov.au/swslhd/ethics/default.html

15th August 2013

[redacted]

Dear Dr [redacted],

Project Title: **Improving evidence based care for men with locally advanced prostate cancer - a randomised phased trial of clinical guideline implementation through a clinical network**
HREC Reference: **HREC/12/RPAH/584**
SSA Reference: **SSA/13/LPOOL/231**
Local Project Number: **13/141**

SITE SPECIFIC AUTHORISATION

Thank you for your correspondence dated 7th August 2013 in response to our request for further information dated 16th July 2013.

I am pleased to inform you that the Chief Executive has granted authorisation for this study to take place at the following site(s):

- [redacted]

The participant documents approved for use at this site are:

- **Clinical Leader Information Statement**, site specific, Version 1.0, dated 26th July 2013 Based on Master Version 2.0, dated 7th January 2013
- **Clinical Leader Consent Form**, site specific, Version 1.0, dated 26th July 2013 Based on Master Version 2.0, dated 7th January 2013
- **Urologist Information Statement**, site specific, Version 1.0, dated 26th July 2013 Based on Master Version 2.0, dated 7th January 2013
- **Urologist Consent Form**, site specific, Version 1.0, dated 26th July 2013 Based on Master Version 2.0, dated 7th January 2013

Note: CV's for Dr [redacted] and associated investigators are not required to be submitted for future 2013 projects as there is now one on file.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

- **Insert Local Project Number 13/141 at the end of the SWSLHD complaints paragraph**
  Changes made to documentation do not need to be forwarded to the office. Please amend before issuing to participants.

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to this office.

2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to this office.

3. Please note that you are responsible for making the necessary arrangements (e.g. identity pass and vaccine compliance as per NSW Health Policy Directive PD2011_005) for any researcher who is not employed by the South Western Sydney Local Health District and is conducting the research on-site.

Yours sincerely,

Merela Ghazal
Manager, Research and Ethics Office
South Western Sydney Local Health District (SWSLHD)

Health
South Western Sydney
Local Health District
Research and Ethics Office
Leadership · Quality · Governance
Locked Bag 7103, LIVERPOOL BC, NSW, 1871
Phone: 02 8738 8304
Facsimile: 02 8738 8310
http://www.sswahs.nsw.gov.au/swslhd/ethics/default.html

28 July 2014

[redacted]

Cc: Bea Brown (bea.brown@saxinstitute.org.au)

Dear Dr [redacted]

Project Title:	**Improving evidence based care for men with locally advanced prostate**
HREC Reference:	**HREC/12/RPAH/584**
SSA Reference:	**SSA/14/LPOOL/317**
Local Project Number:	**14/178**

SITE SPECIFIC AUTHORISATION

Thank you for your correspondence received 22 July 2014 in response to our request for further information dated 4 July 2014.

I am pleased to inform you that the Chief Executive has granted authorisation for this study to take place at the following site(s):

- [redacted]

The participant documents approved for use at this site are:

- **Clinical Leader Information Statement**, site specific, Version 1.0, dated 19 June 2014
  Based on Master Version 4.0, dated 10 February 2014
- **Clinical Leader Consent Form**, site specific, Version 2.0, dated 15 July 2014
  Based on Master Version 5.0, dated 26 May 2014
- **Urologist Information Statement**, site specific, Version 1.0, dated 19 June 2014
  Based on Master Version 4.0, dated 10 February 2014
- **Urologist Consent Form**, site specific, Version 2.0, dated 15 July 2014
  Based on Master Version 5.0, dated 26 May 2014

Note: CV's for [redacted] and associated investigators are not required to be submitted for future 2014 projects as there is now one on file.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

- **Insert Local Project Number 14/178 at the end of the SWSLHD complaints paragraph**
  Changes made to documentation do not need to be forwarded to the office. Please amend before issuing to participants.

1. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to this office.

2. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to this office.

3. Please note that you are responsible for making the necessary arrangements (e.g. identity pass and vaccine compliance as per NSW Health Policy Directive PD2011_005) for any researcher who is not employed by the South Western Sydney Local Health District and is conducting the research on-site.

Yours sincerely,

Annamarie D'Souza
Manager, Research and Ethics Office
South Western Sydney Local Health District (SWSLHD)

Health
Western Sydney
Local Health District

Research Governance Officer
Western Sydney Local Health District
Room 1072, Level 1, Education Block, Westmead Hospital
Hawkesbury Road Westmead NSW 2145

Telephone: (02) 9845 9634
Facsimile: (02) 9845 9636
Email: margaret.piper@swahs.health.nsw.gov.au

08 November 2013

[redacted]

COPY

Dear A/Prof [redacted]

HREC reference number: HREC/12/RPAH/584
SSA reference number: SSA/13/WMEAD/199
Project title: Improving evidence based care for men with locally advanced prostate cancer - a randomised phased trial of clinical guideline implementation through a clinical network
Protocol number: version 1 dated 20 November 2012

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following site:

- [redacted]

The approved information and consent documents for use at this site are:

- Clinical Leader Letter of Invitation [redacted] version 1 dated 26 November 2012
- Clinical Leader Participant Information Statement [redacted] version 1 dated 13 August 2013 based on Master version 2 dated 7 January 2013.
- Clinical Leader Participant Information Consent [redacted] version 1 dated 13 August 2013 based on Master version 2 dated 7 January 2013.

- Urologist Letter of Invitation [redacted] version 1 dated 26 November 2012

- Urologist Participant Information Statement [redacted] version 1 dated 13 August 2013 based on Master version 2 dated 7 January 2013.

- Clinical Leader Participant Information Consent [redacted] version 1 dated 13 August 2013 based on Master version 2 dated 7 January 2013.

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Non WSLHD research team members who will be conducting study visits at Westmead Hospital are to organise a time with the Research Governance Officer to be accredited as an external researcher to conduct study activity within WSLHD.

2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to the research governance officer.

3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the research governance officer.

4. If applicable any electrical equipment to come in contact with participants (for example ECG machine) that is provided by the sponsor for use in the study will need to be checked and documented by WS Biomedical prior to use at Westmead Hospital. Please contact James Wong, Director WS Biomedical WSLHD Phone: 9845 7731 Email: JamesDavid.Wong@swahs.health.nsw.gov.au

5. It is noted that a HREC exemption was granted regarding privacy concerns.

6. As discussed, the Case Data Collection Form will be securely destroyed at the completion of the study.

Yours faithfully

Maggie Piper
WSLHD Research Governance Officer

Western Sydney Local Health District
ABN 48 702 394 764

WSLHD Office, Westmead Hospital Campus
Institute Road, Westmead NSW 2145
PO Box 533, Wentworthville NSW 2145
Tel (02) 9845 5555

Health
Nepean Blue Mountains
Local Health District

COPY

Research Governance Office
Nepean Blue Mountains LHD
Level 5, South Block, Nepean Hospital
PO Box 63, Penrith NSW 2751

Telephone: 4734 1998
Facsimile: 4734 3737
Email: NBMLHD.RGO@swahs.health.nsw.gov.au

26 November 2013

[redacted]

Dear Professor [redacted]

HREC reference number: hrec/12/RPAH/584
SSA reference number: SSA/13/NEPEAN/133
Project title: Improving evidence based care for men with locally advanced prostate cancer - a randomised phased trial of clinical guideline implementation through a clinical network
Protocol number: version 2, 10 September 2013

Thank you for submitting an application for authorisation of this project. I am pleased to inform you that authorisation has been granted for this study to take place at the following sites:

- [redacted]

The approved information and consent documents for use at this site are:

- Letter of Invitation – Clinical Leader, version 2, dated 9 September 2013
- Information for Clinical Leaders – Master version (not site specific) 3 dated 9 September 2013
- Clinical Leader consent form – Master version (not site specific) 3, dated 9 September 2013

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. **All non NBMLHD research team members (Study team coming in to review medical records) involved in your study must organise a time with the Research Governance Officer to sign a confidentiality agreement and obtain ID badge prior to conducting study visits at Nepean Hospital;**

2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and which are submitted to the lead HREC for review, are copied to the research governance officer;

3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project, are to be submitted to the research governance officer.

I wish you every success in your research

Yours Sincerely

Yasoda Sathiyaseelan
NBMLHD - Research Governance Officer

cc:
Ms Kristie Weir, Senior Research Assistant, Cancer Research Division, Cancer Council NSW, PO Box 572, Kings cross, NSW 1340

Mr Selwyn Maynard , Acting HIRS RC&P Manager, Health Information & Record Service (HIRS), PO Box 63, Penrith NSW 2751

Appendix XIII

Evidence of copyright approvals

RE: American Joint Committee on Cancer Prostate Cancer Staging 7th Edition

Lansing, Richard, Springer US <Richard.Lansing@springer.com>

Wed 2/03/2016 9:18 AM

To: Bea Brown <Bea.Brown@saxinstitute.org.au>;

Dear Bea: Apologies for the delay. This permission request is approved without fee for one-time use only in your dissertation in print and electronic format. The thesis can be viewed worldwide electronically. Please use the following attribution line: Used with permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media.

Thanks and best wishes. Richard

Richard Lansing
Springer | Editorial Director, Clinical Medicine
233 Spring Street | New York, New York 10013-1578 USA
tel: 212 460 1532
mobile: 973 262 0316
fax: 212 460 1575
Richard.Lansing@Springer.com

From: Bea Brown [mailto:Bea.Brown@saxinstitute.org.au]
Sent: Tuesday, March 01, 2016 3:20 AM
To: Lansing, Richard, Springer US
Subject: Fw: American Joint Committee on Cancer Prostate Cancer Staging 7th Edition

Dear Richard,

I am writing to follow up on my earleir email to request permission to reproduce an image (as detailed below) in my PhD thesis.

I look forward to your response.

Kind regards,

Bea

Bea Brown
Research Fellow, Implementation Research Group

Sax Institute
ACN 095 542886

Level 13, Building 10, 235 Jones Street Ultimo NSW 2007
Phone: 02 9188 9500
Direct: 02 9188 9540
Mobile: 0425 400 694
Fax: 02 9188 9501
PO Box K617 Haymarket NSW 1240

From: Bea Brown
Sent: Wednesday, 10 February 2016 2:52 PM
To: richard.lansing@springer.com
Subject: American Joint Committee on Cancer Prostate Cancer Staging 7th Edition

Dear Richard,

I am completing a PhD degree at the University of Sydney and would like to request permission to reproduce the above quick reference in my thesis (https://cancerstaging.org/references-tools/quickreferences/Documents/ProstateSmall.pdf). I understand you own the copyright of the work as the publisher.

Prostate Cancer Staging. 7th Edition - AJCC

cancerstaging.org

7th EDITION Primary Tumor (T) CLINICAL TX Primary tumor cannot be assessed T0 No evidence of primary tumor T1 Clinically inapparent tumor neither

I wish to make my research thesis available for public access on the Internet via Sydney Digital Theses, (http://echolarship.usyd.edu.au), the University's digital archive of research theses.

I wish to seek from you a limited, non-exclusive licence to include the work listed above for an indefinite period in the electronic version of my thesis to be made available on open access via Sydney Digital Theses. I would welcome the opportunity to use this resource in my research thesis and look forward to your granting permission on the attached form by return email. Should you wish not to grant permission, or if you are not the copyright holder of this resource, I would appreciate it if you would notify me in writing.

Yours sincerely,

Bea Brown.

Bea Brown
Research Fellow, Implementation Research

saxinstitute

Sax Institute
ACN 095 542886

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Appendix XIV

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Publication statement for thesis Chapter Two

Title: The effectiveness of clinical networks in improving quality of care and patient outcomes: A systematic review of quantitative and qualitative studies

Authors: Brown B, Patel C, McInnes E, Mays N, Young J & Haines M

Journal: BMC Health Services Research (under review)

As co-authors of the above paper, we confirm that Bernadette (Bea) Brown's contribution to the paper is consistent with her being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conceptualised and designed the systematic review
- Conducted the literature search
- Synthesised results
- Drafted the manuscript

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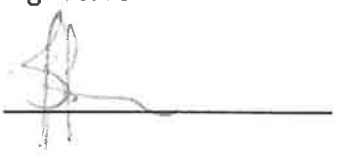
Bernadette (Bea) Brown		8/3/16
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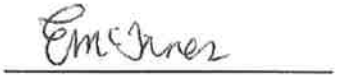
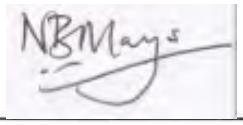
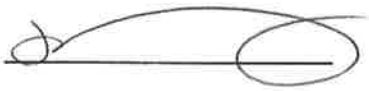
Elizabeth McInnes		8/3/2016
Nicholas Mays		9/3/16
Jane Young		9/3/16
Mary Haines		9/3/16

Publication statement for thesis Chapter Three

Title: Knowledge, Attitudes and Beliefs Towards Management of Men with Locally Advanced Prostate Cancer Following Radical Prostatectomy: An Australian Survey of Urologists.

Authors: Brown B, Young J, Kneebone AB, Brooks AJ, Dominello A & Haines M.

Journal: BJU Int. 2015 Jan 14. DOI: 10.1111/BJU.13037. [Epub ahead of print]

As co-authors of the above paper, we confirm that Bernadette (Bea) Brown's contribution to the paper is consistent with her being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conceptualised and designed the survey
- Analysed and interpreted the results
- Drafted the manuscript

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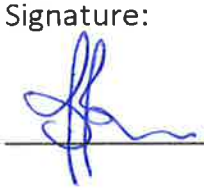
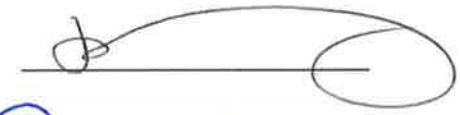
Name:	Signature:	Date:
Bernadette (Bea) Brown		9/3/16
Jane Young		9/3/16
Andrew Kneebone		8/3/16
Andrew Brooks		9/3/16
Amanda Dominello		9/3/16
Mary Haines		9/3/16

Publication statement for thesis Chapter Five

Title: Clinician-Led Improvement in Cancer Care (CLICC) - testing a multifaceted intervention to increase evidence-based prostate cancer care: phased randomised controlled trial - study protocol

Authors: Brown B, Young J, Smith D, Kneebone A, Brooks A, Xhilaga M, Dominello A, O'Connell D & Haines M.

Journal: Implementation Science 2014;9:64

As co-authors of the above paper, we confirm that Bernadette (Bea) Brown's contribution to the paper is consistent with her being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conceptualised the program logic framework
- Developed the CLICC intervention and protocol
- Drafted the manuscript

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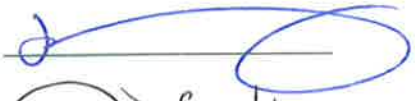
Name:	Signature:	Date:
Bernadette (Bea) Brown		9/3/16
Jane Young		9/3/16
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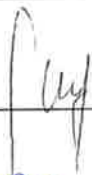
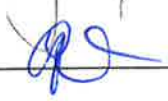
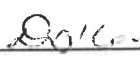
Miranda Xhilaga		8 March '16
Amanda Dominello		9/3/16
Dianne O'Connell		9 March 2016
Mary Haines		9/3/16

Publication statement for thesis Chapter Nine

Title: Changing Attitudes toward Management of Men with Locally Advanced Prostate Cancer following Radical Prostatectomy: A Follow-up Survey of Australian-based Urologists.

Authors: Brown B, Egger S, Young J, Kneebone AB, Brooks AJ, Dominello A & Haines M.

Journal: Journal of Medical Imaging and Radiation Oncology (under review).

As co-authors of the above paper, we confirm that Bernadette (Bea) Brown's contribution to the paper is consistent with her being named first author. In particular, the candidate's contribution to the following items should be noted:

- Conceptualised and designed the survey
- Informed analyses
- Interpreted the results
- Drafted the manuscript

Author signatures:

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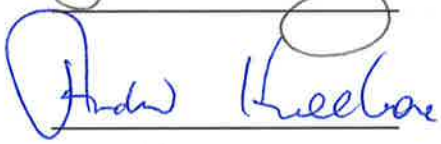
Sam Egger		9/3/16
Jane Young		9/3/16
Andrew Kneebone		9/3/16
Andrew Brooks		9/3/16
Amanda Dominello		9/3/16
Mary Haines		9/5/16