THE RECRUITMENT OF CHILDREN TO RANDOMISED CONTROLLED TRIALS

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Declaration

I hereby certify that the work embodied in this thesis is the result of original research and is not being submitted for a higher degree to any other university of institution.

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Patrina Ha Yuen Caldwell Date

Author's Contribution

The work presented in this thesis has been carried out by the author under the supervision of Associate Professor Jonathan Craig, from the School of Public Health, and Associate Professor Phyllis Butow, from the Medical Psychological Research Unit and Surgical Outcomes Research Centre, University of Sydney.

Ethics Clearance

The studies described in this thesis were approved by the Ethics Committee of the Children's Hospital at Westmead. The parents involved in the study gave written informed consent for participation in the study.

Acknowledgements

I wish to thank my supervisor A/Prof Jonathan Craig and associate supervisor A/Prof Phyllis Butow for their teaching, friendship, guidance, hard work and perseverance which has made the last three years very enjoyable, and given me a desire to pursue excellence in research. My special thanks to Dr Elisabeth Hodson and A/Prof Louise Baur for their encouragement along the way. Thanks also to Tamara Borysko, Sana Hamilton, Sandra Puckeridge, Prof Paul Roy, Giovanni Stripolli, Premala Sureshkumar, Gabrielle Williams, Narelle Willis and the other staff from the Centre for Kidney Research for all their help.

I wish to also thank my colleagues from the Children's Hospital at Westmead for their participation and feedback in this research and for access to their patients. Thanks also to the parents who participated in this research.

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This thesis is dedicated to my family – to my husband, Bruce for his support and help, to Lauren and Sam for putting up with their mother's absence during the many hours I worked on this thesis, and to my parents Francis and Julie Au-Yeung for their encouragement through the years.

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List of Abbreviations

BAS	Before after study
CHW	The Children's Hospital at Westmead
95% CI	95% Confidence Interval
COMS	Collaborative Ocular Melanoma Study
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FRACP	Fellowship of the Royal Australasian College of Physicians
HCP	Health care provider
NHMRC	National Health and Medical Research Council
PCS	Prospective cohort study
POP	Physician Oriented Profile
QRCT	Quasi- randomised controlled trial
RCS	Retrospective cohort study
RCT	Randomised controlled trial
RR	Relative risk
UK	United Kingdom
US	United States of America
WOM	Word of mouth

Abstract

Background

The randomised-controlled trial (RCT) provides the best evidence for evaluating treatment effects and is accepted as a gold standard for clinical and regulatory decision making (1;2). One of the major challenges to the conduct of RCTs is the recruitment of adequate numbers of participants. Inadequate numbers reduce the power of a study to detect statistically significant treatment effects, and may cause delays, increased costs and failure to complete trials.

The need for clinical trials in children has been increasingly recognised by the scientific community, resulting in increased demands for the inclusion of children in trials. For several reasons, recruiting children to trials is more challenging than recruiting adults, as consent issues are more difficult because parents make decisions about trial participation on behalf of their child. Despite general professional and community support for paediatric clinical trials, parents and paediatricians express reluctance when their own child or patient is asked to participate. Although researchers working with children commonly experience difficulty with recruiting children to RCTs, little is known about this very important subject.

The method by which potential participants are approached for trial participation, the influence of their health care provider and the attitude of potential participants (or their parents, in the case of children), are critical to the understanding of the decision making process for trial participation. This thesis is one of the first major attempts to

explore the issues surrounding the recruitment of children to RCTs, and is divided into four studies which address these issues.

Methods

Recruitment strategies used to encourage participation in randomised controlled trials (systematic review)

Eligible experimental and observational studies comparing methods of recruiting participants for RCTs were identified after a comprehensive search of Medline, Embase, the Cochrane Library and reference lists. Independent data extractions were completed by two reviewers who assessed the studies for eligibility and methodological quality. Outcome measures were consent rates, proportion enrolled by each method and cost of recruitment per participant. Summary estimators of effects were calculated using a random effects model and expressed as relative risk with 95% confidence intervals. Heterogeneity was analysed using the Q statistic.

Paediatricians' attitudes to children's participation in randomised controlled trials (focus group research)

Qualitative analysis of focus group discussions involving 16 paediatricians and 5 trainees from a paediatric teaching hospital in Sydney was undertaken. Doctors varied in occupation, experience, research activity, age, gender, ethnicity and parenthood experience. A professional facilitator conducted the semi-structured group discussions. Recruitment ceased when informational redundancy was reached, after 4 focus groups involving 21 participants. The transcribed audiotapes were analysed by theme linkage using the constant comparative method.

Australian paediatricians' and adult physicians' attitudes to randomised controlled trials (survey)

A 44-item questionnaire was sent to 250 paediatricians and 250 adult physicians randomly selected from the membership list of the Royal Australasian College of Physicians. Questions assessing doctors' treatment philosophies and attitudes to trials were compared with demographic and practice variables.

Parents' attitudes to children's participation in randomised controlled trials (focus group research)

Qualitative analysis of focus group discussions involving 33 parents from 5 different settings (representing parents of children with a life threatening, chronic or acute illness, with experience in trials and of healthy children) was undertaken. Parents varied in age, gender, ethnicity, level of education, research experience and their child's health status. The transcribed discussions were analysed by theme linkage using the constant comparative method.

Results

Recruitment strategies used to encourage participation in randomised controlled trials (systematic review)

Fifty papers were included (out of 8602 titles and abstracts searched) which described 8 RCTs, 2 quasi RCTs, 13 prospective cohort studies, 30 retrospective cohort studies and 2 before-after studies. These studies assessed how over 4 million people were approached for RCT participation using 87 different recruitment

strategies, with 103,406 people enrolling in RCTs. Health care provider (HCP) referrals had the highest participant consent rates at the time of exposure to trial information (HCP referral versus target mailing: relative risk (RR) 1.84 (95% confidence interval (95%CI) 1.08, 3.13)). They also had the highest consent rates when potential participants respond to the recruitment material by further enquiry about the trial (HCP referral versus community presentation: RR 1.37 (1.06; 1.78); HCP referral versus worksite approach: RR 25.20 (20.19, 31.45); HCP referral versus general community approach: RR 2.53 (0.46, 14.05); HCP referral versus mailing: RR 3.29 (1.26, 8.60); HCP referral versus media: RR 2.66 (1.31, 5.41)). However, by the time potential participants attend eligibility assessment for trial participation, no difference in consent rates could be distinguished by method of recruitment. Higher proportions of study participants were recruited by methods that exposed larger numbers of potential candidates to trial information (despite their lower consent rates). The stated recruitment cost ranged from US$0 to $1108 per participant, with mailing being the most cost-effective method and community methods (such as community presentations, pamphlets and posters displayed at community sites) the least effective.

Paediatricians' attitudes to children's participation in randomised controlled trials (focus group research)

From the focus group discussions, paediatricians thought parents balanced perceived gains and risks when deciding about trial participation. They also believed the child's condition and parents' health beliefs and personal attributes influenced parents' decisions. Other factors thought to be important by paediatricians were the doctors' beliefs and their relationship with the investigators. Paediatricians perceived gains for

trial participation including professional benefits for themselves, improved patient care, convenience for the families and themselves and scientific advancement. Perceived risks included inconvenience, inadequate resources and potential harms to the patient and the doctor-patient relationship. Paediatricians with previous research experience were most knowledgeable about RCTs and perceived greatest gains from trial participation. Paediatricians' personal treatment preferences hindered trial support.

Australian paediatricians' and adult physicians' attitudes to randomised controlled trials (survey)

Response rate from the paediatricians' and adult physicians' survey was 60% (300/500). Australian paediatricians and adult physicians are very similar in their treatment philosophies, and are clinician-oriented rather than research-oriented in their attitudes, with primary allegiance to their patients and preference for selecting treatment rather than referring for trial participation in the face of treatment uncertainty. Professional activities are clinically focused, with limited time assigned for research. Australian doctors perceive little reward for trial participation and claim that the opinions of referring doctors regarding RCTs does not influence them.

Predictors of favourable attitudes to trial participation from the survey were time allocation for research, a history of referring patients to trials in the past and younger age (all p values <0.0001).

Parents' attitudes to children's participation in randomised controlled trials (focus group research)

When parents were interviewed, they acknowledged balancing risks and benefits when deciding about trial participation for their child. Perceived benefits include the offer of hope, better care of their child, the opportunity to access new treatments, healthcare professionals and health information, meeting others in similar circumstances and helping others. Perceived risks include potential side effects, being randomised to ineffective treatments and the inconvenience of participation. The decision for trial participation is also influenced by parental factors (parents' knowledge, beliefs and emotional response), child factors (the child's health status and preference about participation), trial factors (the use of placebos and the uncertainties of research) and doctor factors (doctor's recommendations and communication of trial information).

Conclusions

There are many challenges to the successful conduct of RCTs. Ways of addressing these include: using effective methods of recruiting potential study participants (such as mailing of recruitment material to potential participants) and abandoning ineffective strategies (such as community methods): fostering greater willingness for trial participation by addressing parents' and paediatricians' concerns including enhancing communication between researchers, paediatricians and parents, and improving the gains-hazard balance (by increasing incentives while decreasing inconveniences); and reforming in the health care system to raise the priority placed on clinical

research by restructuring clinical research in a clinically predominant workplace and with a clinically predominant workforce.

The findings from this study have implications for researchers planning RCTs for children in the future. Careful consideration of the above will enhance RCTs participation for children improving efficiency, lowering costs and ultimately improving the future health care of children.

Publications arising from this thesis

Published papers

1. Caldwell PHY, Butow PN, Craig JC. Pediatricians' attitudes toward randomized controlled trials involving children. Current Pediatrics (Russia) 2003: 2 (1): 21-26.
2. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to randomised controlled trials involving children. J Pediatr 2003: 145(5):555-560
3. Caldwell PHY, Butow PN, Craig JC. Pediatricians' attitudes towards randomized controlled trials involving children. J Pediatr 2002: 141:798-803.

Articles in preparation

1. Caldwell PHY, Butow PN, Craig JC, Murphy S. Clinical Trials Involving Children – on trial. Commissioned article for the Lancet. Submitted January 2004.
2. Caldwell PHY, Craig JC, Hamilton S, Butow PN. Recruitment strategies for recruitment to RCTs: a systematic review of controlled trials and observational studies.
3. Caldwell PHY, Craig JC, Butow PN. Australian physicians' and paediatricians' attitudes to randomised controlled trials participation. Submitted to MJA.

Abstracts

1. Caldwell PHY, Craig JC, Hamilton S, Butow PN. A systematic review of strategies for encouraging participation in randomised controlled trials "From Cell to Society II" University of Sydney Postgraduate Conference 2000.

2. Caldwell PHY, Butow PN, Craig JC. Paediatricians' attitudes to randomised controlled trials involving children. 10th Annual Australasian Epidemiological Association Conference 2001.
3. Caldwell PHY, Butow PN, Craig JC. Paediatricians' attitudes to randomised controlled trials involving children. University of Sydney 2002 Postgraduate Student Conference.
4. Caldwell PHY, Butow PN, Craig JC. Paediatricians' attitudes to randomised controlled trials involving children. International Clinical Trials Symposium 2002.
5. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to randomised controlled trials involving children. Paediatric Research Seminar at the Children's Hospital at Westmead 2002.
6. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to randomised controlled trials involving children. International Clinical Trials Symposium 2002.
7. Caldwell PHY, Craig JC, Hamilton S, Butow PN. Recruitment strategies for recruitment to RCTs: a systematic review of controlled trials and observational studies: at the RACP Annual Scientific Meeting 2003 (Hobart).
8. Caldwell PHY, Butow PN, Craig JC. Parents' attitudes to randomised controlled trials involving children: at the RACP Annual Scientific Meeting 2003 (Hobart).
9. Caldwell PHY, Craig JC, Butow PN. Questionnaire on attitudes of Australian physicians and paediatricians to randomised controlled trials (RCTs): at the RACP Annual Scientific Meeting 2003 (Hobart).

Presentations arising from this thesis

1. 1/11/00 “Preliminary data - a systematic review of strategies for encouraging participation in randomised controlled trials” at the “From Cell to Society II” College of Health Sciences, University of Sydney Postgraduate Conference (Leura): oral presentation.
2. 12/3/01 “Preliminary data - a systematic review of strategies for encouraging participation in randomised controlled trials” and “Paediatricians’ attitudes to randomised controlled trials involving children” at the University of Sydney 2001 Department of Paediatrics and Child Health Postgraduate Students Conference: oral presentation (Parramatta).
3. 27/9/01 “Paediatricians’ attitudes to randomised controlled trials involving children” at the “10th Annual Australasian Epidemiological Association Conference” : oral presentation (Sydney).
4. 8/10/01 “Paediatricians’ attitudes to randomised controlled trials involving children” and “Preliminary data on parents’ attitudes to randomised controlled trials involving children” at the Department of Immunology Journal Club Meeting at the Children’s Hospital at Westmead (Invited speaker).
5. 21/6/02 “Paediatricians’ attitudes to randomised controlled trials involving children” at the Department of Paediatrics and Child Health Postgraduate Students Conference: oral presentation.
6. 29/7/02 “Parents’ attitudes to randomised controlled trials involving children” at the Paediatric Research Seminar at the Children’s Hospital at Westmead: oral presentation.

7. 18/9/02 “The recruitment of children to randomised controlled trials” at the “From Cell to Society III” College of Health Sciences, University of Sydney Postgraduate Conference (Leura) : oral presentation.
8. 22/10/02 “Recruitment strategies for recruitment to RCTs: a systematic review of controlled trials and observational studies” at the International Clinical Trials Symposium (Sydney): oral presentation.
9. 21-23/10/02 “Parents’ attitudes to randomised controlled trials involving children” at the International Clinical Trials Symposium (Sydney): poster presentation.
10. 21-23/10/02 “Paediatricians’ attitudes to randomised controlled trials involving children” at the International Clinical Trials Symposium (Sydney): poster presentation.
11. 29/11/02 “Recruitment strategies for recruitment to RCTs: a systematic review of controlled trials and observational studies” at the Clinical Oncology Society of Australia 49th Annual Scientific Meeting, Sydney (Invited speaker).
12. 13/3/03 “Recruiting children into RCTs” Annual Hospital Meeting of the Children’s Hospital at Westmead (Invited speaker).
13. 27/5/03 “Recruitment strategies for recruitment to RCTs: a systematic review of controlled trials and observational studies” the RACP Annual Scientific Meeting: poster presentation (Hobart)
14. 27/5/03 “Parents’ attitudes to randomised controlled trials involving children” the RACP Annual Scientific Meeting: poster presentation (Hobart).
15. 27/5/03 “Questionnaire on attitudes of Australian physicians and paediatricians to randomised controlled trials (RCTs)” the RACP Annual Scientific Meeting: poster presentation (Hobart).

16. 30/8/04 “Inclusion of children in clinical trials” 13th International Pediatric Nephrology Association (IPNA) Congress, Adeladie (Invited speaker).