Postmarketing Vaccine Safety Surveillance Using Data Linkage: The Issue Of Consent

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Contents

Abstract

Background: Linked electronic administrative health care databases are a valuable resource that can be used for postmarketing safety surveillance of medicines and vaccines. Australian legislation mandates that individual consent is required for the collection, use and dissemination of health information. However, the requirement for consent is not absolute; a waiver of consent may be granted by an appropriately constituted human research ethics committee, provided certain qualifying criteria are met and the research (or other activity) is deemed to be substantially in the public interest. In Australia, data linkage research projects are recommended to abide by a best practice protocol, whereby individual privacy is preserved as researchers only receive files of pre-linked data with no personal identifiers. Ethical approval of a waiver of consent is required for the disclosure of identifiable demographic information to an authorised data linkage unit for the purpose of creating a master linkage key. However, some ethics committees and data custodians still require informed consent.

Objective: The overall objective of this thesis was to examine the issue of consent in the context of postmarketing surveillance of vaccine safety using data linkage. A randomised controlled trial (RCT) was used for the primary aim of determining which method of obtaining parental consent (opt-in or opt-out) provided the highest participation rate. The secondary aims of the RCT were to examine reasons for participation and non-participation, socio-demographic factors, consent preferences and attitudes towards a data linkage study of vaccine safety. For this, a follow-up telephone interview of a parent from each family enrolled in the RCT was conducted. The generalisability of findings from the

follow-up telephone interview was examined by repeating selected questions in a population-based survey sample of South Australians.

Method: A total of 1129 families of children born at a South Australian hospital in 2009 were enrolled in a single-blind parallel group RCT of opt-in and opt-out consent at six weeks post-partum, with four weeks to respond by reply form, telephone or email. Interviews were conducted at 10 weeks post-partum (response rate 91%, *n*=1026). Computer-assisted telephone interviewing (CATI) of rural and metropolitan South Australian residents was conducted in 2010 (response rate 56%, *n*=2002).

Results: The participation rate was 21% (*n*=120/564) in the opt-in arm and 96% (*n*=540/565) in the opt-out arm [χ^2 (1df) = 567.7, *P*<0.001]. Participants in the opt-in arm were more likely than non-participants to be older, married or in a de facto relationship, university educated and of higher socioeconomic status. Participants in the opt-out arm were similar to non-participants, except men were more likely to opt out.

Substantial proportions did not receive, understand or properly consider study invitations, and opting in or opting out behaviour was often at odds with parents' stated underlying intentions. Three-fifths of the parents in the opt-in and opt-out arms reported reading the information (63% *vs* 67%, *P*=0.11), but only two-fifths correctly identified the health records to be linked (43% *vs* 39%, *P*=0.21). Parents who actively consented (opted in) were more likely than those who passively consented (did not opt out) to correctly identify the data sources (60% *vs* 39%, *P*<0.001).

Data linkage for postmarketing surveillance of vaccines was widely supported by parents enrolled in the RCT and by the wider community (96% and 94% respectively) and there was trust in its privacy protections (84% and 75%). The majority also preferred minimal or no direct involvement: either opt-out consent (40% and 40%) or no consent (30% and 31%). Only a quarter preferred opt-in consent (24% and 25%). Over half gave higher

priority to rapid vaccine safety surveillance (61% and 56%) rather than first seeking parental consent (21% and 27%), while one in seven was undecided (15% and 15%). Despite generally vaccinating their children (91% and 96%) and trusting vaccines as safe (90% and 92%), many were concerned that vaccines may be ineffective (42% and 40%) and may cause serious reactions (62% and 53%).

Conclusions: The opt-in approach resulted in low participation and a biased sample that would render any subsequent data linkage to be not feasible, whereas the opt-out approach achieved high participation and a representative sample.

Neither the opt-in nor opt-out approach was effective in achieving informed consent. The study's purpose was poorly understood, although comprehension was moderately better when parents actively rather than passively consented. Nonetheless, most parents and the general public supported data linkage for vaccine safety surveillance. A system utilising opt-out consent or no consent was preferred to one using opt-in consent.

These findings should inform public health policy and practice; the waiver of consent afforded under current privacy regulations for data linkage studies meeting all appropriate criteria should be granted by ethics committees, and supported by data custodians.

Declaration

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Jesia Berry (Candidate)

Date .....

Publications during candidature

- Berry JG, Ryan P, Braunack-Mayer AJ, Duszynski KM, Xafis V, Gold MS, the Vaccine Assessment using Linked Data (VALiD) Working Group. A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage: study protocol. *Trials* 2011;12:1, doi: 10.1186/1745-6215-12-1.
- Berry JG, Ryan P, Gold MS, Braunack-Mayer AJ, Duszynski KM, the Vaccine Assessment using Linked Data (VALiD) Working Group. A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage. *J Med Ethics* 2012;38(10):619-25.
- Berry JG, Ryan P, Duszynski KM, Braunack-Mayer AJ, Carlson J, Xafis V, Gold MS, the Vaccine Assessment using Linked Data (VALiD) Working Group. Parent perspectives on consent for the linkage of data to evaluate vaccine safety: a randomised trial of opt-in and opt-out consent. *Clinical Trials* (accepted 1/2/13).
- Berry JG, Gold MS, Ryan P, Duszynski KM, Braunack-Mayer AJ, the Vaccine Assessment using Linked Data (VALiD) Working Group. Public perspectives on consent for the linkage of data to evaluate vaccine safety. *Vaccine* 2012;30(28):4167-74.

Conference presentations during candidature

- Berry JG, Ryan P, Gold MS, Duszynski KM, Braunack-Mayer AJ, Carlson J, Xafis V. *Parent and public perspectives on consent for the linkage of data to evaluate vaccine safety.* International Data Linkage Conference 2012; 2012 May 2-4; Perth.
- Berry JG, Ryan P, Gold MS, Braunack-Mayer AJ, Duszynski KM, Xafis V, White J. *A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage.* Australasian Epidemiological Association (AEA) of Australia Conference 'Combining Tradition and Innovation'; 2011 Sep 19-21; Perth.
- Berry JG. *A study of opt-in and opt-out consent for checking the safety of vaccines using data linkage.* Expert presentation for the 'Vaccine Safety Data Linkage Community Forum' Citizens' Jury; 2011 Mar 26; Adelaide.
- Berry JG, Ryan P, Gold MS, Braunack-Mayer AJ, Duszynski KM, Xafis V, Carlson-White J. *A randomised trial of consent options in data linkage for vaccine surveillance.* Public Health Association of Australia (PHAA) 12th National Immunisation Conference; 2010 Aug 17-19; Adelaide.
- Berry JG. *Using multiple imputation to fill in missing data for a randomised controlled trial of opt-in and opt-out consent to data linkage.* University of Adelaide, School of Population Health Seminar Series; 2011 Apr 7; Adelaide.
- Berry JG. *A randomised trial of consent options in data linkage for vaccine safety surveillance.* University of Adelaide, School of Population Health, Higher Degree by Research Symposium; 2010 Oct 1; Adelaide.

- Berry JG. *The feasibility of data linkage using routine administrative datasets for vaccine safety surveillance in Australia*. University of Adelaide, School of Population Health Seminar Series; 2009 Apr 24; Adelaide.

Poster presentations:

- Berry JG, Ryan P, Gold MS, Braunack-Mayer AJ, Duszynski KM, for the VALiD Working Group. *Is it feasible to obtain consent for data linkage studies of vaccine safety?* PHAA (SA branch) Conference 'Population Health: Working across sectors, settings and ages'; 2011 Oct 29; Adelaide. (Also presented at the University of Adelaide, Faculty of Health Sciences Postgraduate Research Conference; 2011 Aug 25; Adelaide.)

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'There's more to life than books, you know. But not much more.'

Morrissey

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Abbreviations

ABS	Australian Bureau of Statistics
ACIR	Australian Childhood Immunisation Register
ACSOM	Advisory Committee on the Safety of Medicines
ACT	Australian Capital Territory
ACTRN	Australian New Zealand Clinical Trials Registry
AEA	Australasian Epidemiological Association
AEFI	Adverse Event(s) Following Immunisation
AIHW	Australian Institute of Health and Welfare
APSU	Australian Paediatric Surveillance Unit
ARC	Australian Research Council
ASGC	Australian Standard Geographical Classification
CATI	Computer-Assisted Telephone Interviewing
CDC	Centers for Disease Control and Prevention
CDL	Centre for Data Linkage
CEO	Chief Executive Officer
CHeReL	Centre for Health Record Linkage
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CYWHS	Children, Youth and Women's Health Service
DAEN	Database of Adverse Event Notifications
DEC	Departmental Ethics Committee
DLU	Data Linkage Unit
DTP	Diphtheria-tetanus-pertussis

ED	Emergency Department
EMR	Electronic Medical Record
FCS	Fully conditional specification
GP	General Practitioner
H1N1	Pandemic influenza A
Hep B	Hepatitis B
Hib	Haemophilus influenzae type B
HIPAA	Health Insurance Portability and Accountability Act Privacy Rule
HIPPO	Health Informatics, Policy and Performance Outcomes Unit
HMO	Health Maintenance Organization
HPV	Human papillomavirus
HREC	Human Research Ethics Committee
ICD	International Classification of Diseases
ID	Identification
IHDLN	International Health Data Linkage Network
IPV	Inactivated poliovirus vaccine
IQR	Interquartile range
IRR	Incidence rate ratio
IRSD	Index of Relative Socio-economic Disadvantage
MACSS	Multipurpose Australian Comorbidity Scoring System
MAR	Missing at random
MCV4	Meningococcal conjugate vaccine
MenCCV	Meningococcal C conjugate vaccine
MMR(V)	Measles-mumps-rubella(-varicella)
MNAR	Missing not at random
MVNI	Multivariate normal distribution

NCIRS	National Centre for Immunisation Research and Surveillance
NCRIS	National Collaborative Research Infrastructure Strategy
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICU	Neonatal Intensive Care Unit
NIP	National Immunisation Program
NSW	New South Wales
NT	Northern Territory
OPR	Office of Product Review
OPV	Oral poliovirus vaccine
7vPCV	Seven-valent pneumococcal conjugate vaccine
13vPCV	Thirteen-valent pneumococcal conjugate vaccine
PAEDS	Paediatric Active Enhanced Disease Surveillance
PHAA	Public Health Association of Australia
PHRN	Population Health Research Network
PIAG	Patient Information Advisory Group
PRISM	Post-licensure Rapid Immunization Safety Monitoring system
RCT	Randomised controlled trial
RR	Relative Risk
SA	South Australia
SAEFVic	Surveillance of Adverse Events Following Vaccination in Victoria
SAVeS	South Australian Vaccine Safety Data Linkage Pilot Project
SCCS	Self-controlled case series
SCR	Summary care record
SEIFA	Socio-Economic Indexes For Areas
SURE	Secure Unified Research Environment

TdaP	Tetanus-diphtheria-acellular pertussis
TGA	Therapeutic Goods Administration
TIV	Trivalent influenza vaccination
TP	Thrombocytopenic purpura
UK	United Kingdom of Great Britain and Northern Ireland
US	United States of America
VAESCO	Vaccine Adverse Event Surveillance and Communication
VALiD	Vaccine Assessment using Linked Data study
Vic	Victoria
VSD	Vaccine Safety Datalink
WA	Western Australia
WADLS	Western Australia Data Linkage System
WCH	Women's and Children's Hospital

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1 Introduction

In 2006, the Australian Government announced 12 priority areas in The National Collaborative Research Infrastructure Strategy (NCRIS) to facilitate world-class research. Under this initiative, $A20 million was allocated to establish a national capability in population health and clinical data linkage.[1,2] The aim was to establish an integrated national resource of population health and biological data, which provides efficient secondary use of the data collected from the annual $A66.6bn spent on health care,[1] and positions Australian researchers closer to the forefront of internationally competitive health and medical research.

The research applications of data linkage are wide-ranging and include postmarketing surveillance of medicines and vaccines; tracking uses and costs of hospital care and out-of-hospital care; monitoring safety and quality in health care; identifying the causes and outcomes of diseases and the impact of specific clinical and therapeutic interventions; elucidating the relative impact of environmental, social, biological and genetic influences on health status; and studying the effects of social factors on health throughout the life course, among other potential uses.[1]

The secondary use of electronic health data brings to the forefront concerns about security and privacy. The pioneer of data linkage in Australia, operating since 1995, is the Western Australian Data Linkage System (WADLS).[3] The Centre for Health Record Linkage (CHeReL) in New South Wales was later established in 2006.[4] These two jurisdictions have adopted a best practice protocol to preserve privacy, whereby personal identifiers are separated from the actual health information and the use of personal identifiers is confined to the initial linkage stage.[5] Since 2006, through the work of the NCRIS-funded Population

Health Research Network (PHRN),[1] Australia has moved towards establishing a national health data linkage network comprising data linkage nodes and units across the country representing each state and territory, as well as a national data linkage unit specifically assigned to performing linkage with national datasets through the Centre for Data Linkage (CDL) in conjunction with the Australian Institute for Health and Welfare (AIHW).

Australia's legislative framework provides a mechanism to allow data linkage projects to proceed lawfully. In Australia, the Commonwealth *Privacy Act 1988* (the *Privacy Act*) initially applied only to Commonwealth public sector agencies. It was amended in 2000 and now also applies to the private sector throughout Australia.[6] The *Privacy Act* (Cth) stipulates that 'unless a limited range of exceptions applies, health information cannot be collected, used or disclosed without the consent of the data subject'.[6] However, the requirement for consent is not absolute. According to the *Privacy Act* (Cth), Sections 95 (for Commonwealth agencies) and 95A (for the private sector) provide for guidelines to be developed 'to enable the use of health information in the conduct of specific activities (including research of various types) without the consent of the data subject, provided an assessment is made by a Human Research Ethics Committee (HREC) that the research and other activities are, on balance, substantially in the public interest'.[6] The National Health and Medical Research Council (NHMRC) has developed and published such guidelines, which are approved by the Privacy Commissioner, under Sections 95 and 95A.[7,8] In addition, the primary set of guidelines for human research, developed jointly by the NHMRC, the Australian Research Council (ARC), and the Australian Vice Chancellors' Committee, entitled the *National Statement on Ethical Conduct in Human Research* (the *National Statement*) provides guidance on the ethical principles and grounds for waiving consent in relation to the use of linked data.[9] It is important to note that, although an HREC may approve a data linkage project, the relevant data custodians make the final decision as to whether the data linkage can proceed.

Australia's legislative framework is complex. In addition to the *Privacy Act* (Cth), a number of states and territories have their own legislation regulating the handling of health information in the public sector and private sector. The co-existence of Commonwealth, state and territory health information privacy legislation may create uncertainty and confusion for key decision-making bodies.[10] HRECs and data custodians may lack sufficient guidance as to when it may be acceptable to release data without individual consent.[10-12] Even though data linkage is ethically and legally acceptable when certain qualifying criteria in the *National Statement* are met,[9] researchers have encountered inconsistencies and lengthy delays in decisions made by HRECs and data custodians, refusals to grant consent waivers, or insistence on opt-in approaches to seeking consent.[10,12-15]

Leading Australian researchers have been advocating for an Australia-wide program of data linkage to evaluate the benefits and risks of medicines[16,17] and vaccines.[18,19] Australia is one of only a small number of countries that have existing capacity to use data linkage to evaluate the safety of vaccines.[20] This potential capacity exists because of the Australian Childhood Immunisation Register (ACIR), which contains immunisation records for all children under seven years of age, and good quality national electronic administrative databases of hospital morbidity and mortality outcomes. However, progress in achieving linkage of the datasets has been slow because of privacy concerns, lack of political will, and barriers in access to, and linkage of, the various datasets across jurisdictions.[15-18]

There have been calls for appropriate consultation and public debate about where the appropriate balance may lie between facilitating health and medical research for public benefit on the one hand, and individual privacy and the right to consent on the other.[11,12] Few studies have been conducted to investigate the public acceptability of data linkage and attitudes towards the need for consent in this context. Only a handful of studies[21-25] have

compared two consent approaches — opt-in and opt-out, using the highest level of evidence: a well-designed randomised controlled trial, and none of them examined the consent processes in the context of data linkage.

1.1 Thesis objective

The overall objective of this thesis was to examine the issue of consent in the context of postmarketing surveillance of vaccine safety using data linkage. In particular, I consider the feasibility of obtaining parental consent, and the attitudes of parents to methods of consent. The feasibility of seeking parental consent to data linkage for childhood vaccine safety surveillance was examined by comparing two approaches to consent — opt-in and opt-out, using a randomised controlled trial (RCT) conducted in South Australia. In a follow-up telephone interview of enrolled families in the RCT, we elicited parental opinion on data linkage for the purpose of vaccine safety surveillance and preferences for any requirement for consent. To compare the findings to the general South Australian population, we conducted a computer-assisted telephone interview of South Australians randomly sampled from the Electronic White Pages.

An RCT of the opt-in and opt-out approaches to gaining parental consent

- The primary aim was to determine which method of obtaining parental consent (opt-in or opt-out) provided the highest participation rate for a population-based vaccine safety surveillance program using data linkage.

The secondary aims of the RCT involved comparisons between the opt-in and opt-out arms and between participants and non-participants in each arm, and were:

- To examine socio-demographic differences and reasons for participation and non-participation;
- To examine parental recall and understanding of the study invitation material; and

- To examine parental consent preferences, trust in the protection of privacy in data linkage, attitudes towards vaccination in terms of its public health benefit, safety, and effectiveness and vaccination practices in relation to the newborn.

The implications of these outcomes on the feasibility of the opt-in and opt-out approach were examined.

A population-based sample survey of community views regarding consent

The generalisability (or external validity) of findings from the follow-up telephone interview of enrolled families in the RCT was examined by repeating select questions in a survey sample of South Australians using Computer-Assisted Telephone Interviewing (CATI). Specifically, the aim was:

- To examine the public's consent preferences, trust in the protection of privacy for data linkage, and attitudes towards vaccination in terms of its public health benefit, safety, and effectiveness. For the subset of the survey sample in which the respondents were legally registered parents, vaccination practices in relation to all children in their care were determined.

1.2 Thesis outline

The remainder of the thesis is organised as follows. In Chapter 2, I review the relevant literature that provides the context to the thesis objective, introduced above. I explain the concept of data linkage, describe the best practice protocol to preserve privacy, and illustrate the utility of data linkage for the postmarketing surveillance of vaccine safety. Challenges in the implementation of data linkage in Australia for vaccine safety surveillance are outlined. The legislative regulations for the release of identifiable demographic information from the ACIR for linkage purposes are discussed. The focus then moves to the ethical requirements for consent, the qualifying criteria for a waiver of

consent, and a review of epidemiological studies in relation to the feasibility of seeking opt-in or opt-out consent.

In Chapter 3, the study protocol for the randomised controlled trial of opt-in and opt-out consent is presented as a published manuscript. The background of the study protocol summarises the findings of five prior RCTs relating to other aspects of medical research, and establishes the rationale for conducting the RCT. The protocol of the RCT follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

The results of this thesis are presented as manuscripts in Chapters 4, 5, and 6. Chapters 4 and 5 address the primary and secondary aims of the RCT of opt-in and opt-out consent. In Chapter 4, comparisons are made according to randomised allocation in relation to participation rates, evidence of selection bias, and parental reasons for participation and non-participation in each arm. In Chapter 5, comparisons are made according to randomised allocation in relation to parental recall and understanding of the study invitation material, parental opinions on data linkage for vaccine safety surveillance, the level of trust in its privacy protections, preferences for any requirement for consent, and opinions on the safety and effectiveness of vaccines, and parental vaccination practices. In Chapter 6, a community survey is conducted to canvass the public's view regarding the acceptability of data linkage for vaccine safety surveillance, the level of trust in its privacy protections, preferences for any requirement for consent, and opinions on the safety and effectiveness of vaccines, and parental vaccination practices.

Chapter 7 examines the generalisability of the findings of the RCT in relation to the survey sample of South Australians.

Finally, Chapter 8 follows with a general discussion of the results, potential areas requiring future research, and concluding remarks concerning the translation of findings into practice.

2 Literature review

2.1 Population health surveillance using data linkage

Data linkage is defined as 'the bringing together, from two or more different sources, data that relate to the same individual, family, place or event.'[26] Information is already widely collected on large populations for administration and health service planning, and costing/casemix in the case of hospital morbidity collections. The types of collected data vary from place to place, but the records can include births, deaths, marriages, hospital morbidity collections, ambulatory and emergency department attendances, maternity and neonatal care, mental health, cancer and other disease/condition registers, prescription and health professional claims, immunisation, aged care, population census, electoral roll, longitudinal surveys, criminal justice, drug and alcohol services, child protection agencies, education and community services, policing of road crash casualties, among others.

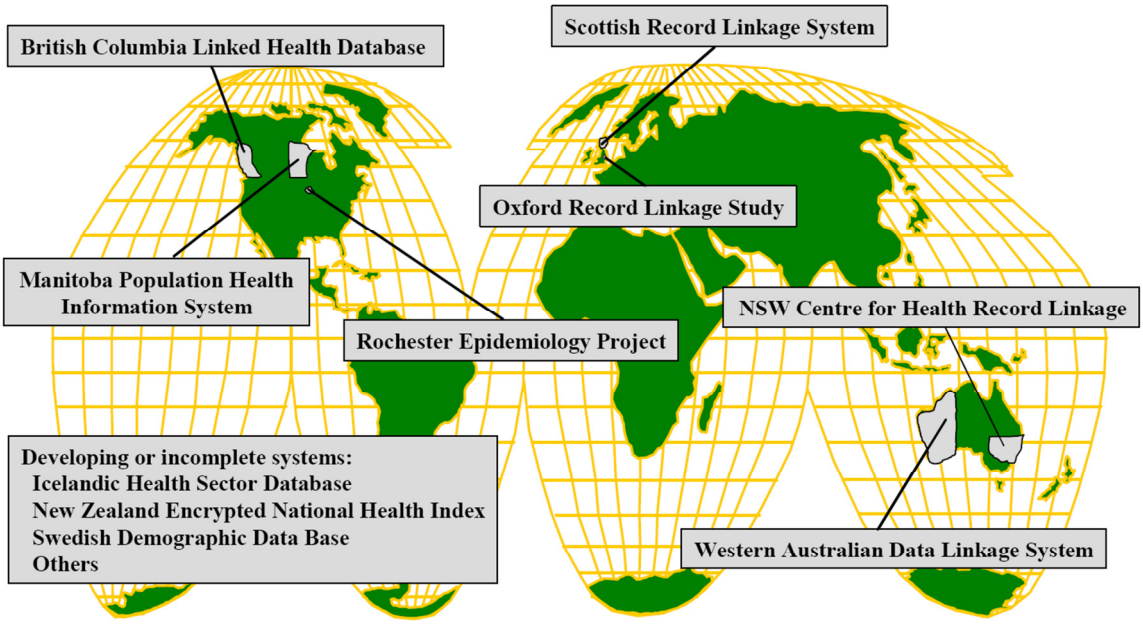
Advances in technology in recent decades have seen countries moving towards integrated electronic health care databases including population-based systems of linked health records, which provide an opportunity to undertake sophisticated and powerful population-level studies.[27] The research applications of data linkage are wide-ranging and include postmarketing surveillance of medicines and vaccines; tracking uses and costs of hospital care and out-of-hospital care; monitoring safety and quality in health care; identifying the causes and outcomes of diseases and the impact of specific clinical and therapeutic interventions; elucidating the relative impact of environmental, social, biological and genetic influences on health status; and studying the effects of social factors on health throughout the life course, among other potential uses.[1]

2.1.1 Developments internationally and in Australia

The creation of an integrated data linkage system (as opposed to ad hoc data linkages) demands vision, leadership, inter-agency and inter-sectoral cooperation and long-term commitment.[28] For these reasons, as of 2008, there were relatively few established population-based data linkage systems internationally, which have linked multiple large administrative datasets to study the use of health care and the epidemiology and aetiology of diseases (Figure 2.1). However, since that time many more developing or incomplete systems are underway worldwide.[27,28] An International Health Data Linkage Network (IHDLN) was inaugurated in December 2008 for the purpose of fostering collaboration, networking and exchange programs between data linkage centres around the world and associated member groups or individuals. The website of the IHDLN is found at: http://www.ihdln.org/.

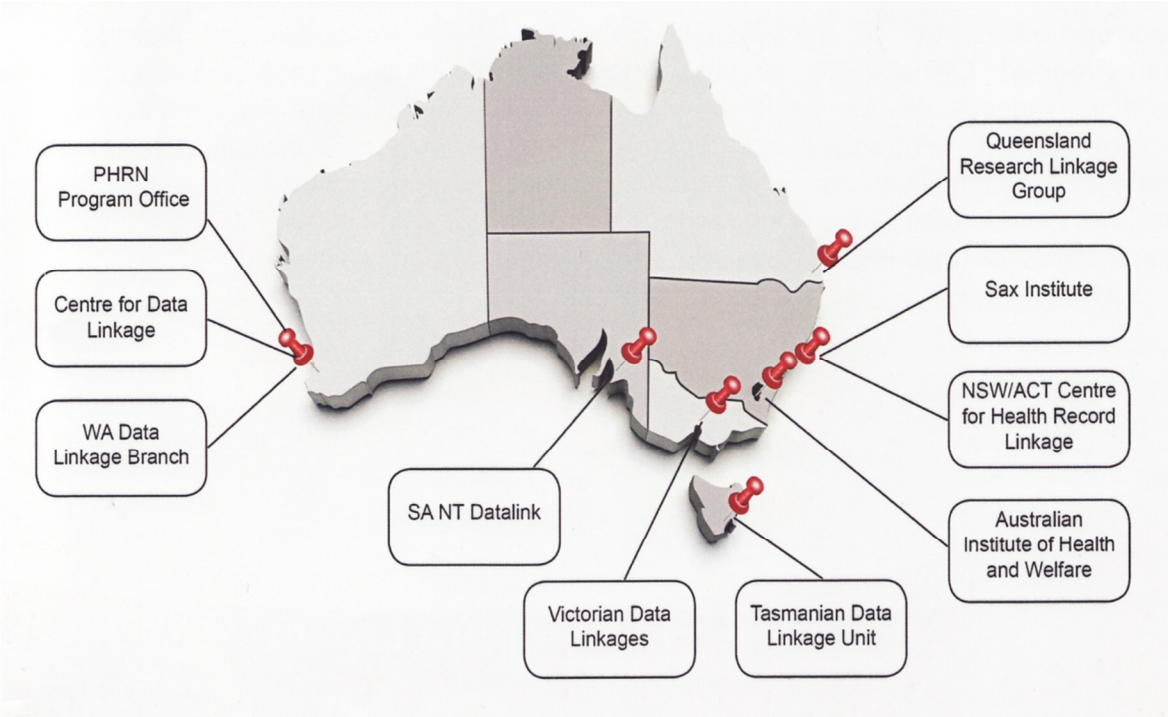
Pioneering data linkage programs specifically for vaccine safety surveillance have been undertaken by single countries such as the United States (US) with its Vaccine Safety Datalink (VSD) in operation since 1990,[29] and Denmark from 2001,[30] and through inter-country collaborations from 1998 in a European consortium, the Vaccine Adverse Event Surveillance and Communication (VAESCO).[31] However, as described in Section 2.2.4, only a small number of countries have existing sources of exposure and outcome data that are, or could potentially be, used for vaccine safety surveillance.

Figure 2.1: Well developed data linkage systems worldwide in 2008[28]



As a fortuitous consequence of a complex two-tier system of federal and state/territory funding arrangements, Australia is an international leader in the scope and quantity of data collected on health and other outcomes at a population level.[1] In 2006, the Australian Government announced 12 priority areas in The National Collaborative Research Infrastructure Strategy (NCRIS) to facilitate world-class research. Under this initiative, $A20 million was allocated to establish a national capability in population health and clinical data linkage.[1,2] The Population Health Research Network (PHRN), established in 2009 and located at the Telethon Institute for Child Health Research in Western Australia (WA), was funded to coordinate the nodes representing each state and territory (Figure 2.2). A further $A10 million has been allocated to the PHRN through the Australian Government's Education Investment Fund Super Science Initiative, as well as $A42 million in direct and indirect support from the collaborating states and territories and their academic partners.[2]

Figure 2.2: The Population Health Research Network[2]



The aim of the PHRN is to establish an integrated national resource of population health and biological data, which provides efficient secondary use of the data collected from the annual $A66.6bn spent on health care.[1] Each node will undertake data linkage on its contributing jurisdictional databases.[3,4,32-35] The national data linkage unit, the Centre for Data Linkage (CDL) at Curtin University of Technology, will develop cross-jurisdictional linkage capability and several 'proof of concept' projects are in progress.[2] The Sax Institute, one of the member organisations of the PHRN, has developed and hosts a secure data exchange/data analysis laboratory, the Secure Unified Research Environment (SURE), to allow researchers access to linked data files in virtually secure analysis facilities, which minimises the potential for risk of privacy breaches.[36]

The Australian Government has outlined a plan to facilitate use of Commonwealth data for statistical and linkage purposes, whereby a responsible 'integrating authority' will be nominated to each statistical data integration proposal, and a comprehensive set of best practice guidelines will be developed.[37] The guidelines will address the governance aspects

of privacy impact statements; proposal approvals and registration; responsibilities of data custodians, integrating authorities, and end users; application of a separation principle in data linkage in relation to identifiers and clinical information; minimum standards for security; consent requirements to access Commonwealth data; confidentiality requirements related to integrated datasets and research outputs; and data retention and destruction.[37]

In 2011, an Australian Government organisation, the Australian Institute of Health and Welfare (AIHW), joined the PHRN as an accredited integrating authority and will collaborate with the CDL and the Sax Institute (in relation to the SURE facilities) to undertake linkages with national datasets, such as Medicare Australia data, national morbidity and mortality collections and cancer registrations.[1]

2.1.2 Best practice protocol and privacy considerations

The secondary use of population health data for public health surveillance involves two competing priorities: protecting patient confidentiality in the use and dissemination of health information and the public health authority's duty to use the information to protect and improve public health.[38] A consent-based approach to the use of health data only conserves the privacy of those who decline to participate, whereas data linkage systems can be designed in such a way to conserve the privacy of all patients.[26]

The pioneer of data linkage in Australia, operating since 1995, is the Western Australia Data Linkage System (WADLS).[3] The Centre for Health Record Linkage (CHeReL) was established in 2006.[4] These two jurisdictions have adopted a best practice protocol to preserve privacy, whereby personal identifiers are separated from the actual health information and the use of personal identifiers is confined to the initial linkage stage (Figure 2.3).[39] Before a data linkage study goes ahead, each data custodian, as well as a Human Research Ethics Committee (HREC), must be convinced that bringing the de-named data together is justified in terms of public health benefit.[39] The researchers are

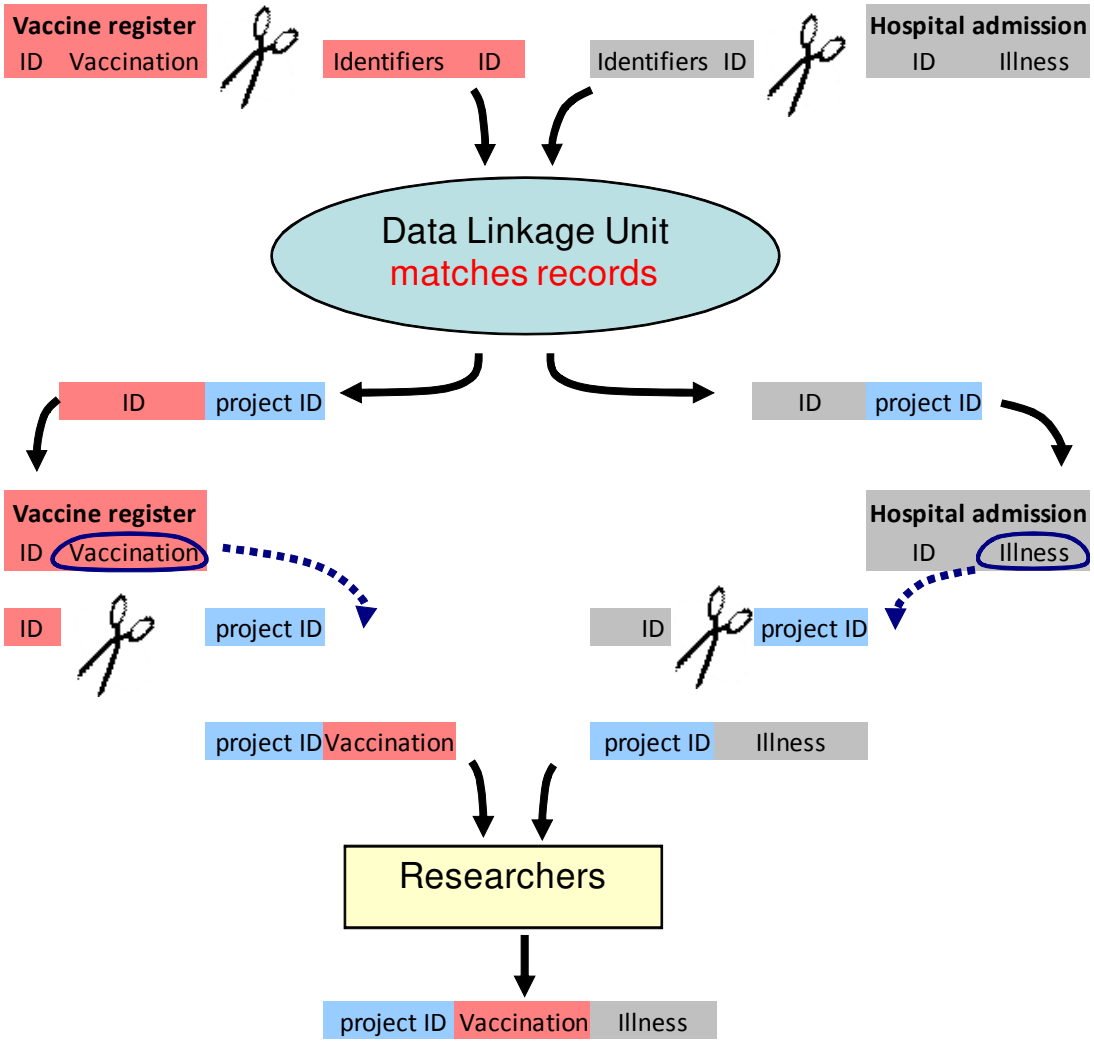
instructed to request only the minimum number of variables required to fulfil the planned analysis and may be asked to justify the need for inclusion of more sensitive variables, such as postcode, date of birth, and geocoding.[2,3]

As illustrated in Figure 2.3, the data custodians of the data sources to be linked uncouple the individual identifiers in a dataset (i.e. name, sex, address, date of birth or a specific identification (ID) number) from the clinical or health care information and attach the unique local identification number for each unit record ('local ID'). The identity files alone are sent on to an independent organisation, the Data Linkage Unit (DLU), which links the identity files and creates a Linkage Key which consists of an arbitrary 'project ID' — a unique number for each individual that is mapped to the 'local ID' in the database used by each data custodian. The DLU strips off the identifiers (i.e. name, sex, address, date of birth or a specific ID number) and returns the relevant Linkage Key ('project ID<->local ID' file) to the data custodians who attach clinical or health care data and send encrypted and non-identifiable clinical data files to a third party — the researchers, to link together via 'project ID'.[5] In addition, informational privacy is guarded through the enforcement of strict standards on physical and technological security and adherence with professional guidelines and codes of conduct for authorised linkage personnel and researchers.[2,9,28,40]

Use of the best practice protocol ensures that:

- Staff of the data linkage unit are never privy to sensitive clinical information and only have access to limited identifiers;
- Data custodians never share sensitive clinical information; and
- Identifying information is never released to researchers.

Figure 2.3: How does data linkage work? An example illustrating data linkage of vaccination and hospital morbidity data



In WA, introducing the best practice protocol resulted in an increase in the proportion of research projects requesting linked data from 0% in 1994, the year before the start of WADLS, to 61% in 2003, which was accompanied by a decline in research projects using name-identified data from 94% in 1994 to 36% in 2003.[39] Prior to the establishment of WADLS, CHeReL and the PHRN, ad hoc data linkage projects were undertaken in which it was common for researchers to receive complete datasets containing both the personal identifiers (e.g. name, address, date of birth) and content information (e.g. health outcomes), thereby posing a potential risk for breaches of privacy. As the source datasets were often sequestered in hosting government/non-governmental agencies and universities,

and not readily shared across research institutions or universities, the scope of research projects that could be conducted was limited.

2.1.3 Linkage methods

A data linkage unit like WADLS does not store any clinical or service data; rather, the information retained in the system consists of 'chains of links' or pointers to the source data elements, ordered chronologically for each person.[28] For example, the source data elements for an individual might include a cancer registry entry, three hospital separation records and a death registration, but the chain itself does not contain any clinical information.[28] The 'chain of links' is retained in a database or file as a dynamic Master Linkage Key, which is continually updated when new information arises, for example, to insert new links when additional data sources are acquired or to correct erroneous links.[28] In WA, the Master Linkage Key spans up to 40 years of data from over 30 collections in reference to a historical population of 3.7 million.[26] The local IDs of linked records are assigned an identical 'chain number', which is stored in a separate database as extra security to ensure the 'chain of links' remains non-identifiable.[3]

When linking databases using computer software packages, there are two common methods: deterministic or probabilistic matching.[28] Deterministic matching is applied when there are one or several unique identifiers, such as a health service number (e.g. unit medical record number or health insurance number) or a national identity number that are matched exactly, or match within defined limits, between datasets.[28] Somewhat counter-intuitively, the process may only identify 80–90% of true matches due to human recording or machine error in use, and less when the match must be exact (80–85%) as opposed to 'fuzzy' matching (85–90%).[28] Fuzzy matching describes the use of partial identifiers such as name, date of birth, sex, postcode or place of birth to aid matching of data that are

almost the same, and can include the use of ciphers, or taking specified characters from partial identifiers.[28]

Probabilistic matching uses partial identifiers such as name, date of birth, sex, postcode, or place of birth that are not unique but have a positive predictive value in identification when used in combination.[28] Probable or improbable links are classified based on an assessment of similarity using decision rules that include weights derived from the probabilities of similarities occurring by chance and checked against a user-defined threshold.[28] The process typically identifies 95–99% of true matches, while 1–2% of matches are false positives — the latter can be reduced to <0.1% if clerical review is applied to records falling in the zone between the user-defined acceptance and rejection thresholds.[28]

2.1.4 Benefits and limitations of data linkage

Some countries have unique identification numbers for every citizen (e.g. Sweden, Norway, Denmark), whereas others capture nearly the whole populace by utilising multiple data sources (e.g. WADLS).[27] As the scope of the linked data collections relate to the total population of a geographical region and not merely a sub-set of those interacting or registered with a health institution or other facility, linkage enables epidemiological surveillance and analytical assessment of a total population, thereby minimising the potential for bias in the results.[27,41] Such endeavours provide cost-efficient alternatives to conducting de novo longitudinal studies, especially in vulnerable or mobile populations.[27,42,43] Data linkage studies include subjects from socioeconomic and ethnic groups that are typically under-represented in other types of studies, provide greater flexibility in study design and duration due to the continuous nature of data collection, and are less susceptible than longitudinal studies to loss-to-follow-up and over-reliance on self-reported measures.[27] Diverse epidemiological study designs can be conducted using linked data, including the well-known conventional longitudinal studies (e.g. case-control, cohort

and experimental studies such as RCTs) as well as more recent innovations (e.g. case distribution and quasi-experimental studies).[28]

Important and unique investigations are made possible by linking data related to public health, clinical medicine, education, community services, housing, police, justice, transport, planning, and other sectors, while conserving privacy by reducing the need for release of personal identifiers across these sectors.[1,27] Linking data from disparate sources provides the capacity at a population-level to study predictors and outcomes of low prevalence diseases, conditions, or procedures; health service utilisation and costs; multiple predictor and outcome domains within the same cohort of individuals (e.g. education, health, social factors, mobility etc.); life course and transgenerational patterns; chronic disease surveillance; cost-estimates of the burden of diseases; and longitudinal evaluation of health and social policy interventions.[27]

The ability to conduct diverse epidemiological studies utilising established links in a Master Linkage Key adds value to otherwise unproductive record keeping systems and conserves the limited resources available for health and medical research, allowing re-investment into further research activities.[26] Within the first decade of operation, the WADLS has amassed $A58 million from a competitive advantage in attracting funds compared to states with no data linkage system, representing a more than 10-fold return on initial expenditure on research infrastructure.[26] In the ten years since its inception, the WADLS has provided linkage services to researchers in academic, government, health industry and community organisations, whose outputs from over 400 distinct studies include at least 250 journal publications and over 35 graduate research degrees.[26] These research outputs contribute to worldwide medical and scientific knowledge, shaping policy development and eventually translating into better prevention, treatment and care programs.[27,28,44] Further benefits include the development of future research leaders,

fostering collaborative research between diverse stakeholders, and community engagement through enhanced interactions between researchers, other stakeholders, community groups and the mass media.[26]

Overall, the benefits of data linkage outweigh the limitations; however, data linkage systems have some constraints. Firstly, the creation of a data linkage system is not straightforward; many barriers are encountered in social organisation, political will, vested interests, privacy and confidentiality concerns, technology, leadership and inter-agency and inter-sectoral cooperation.[28] Secondly, routine administrative data usually lack information on confounders, such as comorbidity and individual-level socioeconomic status.[27] To some extent, these problems can be addressed by the use of comorbidity scores (e.g. Charlson's Index and the Multipurpose Australian Comorbidity Scoring System (MACSS)), and census-derived composite measures of area-based socioeconomic status and remoteness of usual residence (e.g. Socio-Economic Indexes for Areas (SEIFA) and Australian Standard Geographical Classification (ASGC), respectively).[28,45,46]

A standard system of coding diagnoses in hospital inpatient and deaths databases, the International Classification of Diseases (ICD), enables longitudinal and comparative studies.[47] However, ICD-coded administrative data lack clinical details, such as the severity of disease, the clinical sequence of aetiology, and data on comorbidities and risk factors are not routinely collected.[28,47] Therefore, certain conditions may not be accurately captured or represented by ICD codes, necessitating time-consuming validation of ICD codes using medical record review.[47] Data on ethnicity, risk behaviours (e.g. smoking status, alcohol consumption, sexual activity), social supports, wellbeing, and non-familial interpersonal relationships are other types of information often not available in administrative data, unless researchers are able to link in survey data for a subset of the population.[27,48] Thirdly, the quality of published studies can vary, due to the need for

advanced technical expertise in the linkage phase, and statistical and epidemiological skills in the analysis phase, to avoid systematic biases and errors in interpretation.[49]

In summary, data linkage is a cost-effective and powerful use of routine administrative data to inform diverse areas of health and social research. With Australian Government commitment, and the efforts of the PHRN, Australia should be well-placed to contribute to important and powerful advances in public health research.[27]

2.2 Vaccine safety surveillance

High vaccination coverage has led to a substantial decline in vaccine-preventable disease, especially among children.[50] It is estimated that immunisations currently save 2.5 million children's lives per year globally (and avert millions more from suffering illness and disability), and are among the most cost-effective health interventions available.[51]

Vaccines are pharmacological products that contain one or more inactivated (i.e. not live) or live attenuated organisms or their products, and may include components of culture media/culture used in the production process, antibiotics, preservative and stabilisers.[52,53] While the safety of vaccines cannot be directly measured, it can be indirectly inferred from the relative absence or presence of adverse vaccine reactions in a vaccinated population. Because the causal association between vaccination and an adverse event may not be clear, vaccine safety surveillance aims to detect any adverse events following immunisation (AEFI).[54] An AEFI is defined as 'an unwanted or unexpected event occurring after the administration of vaccine(s).'[53] Such an event can be associated with the vaccine or its constituents, arise coincidentally (i.e. it would have occurred irrespective of vaccination) or result from improper vaccine preparation, handling or administration.[53,55]

Serious AEFI rarely occur, and the risk of catching certain vaccine-preventable diseases (such as pertussis) is generally far greater than the risk of morbidity associated with these AEFI.[56,57] However, in the minds of the public, the risk of AEFI are now greater than the

risk of vaccine-preventable diseases, some of which are now almost eradicated.[56,57] Vocal and tireless anti-vaccination groups appeal to parents' deep-seated concerns for the wellbeing of their children; the internet and social networking sites are used as effective tools to sway the undecided and reach new levels of global influence.[58,59]

Nevertheless, immunisation coverage remains high and relatively stable. Like the US,[60]Australia has immunisation coverage at near all-time high levels; immunisation rates for two-year-olds have increased steadily from 64% in 1997 to 92% by December 2009.[61] Loss of confidence in vaccine safety can lead to a decline in vaccine coverage and a resurgence of disease. For example, fears that the measles-mumps-rubella (MMR) vaccine might cause autism resulted in a resurgence of measles in the UK.[62] Now the theory has been debunked, the MMR immunisation rates have rebounded to 89% from a low of 80% in 2004.[59] To ensure the public's trust in immunisation, it is essential that the risks and benefits of each vaccine are evaluated.[63,64]

2.2.1 Changes to the immunisation schedule in Australia

Two decades ago, vaccination coverage of children up to six years of age was estimated to be only 53% in Australia,[65] and by 1994 there were 17,442 notifications of vaccine-preventable diseases, despite the ready availability of free, safe and effective vaccines.[66] Much effort has since been made to improve the immunisation schedule and coverage levels in Australia. Combination vaccines have been released on the market to reduce the number of individual vaccinations that need to take place; the less reactogenic acellular pertussis vaccine has replaced whole-cell pertussis vaccine; inactivated poliovirus vaccine (IPV) has replaced oral poliovirus vaccine (OPV); the ages of administration for some vaccines have been changed to prevent certain AEFI; and new vaccines have been introduced (e.g. varicella vaccine, thirteen-valent pneumococcal conjugate vaccine (13vPCV), meningococcal C conjugate vaccine (MenCCV), and rotavirus vaccine).[53,67,68]

Monitoring the safety of the new combination vaccines and the other newly introduced vaccines is essential to maintain confidence in the safety and effectiveness of the vaccines and sustain high coverage levels.

2.2.2 Prelicensing vaccine safety testing in Australia

All medications and vaccines undergo strict premarketing evaluation in preclinical trials (animal testing) and progressively larger clinical trials (Phases I to III) prior to the Therapeutic Goods Administration (TGA) approving licensure and supply.[16,53,69]

Prelicensing clinical trials rigorously assess vaccine safety, but have a number of important limitations:

- Clinical trials typically do not enrol enough people to detect adverse events occurring at a rate of 1 in 10,000–100,000.[57] Although common reactions are usually detected, rare or delayed reactions are often missed;
- Vaccines are tested on healthy subjects. Vaccine safety and efficacy are not assessed for all members of the public who may eventually be inoculated, including vulnerable populations, e.g. elderly, pregnant women, immunocompromised or sickly;
- Follow-up is usually of a short duration. AEFI that manifest in the long-term may go undetected;
- Usually single vaccines or just the combination vaccine under study are administered; therefore, few or no vaccine-interactions are examined.

After new vaccines are introduced into immunisation schedules, there is continuing surveillance of safety and efficacy through phase IV trials and postmarketing surveillance.[53]

2.2.3 Postlicensing vaccine safety surveillance in Australia

Currently, Australia relies on passive (voluntary) reporting of ad hoc reports of suspected adverse medicine and vaccine reactions by health care providers, parents or vaccinees to state or federal health authorities.[18,19] Adverse events associated with medicines or vaccines can be reported to the Office of Product Review (OPR) of the TGA (formerly known as the Adverse Drug Reactions Unit) by health care professionals or the public by telephone (1300 134 237) or by prepaid reporting form ('blue card') or online at: http://www.tga.gov.au/safety/problem.htm. The reports are examined in depth by staff of the OPR, entered into an internal TGA database and, after a lag of three months, become accessible publicly via the Database of Adverse Event Notifications (DAEN). The data are further analysed by the National Centre for Immunisation Research and Surveillance (NCIRS) and regularly reported in the journal *Communicable Diseases Intelligence*,[67,70] along with annual estimates of immunisation coverage levels in Australia for vaccines recommended for the National Immunisation Program (NIP), as measured using the Australian Childhood Immunisation Register (ACIR).[61] The Advisory Committee on the Safety of Medicines (ACSOM) (formerly known as the Adverse Drug Reactions Advisory Committee) also provides the TGA with expert advice regarding medicine and vaccine safety and risk management.

While passive surveillance systems are useful in identifying safety signals for unexpected adverse events that may have gone undetected in prelicensing trials,[50,67] they have important limitations. For example, Australia's passive reporting system failed to readily detect an increased incidence of febrile convulsions within 24 hours of receiving the seasonal trivalent influenza vaccine as evident in state[71] and federal reviews[72] of the sequence of events leading up to a nation-wide temporary suspension of the 2010 seasonal

influenza vaccination program by Australia's Chief Medical Officer on April 23, 2010.

The main limitations of the Australian passive reporting system include:

- Underreporting — the passive surveillance system depends on individuals becoming suspicious that AEFI are related to a vaccine and then being motivated enough to report it;
- Biased reporting towards events with a close temporal relationship with immunisation and unusual reactions (e.g. severe skin rashes and allergic reactions);
- Delayed notifications — the dual reporting to state and federal authorities has been criticised as confusing and, together with the practice among state authorities of forwarding reports in batches, has resulted in delays in information exchange between the two, and an inability to detect early signals[71,72];
- Lack of agreed case definitions, or standardised reporting forms and protocols across jurisdictions, and variable quality and completeness of information provided in individual AEFI forms.[67,72]
- An inability to establish a causal relationship between a reported event and a vaccine; and
- Incidence rates cannot be calculated because of a lack of a precise numerator (adverse events) and, oftentimes, denominator, if there is a lack of reliable information on the number of administered doses.

In an attempt to overcome the problems of underreporting and delayed reporting, some jurisdictions undertake enhanced sentinel surveillance programs for specific AEFI. There are two separate programs and four participating jurisdictions (New South Wales, South Australia, Victoria and Western Australia).[73] The Australian Paediatric Surveillance Unit (APSU) sends monthly email requests and collates monthly reports of sentinel AEFI from paediatricians.[73] The Paediatric Active Enhanced Disease Surveillance (PAEDS) program

is hospital-based and coordinated through the NCIRS in collaboration with the APSU.[72] In the PAEDS program, surveillance nurses prospectively monitor cases of uncommon serious childhood conditions such as intussusception, varicella (vaccine failures) and acute flaccid paralysis.[72] The information gleaned from passive reporting systems is primarily intended for signal detection and hypothesis generation.[67] Passive reporting systems identify AEFI that are temporally associated with vaccination, but are unable to confirm whether a causal association exists.[19] Large population based studies using linked databases, and utilising statistical analyses that provide a measure of association and account for confounding, are required to provide more definitive evidence.[16,19] As described in Section 2.1.4, linking existing data for an entire population has proven to be more time- and cost- efficient than conducting conventional longitudinal studies based on samples, and has further advantages in terms of its inclusivity and representativeness minimising the potential for bias in the results.[28]

2.2.4 Developments internationally and in Australia

A limited number of countries,[20] which include the US,[50] the UK,[74] and some Scandinavian countries,[30,75] as well as a consortium of European countries (VAESCO),[31] use data linkage to test hypotheses about a potential causal association between an AEFI and vaccination (Table 2.1). In the US, the Centers for Disease Control and Prevention (CDC) has developed further capacity, through the Vaccine Safety Datalink (VSD) project, to undertake near real-time rapid monitoring of possible safety signals which may emerge after the introduction of newly licensed vaccines or changes to the immunisation schedule for existing vaccines.[50] The VSD project has the ability to link and analyse data pertaining to an annual population of 8.8 million members (3% of the US population) of its eight manged care organisations, known as Health Maintenance Organizations (HMOs).[50] Data

linkage has been successfully used to confirm or refute a causal association between a reported safety signal and vaccination (Table 2.1).

Other industrialised countries, including Australia,[16-18,76] lag behind in developing privacy-preserving data linkage systems, as do low- and middle- income countries, which lack the appropriate e-health infrastructure and expertise.[77,78] This is unfortunate, as Australia is one of only 15 countries identified by Black (2008) as having existing electronic records of immunisations and health outcomes which could potentially be used for linkage (Table 2.2).[20]

As it may not be possible to detect very rare reactions within a single country due to an insufficiently large population, there is potential for Australia to join a budding international collaboration to develop a global vaccine safety surveillance system using common protocols and data sharing,[31,77,83] provided it establishes data linkage capacity in the near future.

Table 2.1: Examples of data linkage studies for vaccine safety surveillance

Study	Country	Vaccine database	Outcome database	Vaccine	Condition	Causal association
VSD						
Glanz 2011[50]	US	7 HMOs	inpatient and emergency	TIV	medically attended events[a]	√
Haber 2008[79]	US	6 HMOs	medical outcomes[b]	RotaTeq	intussusception	×
Kramarz 2000[80]	US	4 HMOs	medical outcomes[b]	Influenza	asthma	×
Yih 2011[81]	US	8 HMOs	medical outcomes[b]	MCV4, TdaP, MMRV, HPV	30 health outcomes[c]	×
PRISM						
Yih 2012[82]	US	regional	claims data[d]	H1N1 2009	Guillain-Barré syndrome	×
VAESCO						
Andrews 2012[31]	England & Denmark	regional/national	hospital admissions	MMR	TP	√
Dieleman 2011[83]	5 European countries	regional/national	medical outcomes[e]	H1N1 2009	Guillain-Barré syndrome	×
Other						
Farrington 1995[84]	England	regional	hospital admissions	DTP, MMR	febrile convulsions, TP	√
Madsen 2002[85]	Denmark	national	autism register	MMR	autism	×
Cameron 2006[86]	Scotland	national	hospital admissions	OPV	intussusception	×

DTP=diphtheria-tetanus-pertussis, HMO=Health Maintenance Organization, H1N1=pandemic influenza A, HPV=human papillomavirus, MCV4=meningococcal conjugate vaccine, MMR(V)= measles-mumps-rubella(-varicella), OPV=oral polio vaccine, PRISM=Post-licensure Rapid Immunization Safety Monitoring system, TdaP=tetanus-diphtheria-acellular pertussis, TIV=trivalent influenza vaccination,TP= thrombocytopenic purpura, VSD=Vaccine Safety Datalink.

[a]TIV was associated with 4 common AEFI. [b]Can include hospitalisations, emergency visits, outpatient visits, pharmacy files and deaths. [c]10 signals observed, of which 9 were spurious. [d]From 5 national health insurers. [e]Hospitalisations, general practice, neurology and laboratory records.

Table 2.2: Survey results of available data linkage infrastructure in 2007 for monitoring childhood vaccine safety by country[20,87]

Country	Immunisation registry	Scope	Hospital outcomes data	Scope
With suitable data sources (potential population >75 million)				
Australia	√	N	√	R
Belgium	√	R	√	N
Brazil	√	N	√	N
Canada[a]	√	R	√	R
China	√	R	√	N
Costa Rica	√	N	√	N
Denmark	√	N	√	R
Italy	√	R	√	R
Mexico	√	N	√	N
New Zealand[b]	√	R	√	R
Singapore	√	N	√	N
Thailand	√	R	√	R
UK	√	R	√	N
US[c]	√	R	√	R
Vietnam	√	R	√	R
Without suitable data sources				
Bangladesh	√	R	×	×
Chile	×	×	√	N
Finland[a]	√	R	√	S
Germany	×	×	√	N
India	√	S	√	S
South Africa	×	×	√	S
Switzerland	×	×	√	N

N=National, R= Regional, S=select sites. [a]Projected nationally within 5 years. [b]Using sentinel GP practices. [c]Data specific to Health Maintenance Organizations.

2.2.5 Study designs to detect adverse reactions to vaccines

Along with the development of surveillance systems, study designs and statistical methods have been introduced to try to establish causal associations between exposure to vaccines and adverse events. One such design is the self-controlled case series (SCCS) method, which was developed in the early 1990s to handle data obtained from large administrative datasets.[88] The SCCS method provides an alternative to more established cohort or case-control methods for investigating the association between a time-varying exposure and an outcome event.[89] The SCCS method has been used widely to investigate associations between vaccination and acute potential adverse events[90,91] and non-acute events such as autism,[92] and has been used more widely in pharmacoepidemiology and other areas of epidemiology.[93,94] The method is based only on cases: the incidence of an outcome during a 'high-risk' exposure time (i.e. post-vaccination) is compared with the incidence during the remaining 'control' time within person; the latter may consist of time both before and after 'high-risk' time. The within person design allows for the control for all time-invariant confounders (e.g. gender, socioeconomic status, genetic characteristics, location, co-morbidities).[89] Confounding due to age or temporal variation can be allowed for in the model.[89] Routine administrative databases, such as national hospital separations and deaths data, often do not include as much information on potential confounders as researchers would like, making the case series design attractive for studies using database data.[94] The SCCS method has been shown to provide better control of confounding that standard study designs such as cohort or case-control.[80,88,95]

2.2.6 Rationale for developing data linkage capacity for vaccine safety surveillance in Australia

As discussed in Section 2.2.3, existing means of vaccine safety surveillance do not provide population-wide coverage and unbiased reporting of adverse events. However, Australia

does possess the most important elements required for a national system based on data linkage. As a by-product of administrative and funding arrangements, Australia has:

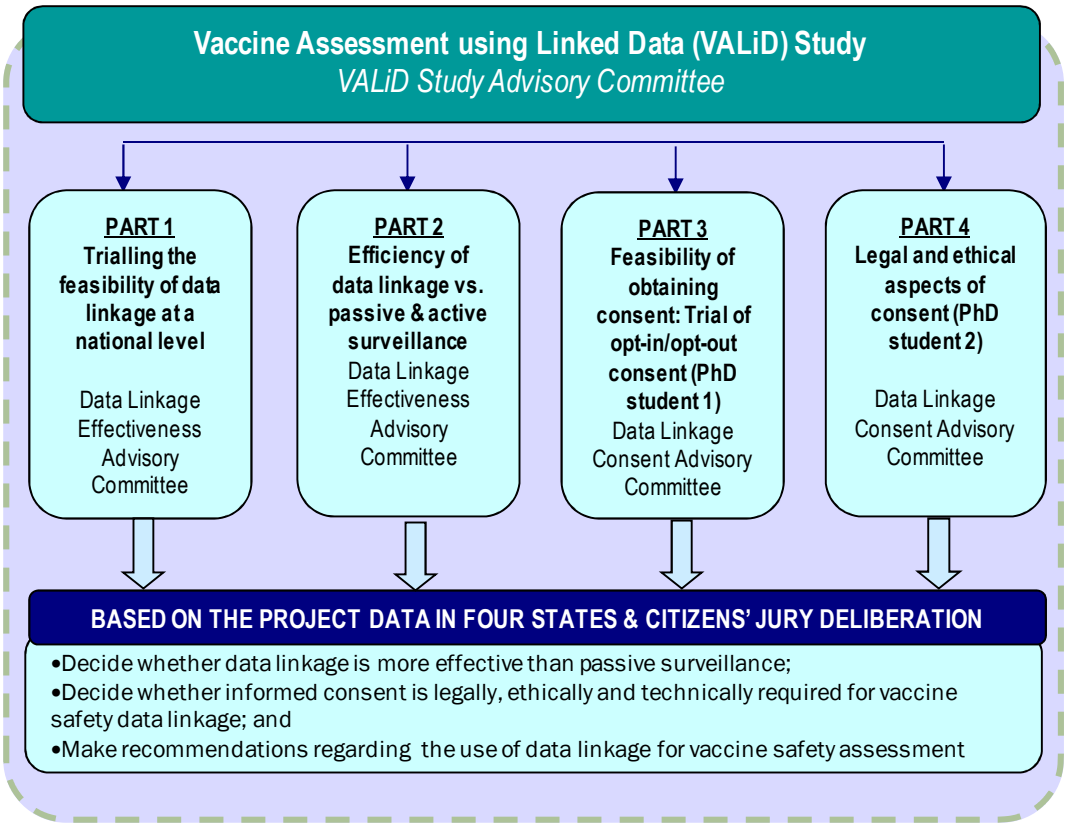
- The national Australian Childhood Immunisation Register (ACIR); the register was established on January 1, 1996 as a near-census of children less than seven of years of age receiving immunisations according to recommendations on the National Immunisation Program (NIP) schedule.[96] Approximately 99% of the 250,000 children born each year are registered with Medicare by 12 months of age.[96] Vaccine providers are funded to provide ACIR with vaccination details (name of child, date of birth, vaccination date, and vaccine antigens administered).[61,76]
- High quality administrative health care data in linkable databases spanning several decades, which cover the spectrum of health care encounters across the nation.[16] In the context of vaccine safety surveillance, the relevant databases are birth registrations, hospital separations, emergency department (ED) attendances, GP visits, disease registers (e.g. communicable diseases) and death registrations.

It is true that in addition to legislative restrictions, a researcher may need to negotiate with a number of different data custodians, depending on which datasets are to be linked. There are also practical barriers to data access. Some databases are standardised across jurisdictions in terms of collected data fields and data dictionaries (e.g. hospital separations, mortality data), but others are not (e.g. emergency visits, GP visits, disease registers). Nevertheless, the two most established data linkage units, the WADLS and CHeReL, have shown that it is feasible to standardise jurisdictional datasets spanning decades and deliver important research output,[26,97] and the other jurisdictional data linkage units are making good progress.[2] Due to the quality and span of the available datasets, Australia is ideally placed to become competitive on a global scale in the development of a modern pharmacovigilance system for both medicine[16] and vaccine[76] safety.

In Australia, data linkage for vaccine safety surveillance has been successfully piloted in one jurisdiction — South Australia (SA) — by linking the national ACIR with hospital inpatient and ED attendance data for all children registered for immunisations over a six-year period from 1997–2002. This pilot study by Gold et al. was entitled the South Australian Vaccine Safety (SAVeS) Data Linkage Pilot Project and was funded by the SA Department of Health from 2004–2006.[76] A total of 696,013 vaccine records were linked with 174,136 hospital inpatient and ED attendance records from the two major paediatric hospitals in SA: the Women's and Children's Hospital and Flinders Medical Centre. Using a self-controlled case series (SCCS) design[88,89] to control for both time and individual characteristics, the study demonstrated an increased incidence rate of febrile convulsions 6–11 days post-MMR vaccination (IRR 2.11, 95% CI 1.43–3.10; $P<0.001$), which equates to a vaccine-attributable risk of 1 convulsion per 6753 vaccines.[76] Although convulsions are a known complication of MMR vaccination,[84,98] the concurrent passive surveillance system did not detect any of the cases detected by data linkage, demonstrating its major limitations.[76]

An extension to the SAVeS pilot project entitled the VALiD study (Vaccine Assessment using Linked Data) was successful in procuring Australian Government funding through a competitive peer-review process from the Australian Research Council (ARC) in 2008–2010 (Linkage Project Grant LP0882394). The VALiD study consists of four components with the title, 'Can and should we link data at a national level? Vaccine safety surveillance: a case study'. The overarching objective of the VALiD study is to explore the feasibility and effectiveness of cross-jurisdictional linkage of Commonwealth and state health datasets in order to evaluate the safety of vaccines and to examine the ethical and legal acceptability aspects (Figure 2.4). A list of members of the VALiD Working Group and details of the funding sources are provided in Appendix 1.

Figure 2.4: Four components of the VALiD study[i]



Part one investigates the feasibility of data linkage at a national level. Part two compares the effectiveness of data linkage compared to current surveillance approaches, that is, passive surveillance by the Therapeutic Goods Administration (TGA), and the two enhanced sentinel surveillance programs: the hospital-based PAEDS and APSU collation of monthly paediatrician reports. Part three is the subject of this PhD thesis, and its main component is a randomised controlled trial of the feasibility of obtaining consent via two methods, 'opt-in/opt-out'. Part four is the subject of another PhD candidate's thesis, and comprises an examination of the ethical and legal considerations of data linkage for vaccine safety surveillance through a theoretical and qualitative analysis of community risks and benefits and privacy considerations. A citizens' jury was convened in March 2011 to deliberate on the VALiD study findings for the purpose of social decision making and the development of public policy.

[i] Diagram reproduced from the Chief Investigators' original ARC grant application with minor amendments.

2.2.7 Challenges in the implementation of data linkage in Australia

The preceding sections of this chapter have illustrated that, despite generally high parental immunisation compliance with childhood vaccines, concerns about the safety of vaccines can lead to decreases in immunisation coverage and resurgence of disease. Australia's current postmarketing system for identifying AEFI is passive surveillance, but is not adequate for this purpose due to inherent flaws. Reliable postmarketing surveillance is needed to monitor the safety of ongoing changes made to Australia's immunisation schedule. Data linkage has the power to detect rare adverse reactions to vaccines that are not detected in clinical trials due to size and cost limitations and biased subject selection. Leading Australian researchers have been advocating for an Australia-wide program of data linkage to evaluate the benefits and risks of medicines[16,17] and vaccines.[18,19]

Australia is one of only a small number of countries that have existing capacity to use data linkage to evaluate the safety of vaccines,[20] through the availability of a national childhood immunisation register, and good quality national electronic administrative databases of hospital morbidity and mortality outcomes. However, progress in achieving linkage of the datasets has been slow because of privacy concerns, lack of political will, and barriers in access to, and linkage of, the various datasets across jurisdictions.[15-18] The VALiD study aims to progress Australia's capacity to use data linkage as a national vaccine safety surveillance system. It plans to address the technical, legal and ethical barriers to implementing data linkage across jurisdictions and, through community engagement, explore the public views about the use of medical information for this purpose.

2.3 The feasibility of consent for data linkage

This thesis deals with the secondary use of administrative health records in research; the primary use of the data collection was for the original medical treatment. The collection and use of linked administrative databases for secondary purposes such as the conduct of health, medical and social research continues to be challenged by concerns regarding privacy, confidentiality and informed consent, despite rigorous safeguards on the security of health information and demonstrated public benefit.[27] Although Australia's legislative framework is complex, it does not present an insurmountable barrier to such research.

2.3.1 Australia's legislative framework and consent waivers

The Commonwealth *Privacy Act 1988* (the *Privacy Act*) initially applied only to Commonwealth public sector agencies (the original 11 *Information Privacy Principles* in Section 14), but was amended in 2000 to cover the private sector (the 10 *National Privacy Principles* in Schedule 3). The *Privacy Act* (Cth) defines the basis for use or disclosure of identifiable data[ii] for a secondary purpose as being closely related to the primary purpose of the data collection or otherwise in line with what a patient can reasonably expect based on information provided to him or her at the time of collection. The limited exceptions for identifiable data release include: the individual has given express or implied consent; the use or disclosure is authorised by law; or a waiver of consent has been granted by a properly constituted Human Research Ethics Committee (HREC). Individual consent is not required for the use of non-identifiable data[iii] (if data are anonymised so that there is no reasonable way of identifying the individuals involved) and such use can be exempt from HREC review if it involves negligible risk.[9,99]

[ii] Data in which the identity of the individual can be reasonably ascertained from identifiers including the person's name, sex, date of birth and residential address.

[iii] Data in which identifiers were never present, or have been removed, so that the identity of the individual cannot reasonably be ascertained. The definition includes linked records in which it is known that the data relate to the same individual, but the identity of the individual is unknown.

According to the *Privacy Act* (Cth), Sections 95 (for Commonwealth agencies) and 95A (for the private sector) provide for guidelines to be developed by the National Health and Medical Research Council (NHMRC) and approved by the Privacy Commissioner.[7,8] The guidelines enable an HREC to decide to waive the requirement for consent if they conclude that the public interest in the research outweighs, to a substantial degree, the public interest in privacy, and certain qualifying criteria are met. The primary set of guidelines for human research, developed jointly the NHMRC, the Australian Research Council (ARC), and the Australian Vice Chancellors' Committee, entitled the *National Statement on Ethical Conduct in Human Research* (the *National Statement*)[9] does not have legal force other than as a contractual obligation for researchers in receipt of NHMRC grants.[99] However, it provides guidance to HRECs and researchers regarding the qualifying criteria necessary to justify a consent waiver within its Chapter 2.3.6.[9] To waive consent, an HREC must be satisfied that:

a) the research carries no more than low risk;
b) the benefits justify any risks;
c) consent is impracticable;
d) there is no reason to think that participants would not consent if asked;
e) there is sufficient protection of privacy;
f) there is an adequate plan to protect confidentiality;
g) there is a plan for making important findings available to research participants;
h) participants will not be deprived of any financial benefits to which they would be entitled, and;
i) the waiver is lawful.

The *National Statement* clarifies in its Chapter 3.2.4 that the use of identifiable data in creating a master linkage key[5] is allowed:

> Where research involves linkage of data sets, approval may be given to the use of identifiable data to ensure that the linkage is accurate, even if consent has not been given for the use of identifiable data in research. Once linkage has been completed, identifiers should be removed from the data to be used in the research unless consent has been given for its identifiable use.[9]

The onus is on the researchers to demonstrate that the exemption is in the public interest as benefits outweigh any potential risks. It is important to note that, although an HREC may approve a consent waiver for a data linkage project, the relevant data custodians make the final decision as to whether the data linkage can proceed.[10]

Researchers' responsibilities in terms of proper management, security and retention of research data and abiding by the principles of honesty, integrity, accuracy and responsibility in the publishing and dissemination of research findings are outlined in the *Australian Code for the Responsible Conduct of Research*,[40] developed jointly the NHMRC, the ARC, and Universities Australia. As part of their contractual obligations, researchers usually sign confidentiality agreements to state they will never attempt to ascertain the personal identity associated with any anonymous patient-related subject matter.[99] This means that a person's identity cannot be reasonably ascertained unless the researcher uses list-matching or some other illegal means to unmask identities, for which there are severe penalties.[99] This, in combination with the privacy protections from the use of the strict separation principle when linking data, leaves only a minute residual risk of reidentification that would require illegal activity on behalf of the researcher.[99]

An HREC can decide that seeking consent is impracticable when either (i) information or (ii) economic resources are insufficient.[100] Insufficient information can describe the situation where the participant is untraceable or deceased, and insufficient economic

resources when the costs of obtaining consent are prohibitively expensive and unlikely to achieve a good return.[100] As time elapses from the point of data collection (birth, GP visit, hospital admission), people are more likely to move between primary care practices and/or residential addresses or die (depending on the age of the cohort), leading to a higher rate of non-response and increased costs as establishing contact becomes more difficult.[101]

In addition to the *Privacy Act* (Cth), a number of states and territories also have their own legislation regulating the handling of health information in the public sector and private sector and the co-existence of a dual-tier of health information privacy legislation can lead to confusion and hesitancy among government bureaucrats, HRECs and data custodians.[10] Research that crosses borders creates further problems as there are jurisdictional differences in legislation and this leads to concerns over loss of control of the data and uncertainty about the equivalency of legislation.[10] Since December 2001, a range of key stakeholders have expressed concern to the NHMRC that the implementation and/or interpretation of Commonwealth and State privacy legislation is compromising research and health care, and ultimately undermining the ability to achieve improvements in individual and public health.[6]

There are examples where an Australian HREC has decided to reject an application for research involving data linkage of health information without consent in the mistaken belief that such projects are not ethically or legally acceptable.[102] Since the consent waiver provision is broadly defined, HRECs and data custodians may lack sufficient guidance as to the exact conditions under which it may be acceptable to release data for research purposes without individual consent and, therefore, may err on the side of conservatively applying the guidelines.[10-12,102] Researchers have encountered inconsistencies and lengthy delays in decisions made by HRECs and data custodians, refusals to grant consent waivers, or insistence on opt-in rather than opt-out approaches to seeking consent.[10,12-15]

Similar privacy principles introduced in law by many governments in other countries in the last two decades have also created confusion for HRECs, data custodians and researchers in the interpretation of the legislation and the application of the provision of the consent wavier.[103-107] These include the Health Insurance Portability and Accountability Act Privacy Rule (HIPAA) 1996 in the US; the European Union Data Protection Directive 1995; the Data Protection Act 1998 and the National Health Service Act 2006 (formerly the Health and Social Care Act 2001) in the UK; and the Personal Information Protection and Electronic Documents Act 2000 in Canada.[103,105] Internationally,[104,108] and in Australia,[24] the opt-out approach was commonly used in the past. However, many HRECs and institutional review boards now consider the opt-out approach to be intrusive and unethical, since it is unclear whether people who have not opted out have tacitly consented or have simply failed to opt out through a lack of a reasonable opportunity or simple inaction.[104] Instead, many HRECs and institutional review boards now mandate an opt-in approach.[24,104,106,108]

2.3.2 Legislative requirements of the Australian Childhood Immunisation Register (ACIR)

The ACIR is considered a nearly complete population register; it commenced on January 1, 1996, and is administered by its data custodian, Medicare Australia.[96] The high rate of participation is attributable to its operation on an opt-out basis, whereby unless parents object, children aged less than seven years who are enrolled in Medicare are automatically included on the ACIR and those who are not enrolled in Medicare are added when details of a vaccination are sent to ACIR by the immunisation provider.[96]

The ACIR is a statutory register and the information collected by the Australian Government is protected by legislation under the *Health Insurance Act 1973* (Cth) Part IVA and the secrecy provisions in Section 130 and the *Information Privacy Principles* of

the *Privacy Act 1988* (Cth).[99] Section 46E(1)(a)(iiia) of the *Health Insurance Act* authorises the Chief Executive Officer (CEO) of Medicare Australia to release anonymous data about the immunisation of children to researchers.[99] Access to identified information is restricted to purposes relating to the immunisation or health of children, which is narrowly defined and not inclusive of research *per se* (see Section 46A). Disclosure of identified information to recognised immunisation service providers requires parental consent (Section 46E (2)(b)), whereas disclosure to Australian Government Department officials, recognised immunisation service providers authorised by the Medicare CEO, and officials and employees of prescribed bodies does not (Section 46E (d) and (e)).

The CEO of Medicare Australia may disclose identifiable data for research to a person who, in the Federal Health Minister's opinion, is expressly or impliedly authorised by the person to whom the information relates to obtain his or her data, or where the Minister certifies that the disclosure is in the public interest; *Health Insurance Act 1973* (Cth) Section 130(3); *National Health Act 1953* (Cth) Section 135A(3).[99] For a data linkage study, researchers only receive coded files of pre-linked data without personal identifiers.[100] However, disclosure of identifiable information to a data linkage unit is required for the purpose of creating a master linkage key.[5,26] The lawful disclosure of identifiable information from ACIR is allowed under the Guidelines Under Section 95 of the *Privacy Act* (Cth)[8] if the proposed medical research is approved by a properly constituted HREC in accordance with these guidelines. The HREC can grant a waiver of consent if the public interest in the research use outweighs to a substantial degree the public interest in privacy and certain qualifying criteria are met, as listed in Australia's *National Statement*.[9] Otherwise, HRECs are guided to seek opt-in consent for research, whereby people are informed about the research and included if they actively signal willingness to participate.[9]

2.3.3 Translation of legislation into practice: experience of two vaccine safety studies

As Section 2.3.2 explain, the ACIR has a release mechanism which allows identifiable data to be released for research purposes, including data linkage, if an appropriate delegate of the Australian Government Department of Health and Ageing deems the release to be in the public interest, and an HREC grants a consent waiver. The bureaucratic cascade of events that is required to engage the appropriate delegate may not be straightforward or transparent. Also, there can be a lack of transparency in the decision-making process of the delegate; researchers are not informed of the criteria used by the delegate to decide whether the project is in the public interest. In the pilot study conducted using linked immunisation and hospital morbidity data for SA over a six-year period (1997–2002) by Gold et al.,[76] obtaining a consent waiver from the HRECs of the two hospital involved and the Departments of Health at state and federal level was timely, but obtaining authorisation for ACIR data release from a delegate from the Australian Government Department of Health and Ageing for the pilot study was long and protracted. Two years elapsed from the initial ethics application submissions to receipt of ACIR data.[76]

The VALiD study has encountered similar barriers; nearly four years have elapsed since the initial ethics application submission to the Departmental Ethics Committee (DEC), Australian Government Department of Health and Ageing, on May 4, 2009, and the ACIR data have not yet been received (as of February 2013). Approvals were granted for cross-jursidictional linkage of ACIR data with hospital morbidity data on June 21, 2010 and for mortality data on May 24, 2011. After extensive negotiations with the Australian Government Department of Health and Ageing, delegate approval for data release was given in the form of a signed Public Interest Certificate by Australia's Chief Medical Officer, Professor Chris Baggoley, on April 26, 2012. Meanwhile, the ARC funding has

been gradually whittled away to sustain staff salaries although progress in the achievement of the VALiD study milestones has stalled.

In summary, although Australia's legislative framework does not, of itself, present a barrier to research, bureaucratic complexity and stonewalling by the Australian Government in the administration of the legislation can obstruct projects from meeting their milestones, despite the funding for such projects also originating from the Australian Government through a nationally competitive peer-review process.

2.3.4 Consent options for epidemiological studies

The Macquarie dictionary defines consent as follows: 'to give assent; agree; comply or yield.'[109] The options that are available for all types of research, including data linkage, are:

- Use without consent — using non-identifiable data that may be exempt from ethical review, or using identifiable data and requiring ethical review;
- Opt-in — an approach requiring ethical review in which each person is individually informed about the study and their consent is sought (either verbally, written, or computer-mediated); or
- Opt-out — an approach requiring ethical review in which each person is individually informed about the study and included unless they indicate an unwillingness to participate (either verbally, written or computer-mediated).
- Notification or 'social contract' — a less stringent variation of the opt-out approach requiring ethical review, in which people are informed generally about the use of their health records for research using mass media, declarations on organisational forms, or notices or brochures in clinical practices and included unless they approach their physician, a designated contact number or website to opt out.[110]

The request for consent may be either project-specific; future extended use for projects that are extensions of, or closely related to, the original project or in the same general field; or a broad (unspecified) authorisation for research use.[9,110]

Individual patient consent by the opt-in method is a principle embodied in the Declaration of Helsinki[111] and the preferred option by HRECs and data custodians under most circumstances. The *National Statement* does not even make mention of the opt-out approach, but rather states in its Chapter 2.2:

> Respect for human beings involves giving due scope to people's capacity to make their own decisions. In the research context, this normally requires that participation be the result of a choice made by participants—commonly known as 'the requirement for consent'. This requirement has the following conditions: consent should be a voluntary choice, and should be based on sufficient information and adequate understanding of both the proposed research and the implications of participation in it. [And in Chapter 2.2.5] Consent may be expressed orally, in writing or by some other means (for example, return of a survey, or conduct implying consent), depending on: (a) the nature, complexity and level of risk of the research; and (b) the participant's personal and cultural circumstances.[9]

Singleton (2006) asserts that the opt-in approach is the better strategy only when the researcher does not know what people's preferences are likely to be.[110] For both opt-in and opt-out approaches, the choice is being made for people who choose not to choose.[110] Under the opt-in approach, the failure to act leads to non-inclusion, but 'non-participation' may not stem from a meaningful consideration of the pros and cons, resulting in a firm decision.[112] Under the opt-out approach, recruitment may largely depend on the inertia of individuals and therefore the true proportion of people who do not wish to participate may be understated. In the circumstance where most people would probably agree to take part

in a study (say 90%), then the opt-out method is the most efficient method for participants and researchers and does not undermine the principle of providing choice.[110]

Others also agree that the opt-out approach is a valid default strategy for studies that pose a low risk to patients as it is less susceptible to selection biases and low participation rates,[23,108,113-117] whereas particularly sensitive topics might justify the need for opt-in consent.[108] However, there is also considerable opposition to an opt-out approach because it is argued that it does not fulfil the moral function of informed consent as one cannot be sure that all who tacitly consented really intended to participate.[118] Nowhere is the polarised opinion more evident than in the controversial debate taking place in the medical literature over the last decade about whether organ donation after death should move from an opt-in to an opt-out strategy to improve donation rates.[119-122]

In summary, the opt-out strategy is viewed as being controversial and it is omitted from research guidelines. However, few studies have actually explored and compared the reasons for participation and non-participation using the opt-in and opt-out approach. Therefore, little is known about the relative performance of the opt-in and opt-out approach in the level of informed consent achieved, and the extent of under- or over- estimation of the true proportion of people who want to participate.

2.3.5 The ethical principles of consent

The Declaration of Helsinki places an obligation on researchers to procure fully informed consent, without coercion or deception, for patients to participate in health and medical research.[111] In clinical encounters, four ethical principles are proposed to govern the relationship between the health professional and patient — autonomy, beneficence, nonmaleficence (do no harm), and justice.[38,123] Although these four principles are given equal weight in ethical theory, autonomy, or 'the capacity to determine one's own life and

make one's own decisions',[9] has become the prevailing principle in the latter half of the 20th Century and contributed to the dominance of informed consent in clinical care.[38]

Many ethicists claim that informed consent is valuable because it supports individual autonomy,[38,124] although there are varying opinions about what autonomy entails, and examples of how it is an elusive concept that is not always possible to attain.[124-126] Perhaps a better reason for placing so much value on informed consent is that it provides reassurance that people who go through the process are neither coerced or deceived.[124] However, the capacity of people to achieve 'informed consent' is also subject to debate; individual preferences and requirements for information vary, and attempts to obtain the desired level of knowledge as judged by the researcher or clinician can be futile in practice.[110,124,126] A small body of literature demonstrates that the informed consent process among research volunteers in many RCTs is less than ideal.[127-133] For these reasons, the oft-quoted phrase 'fully informed consent' is an illusion.[124] Also, sometimes the process of seeking consent may produce needless distress or alarm (maleficence) among individuals who may think they are being contacted to participate because it is likely they have medical condition under study, when statistics indicate that this is unlikely.[113]

The Declaration of Helsinki espouses opt-in consent as a core principle of medical research and positions the balance towards protecting the rights of the individual over the interests of those who can benefit from research, stating that:

> In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.[111]

There are certain implications that arise from this viewpoint and involve an ethical trade-off between two potential benefits: (a) the maintenance of protections of persons; and (b) the realisation of any benefits that might have been gained through research without consent.[134] While it is important to protect an individual's right to live their life free from

unsolicited intrusion, when the balance is too much in favour of protecting individual rights through a universal consent requirement, important gains in knowledge that can lead to better patient care are inhibited, and, ultimately, individuals in society bear the consequences.[38,134] It may be that people may have (or if given the opportunity for reflection, come to have) legitimate expectations that their health records will be used without their explicit consent for certain purposes,[134] including public health surveillance.[38] Public consultation is required to characterise the reasonable expectations community members may have for research use of their data without consent, and what kinds of research are valued and supported, and what kinds are not.[134]

2.3.6 Practical considerations of consent

Informed consent cannot be provided by patients who are incompetent, unconscious or incapacitated,[135] or secured for all disclosure of third party information (e.g. when family history is provided without the consent of all to whom the information pertains).[124] Neither can individual informed consent be used in choosing public health policies (e.g. water fluoridation, seat-belt use),[124] conducting health services research (i.e. evaluating a model of service provision that may not be subject to freedom of choice)[136] and conducting cluster RCTs (i.e. where randomisation is at the cluster level, for example, randomly allocating GP practices to different interventions).[118] While participation in an RCT in which individual are randomly allocated to each arm is generally with opt-in consent, the scientific validity of the trial may depend on HREC approval of a waiver of consent or an opt-out approach from some aspects of the design, e.g. accessing medical records to identify potentially eligible subjects or continued follow-up of all enrolled subjects after the cessation of the trial.[137]

There is considerable opposition to an opt-out approach because it does not appear to offer people adequate choice to participate or not, since the investigator infers willingness to

participate from non-response, regardless of a person's real interest in the study.[104,118] For this reason, McRae et al.[118] argues that 'it is difficult to see how [the opt-out approach] can reasonably fulfil the moral function of informed consent', although he later concedes that the opt-out approach 'may, however, be justified on pragmatic grounds' as an alteration of the consent procedure, provided an HREC judges that it is necessary for the feasibility of a study and participation involves no more than low risk.

Others argue that the opt-out approach is a valid default strategy for low risk research because it enhances study rigour through minimising selection bias.[23,103,107,108,110,113,114] For example, 21 of 27 (78%) of the voluntary non-statutory clinical registers in Australia[iv] operate using the opt-out consent approach,[114] and there are many documented failures of non-statutory registers due to poor patient enrolment when operation is on an opt-in basis.[138-140] A strategy that may help enhance respect for autonomy when the opt-out approach is being used is for health organisations to provide up-front declarations and opt-out clauses to patients about the use of personal information for electronic health records,[141] clinical registries,[114,142] health research,[108] and the possibility they may be invited to take part in clinical trials.[137] Also, an opt-out system needs to ensure that expressing dissent is easy and costless; there should be no penalty for opting out (e.g. no withdrawal of care); and there should be adequate communication about the ongoing possibility to opt out, for example, by using reply-paid envelopes and/or a web-based opting out facility.

In practice, however, the implementation of any consent model can encounter problems of public apathy, complexities in the governance of consent, and unforseen ethical dilemmas. The following example concerns electronic medical records, for which the implementation

[iv] Some health data is collected compulsorily under legislation without consent for the efficient running of health services (e.g. statutory registers such as the ACIR, registrations of births and deaths, notification of communicable diseases, among others).

of a consent model is likely to be more complex than simply for the secondary use of health information in data linkage, but there is a commonality in some of the problems that might be encountered.

In 2007-08, the UK National Health Service (NHS) initiated a system of shared electronic health records called a summary care record (SCR), which is a centrally stored summary of a person's GP records made accessible over a secure Internet connection to authorised health care providers. The consent model initially chosen for the SCR was opt-out, that is, an SCR would be created unless a person explicitly withdrew consent within a defined timeframe from the start of a public awareness campaign that included letters, posters, leaflets, road shows and media coverage.[143] In addition, NHS patients could access their own SCR via a separate technology (HealthSpace), which operated using an opt-in consent model. The extensive public information program achieved low public awareness and minimal interest in either the SCR or HealthSpace.[143,144] Of the 95% of the population who had received a letter in a sample area, only 30% were aware of the SCR and 8% were aware of HealthSpace.[143]

Information technology problems and unforseen ethical dilemmas arose when trying to design the system to respect the wishes of people who opted out, and NHS staff considered that both the operation of an opt-out model and its access restrictions to staff with a legitimate relationship to the patient were 'too complicated to work in practice'.[145,146] Examples included circumstances in which someone opted out and then chose to opt back in again (or vice versa), or couples disagreed on whether they wanted their child to be included, or cases of vulnerable 'at risk' children whose parents sought to opt out on their behalf.[146]

In 2008-09, the NHS moved to a 'consent to view' model, in which the SCRs are created without a requirement for individual consent, but the health care providers are instructed to

obtain the patient's (opt-in) consent prior to viewing the record, except in the case of medical emergencies.[146,147] The British Medical Association recommended this change be made and civil liberties groups demanded it.[146,147] However, this new consent model also posed operational and ethical problems. These included a downturn in accesses to SCRs by some NHS staff, workarounds (e.g. staff indicating the patient had given consent when, in fact, they hadn't been asked), raised concerns that the extra consent-seeking step could delay treatment, and confusion regarding whether third party consent was acceptable when patients lacked the capacity to consent.[146]

In summary, there are some benefits arising from the current research emphasis on informed consent, but also important limitations and practical implementation barriers that are often overlooked. Public consultation is required to examine whether people may consider research uses of their health information without consent to be a breach of privacy when considered in the light of the potential public benefits. If consent is preferred, the public view on the relative acceptability of the opt-in and opt-out approach needs to be discerned.

2.3.7 Community preferences for consent

Population surveys and focus groups have shown that the public generally expresses support for research that improves public health and the quality of care.[6,10,12,148-151] Nevertheless, many respondents have a poor understanding of health and medical research and regard it as peripheral to their direct medical care.[6,149,151-154] The usual frame for these population surveys is simply to ask respondents about their attitudes and views with little or no elaboration on the way the research is conducted, the privacy safeguards applied, and the potential application of research findings to inform clinical practice and public health policy.[138] In general, cross-sectional telephone and mail surveys, face-to-face interviews and focus groups conducted internationally[148,149,151,154-159] and in Australia[6,102,160-162] have

concluded that when medical records are to be accessed for research purposes rather than for clinical care, respondents prefer to be asked for permission first, either verbally or in writing, including for data linkage studies.[6,148,149,151,157] For example, an NHMRC-commissioned study in Australia that consisted of nine focus groups and a telephone survey of 301 members of the general public and 60 'health consumers' (recent users of the health system) found overall consensus that the consent process, 'despite being cumbersome for researchers, was useful and legitimate'.[6]

Some studies,[12,102,155,156,160-162] but not others,[149,152,153,159] have found that the majority of the respondents want opt-in consent for both the use of identifiable and de-identified (or otherwise known as non-identifiable) data, although people are not usually well-acquainted with the concept of 'de-identified' data and what it entails.[12] In Australia, repeat telephone surveys have shown that opinions have become more favourable towards the use of de-identified information without consent, increasing from 33% of 1524 adults in 2001 to 46% of 1503 adults in 2007, with the proportion who prefer consent to be sought declining from 61% in 2001 to 51% in 2007.[160,162]

Since the regulatory emphasis placed on privacy and consent is informed by these interpretations of public opinion,[138] it is unfortunate that community consultation has been constrained by the provision of limited and undifferentiated contexts to questions. An alternative frame is to provide a contextual framework regarding the intended societal benefits and privacy safeguards [115,163,164] and the costs of obtaining consent in relation to the finite budget for public health,[100] thereby informing participants of the reasons why it might be appropriate to collect identifiable data without consent. When this context is provided, the public has the opportunity to weigh up individual privacy rights against the benefits arising from research, and can be more amenable to research being conducted without individual consent.

For example, a recent telephone survey of 600 adults in Western Australia (WA)[115] and a face-to-face interview of 2872 respondents in the UK[163] garnered strong public support for a proposed new law of statutory notification of cases to the WA Birth Defects Register (79%) and the National Cancer Register (81%), respectively. Respondents were provided with scenarios of how such information would enable researchers to monitor the prevalence of birth defects[115] or cancer incidence[163] and examine environmental determinants.[115,163] Most people in the WA and UK samples did not consider the statutory notification of postcodes (85%[115] and 88%[163]) and names and addresses (65% and 81%) or the unsolicited receipt of a letter, via the registrant's doctor, inviting participation in university research (76% and 87%) to be an invasion of privacy. In contrast, when 49 focus group participants in the UK considered the transfer of patient data to a population disease register, and were simply informed that 'information will be used to plan services and for research', participants demonstrated much anxiety and fear of unauthorised access to data by external agencies.[149]

Prior to the VALiD study, there was one scoping survey conducted as part of the SAVeS pilot study by Gold et al.[15] Face-to-face interviews were conducted in 2004 with 2893 residents of metropolitan and rural SA (response rate of 66.3%) and mail surveys received from 566 immunisation providers (response rate of 68.2%). Most respondents thought it was very important to monitor vaccine safety (95% and 98%, respectively). Data linkage was also supported for general health research; most were very (63% and 59%) or somewhat (30% and 32%) comfortable with the concept and four-fifths were very (33% and 32%) or somewhat (50% and 51%) confident personal information would be kept confidential. In contrast, a series of nine focus groups conducted in Australia in 2004 found participants to have cautious attitudes towards the use of linked databases of medical information because of fears the safeguards could fail to prevent potential misuse, although

the only safeguards participants could think of were de-identification and the allocation of a number.[6]

I can find no other published studies on public opinions regarding the use of data linkage for postmarketing surveillance of the safety of childhood vaccines, and this is an important gap. In the closely related field of postmarketing surveillance of medicine safety, a citizens' jury was recently held in New Zealand to explore public views on the use and linkage of identifiable medical information to evaluate the risks and benefits of medicines.[164] Jurors considered expert input regarding the scientific, legal, ethical, clinical and consumer aspects and engaged in personal reflection and group deliberations. After considering the individual privacy and public good arguments, the jurors unanimously concluded that postmarketing surveillance of medicine safety was warranted using identifiable information about people, without their consent, given appropriate privacy safeguards and minimum use of identifiable data.[164] The authors concluded that the citizens' jury process achieved an informed public, whose conclusions diverged from less sophisticated public opinion surveys because jurors were provided with a specific research example, the opportunity to ask questions and the framing of the privacy and public interests.[164]

In summary, there is a paucity of community consultation on the appropriateness of data linkage for postmarketing vaccine safety surveillance. Public consultation is needed on this important topic. In order to aid informed decision-making in relation to the public interest and privacy argument, the public should be provided with a contextual framework within which people can consider aspects such as the individual right to privacy, informational privacy safeguards, public benefits of the research, and the costs of seeking consent.

2.3.8 Cost-benefit evaluation of consent options

In 2007, Zeps et al.[113] argued that Australia was undergoing a time of major economic rationalisation of health care services, and, in such a climate, the use of valuable resources to obtain individual consent 'could in itself be seen as unethical'. A requirement for consent for large population-level data linkage studies may also compromise many of the unique benefits possible through this kind of research.[5,39,100,165] There is little research directly examining the cost-effectiveness of opt-in and opt-out approaches to recruiting patients for different diseases or conditions, but what is known is outlined below.

In a UK trial conducted from 2001–2008 in which it was important to have unbiased assessment of prostate cancer incidence, Noble et al.[101] applied unsuccessfully to the Patient Information Advisory Group (PIAG) for access to medical records without consent under the appropriate legislation at the time (Section 60 approval under the Health and Social Care Act 2001). The authors were instructed by the PIAG, after 18 months deliberation, to undertake a pilot study of the feasibility of obtaining opt-in consent from men diagnosed with prostate cancer when a letter was sent from their treating GP or secondary care clinician. An overall high consent rate of 84% or 179 of 230 men was achieved, at an estimated average cost per consented man of £123. This was a greater cost per case consented than the estimated £82 per case (approximately $161 Canadian) for the establishment of a Canadian Stroke Network Registry between June 2001 and December 2002.[139] However, the Canadian study achieved a much lower participation rate (39% of 4285 eligible patients during phase 1 of the project and 51% percent of 2823 eligible patients during phase 2) and around $500,000 Canadian dollars were funnelled into consent-related issues during the register's first two years of operation. In addition, because it was difficult to approach sick or cognitively impaired patients, important selection biases were apparent, such that registry patients were in better health than the

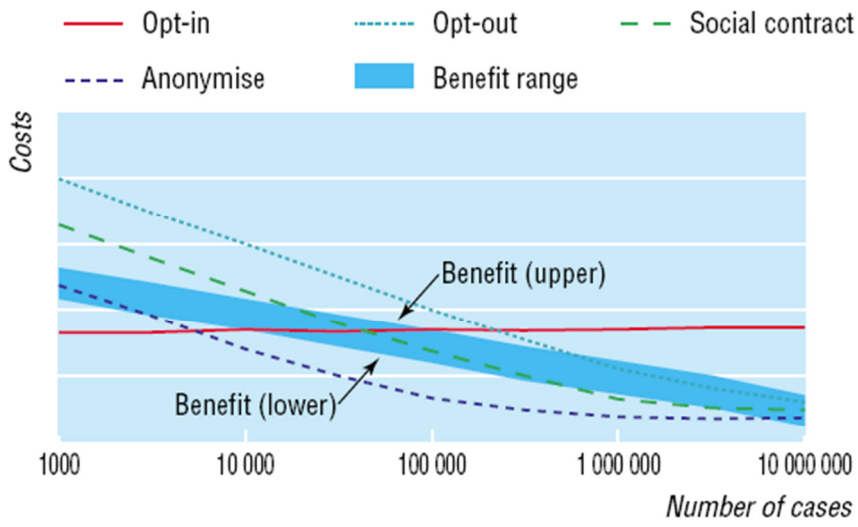
typical patient with stroke in the target population, undermining the utility of the register.[139] In light of these considerations, the registry was shut down, as it was unable to fulfil its main objective of monitoring the delivery of stroke care at each hospital.[139]

Singleton (2006) compared, purely in terms of cost in the UK, four possible consent processes:

1. project-specific opt-in consent;
2. project-specific opt-out consent;
3. notification or 'social contract' (i.e. where people are informed generally about research uses of their health records with a provision to opt out);
4. no consent: presuming that the data have been anonymised prior to use so that consent is not legally required.[110]

From plotting reasonable but arbitrary cost and benefit figures on a log-log scale (Figure 2.5[110]), Singleton concluded that the project-specific opt-in method is viable only for smaller studies; a project-specific opt-out process that includes a funded public information campaign is only just viable for very large studies; the social contract approach is the only real alternative to express consent for population level studies; and anonymisation seems to be suitable for all but the smallest studies.[110] While the methodological detail on how the costs were estimated for each scenario is scant, and may not be directly applicable to the Australian context, the findings appear to be plausible.

Figure 2.5: Cost-benefit comparison for the different forms of consent according to study size[110]



Schroy et al.[104] in the US compared the cost-effectiveness of three methods, using a non-randomised design, on enrolment of patients into an RCT of colorectal screening from March 2005 and April 2006. In the *Click* method, treating providers identified eligible patients within their practice and indicated on an Electronic Medical Record (EMR) tick-box whether a patient opted in to being approached by a researcher to be asked to participate in the trial (i.e. patients were asked to give opt-in 'consent for consent'). The *Letter* method was similar, except treating providers sent a referral letter to eligible patients with an enclosed opt-in return postcard to indicate whether they gave opt-in 'consent for consent'. In the *Call* method, the researchers telephoned eligible patients directly and asked them to participate in the trial with the option to opt out — the treating provider's involvement was limited to oversight of the patient list. The *Call* method was the most feasible and cost-efficient — the participation rate in the trial was 35.4%, and it was estimated it would take 2.4 years at a cost of US$138,518 to recruit a target sample of 900 patients at an average cost of US$156 per patient, and would be even cheaper (US$99 per patient) if the patient identification process was automated by a database analyst. The *Click* method was the least efficient in terms of the time taken to reach the sample size goal —

based on a participation rate of 16.7%, it would take 40.5 years at a cost of US$62,419 with an average cost of US$129 per patient. The *Letter* method was economically the least efficient — based on a participation rate of 2.1%, it would take 27.9 years at a cost of US$1,737,757 with an average cost of US$1967 per patient.

Overall, the investigator-led direct contact 'opt-out' strategy was substantially more cost-effective and feasible than strategies initiated and mediated by the treating provider for patient recruitment to clinical trials. The results of the analysis illustrate that an ethics committee stipulation for opt-in 'consent for consent' will jeopardise study funding and the ability to reach the target goals of recruitment. In a multi-centre cohort study of children born with congenital heart defects in the UK, Knowles et al.[105] asserted that an ethics committee stipulation that the recruiting cardiologist first seek approval from the family's GP (i.e. obtain opt-in 'consent for consent') extended the follow-up by more than one year because of poor recruitment and impeded long-term survival follow-up. A cost estimate of the delays was not provided.

In summary, the research suggests that the opt-in approach, and in particular, a two-tier 'consent to consent' requirement, results in suboptimal enrolment, although this appears to be somewhat dependent on the patient group under study and the disease or condition. Consequentially, the delay to reach the target sample size can lead to significant costs. In contrast, the opt-out approach achieves high enrolment and is much more cost-effective. However, for population-level studies, which are the scale of most data linkage studies, the only viable cost-effective alternatives are the notification/'social contract' or no consent approaches.

2.3.9 Selection bias and consent options

Important considerations in the conduct of health research are statistical precision and scientific validity in terms of striving for complete case enumeration (e.g. clinical registries) or, otherwise, a representative sample of the population at risk. Studies that proceed without the requirement for consent will not be affected by losses in scientific rigour, provided all the data are available. Under a requirement for informed consent, those who participate may not constitute a random sample of all those approached. Therefore, utilising a method of consent that yields the highest possible participation rate can guard against loss of precision and minimise selection bias.

A recent systematic review of 17 prospective observational studies that utilised the opt-in approach found that of the 161,604 eligible patients, 66.9% opted in to the use of data from their medical records, but participation varied substantially across the studies from 36.6% to 92.9%.[106] Consent rates may have been affected by patient group, disease/condition under study and method of recruitment (hospital or community). Differences in the socio-demographic measures of age, sex, race, education, income, or health status were apparent between participants and non-participants, although the same measures were not collected for all studies. However, there was no clear pattern in the magnitude and the direction of the effect, which may be somewhat attributable to the heterogeneity across studies in study design, research and population settings, recruitment methods, and requests for consent. The authors concluded that the requirement for informed consent led to a variety of biases when using data from medical records, but the way in which these biases arose was not clear due to a lack of systematic deviation in the distribution of socio-demographics among consenters.[106]

Another systematic review identified 11 studies where opt-in consent was sought specifically for access to private health information for data linkage.[166] The consent

proportions varied widely from 39% to 97%, although eight studies were at the higher end, with consent proportions of 72% or higher.[166] The variation in consent proportions could not be explained by study design in terms of country, age group, sampling frame (population survey or health service), consent approach (letter or face-to-face) or identity of the person asked to consent (subject, parents or care giver).[166]

The highest participation rates among the two systematic reviews were achieved when consent was sought for the use of health information in data linkage rather than for clinical research, i.e. when the burden imposed by participation was minimal.[106,166] Use of a personal approach and the creation of rapport is known to improve opt-in consent rates.[100] In a national longitudinal study of more than 10,000 Australian children, a face-to-face home interview yielded a 97% parental consent rate to data linkage.[167] In a population-based cohort study of chronic disease aetiology in Alberta, Canada, nearly all adults recruited by telephone interviewers using random digit dialling indicated consent to data linkage by return of a consent form (97%).[168] In the UK Millennium Cohort study (a longitudinal follow-up of almost 19,000 babies born in the UK in 2000–02), a face-to-face home interview yielded a 92.9% parental consent rate to data linkage.[169] Although a personal approach can be effective, extra resources are required, and this is particularly so for socially disadvantaged and ethnic minority groups, which may require over-sampling, interpreter services, and additional visits in order to get adequate representation.[169]

No systematic reviews have been conducted of participation rates among studies that use the opt-out strategy; however, it is generally observed that participation rates are higher using this approach.[113,115,170,171] An opt-out to opt-in procedural change may be accompanied by a drop in the participation rate, and vice versa. For example, participation in a telephone survey of registry patients with acute coronary syndrome dropped from 96% to 34% after the introduction of a requirement to opt in by returning a mailed consent form

first; whereas, previously patients could verbally opt out at the time of the call.[172] A change in legislation in three countries (Spain, Austria and Belgium) from an opt-in to an opt-out organ donation system resulted in an increase in organ donation rates.[121] For two types of electronic health records in England: the summary care record (opt-out), which is controlled by the National Health Service (NHS), and HealthSpace (opt-in), which is a separate patient-controlled initiative for recording their own internet-based health record, participation was substantially higher using the opt-out approach (99% *vs* 0.12%).[173]

Some studies have found a directional difference between participants and non-participants using the opt-in approach, in which participants are more likely to be in better health and of higher socioeconomic status. In Scotland, 10,000 randomly sampled adults were invited to communicate their views about the NHS by opting into being sent a postal or electronic survey. Adults who consented (20%) were more likely to be older, female and not living in a socially deprived postal area.[174] In a hospital-based stroke study, patients who opted in were more affluent those who did not opt in, had a better prognosis, experienced milder illness of a long enough duration to be consented (rather than transient events that result in short hospital stays), and fewer were admitted to less accessible outlying wards of the hospital.[116]

In contrast, minimal differences between participants and non-participants have been observed using the opt-out approach. In a longitudinal study of breast cancer conducted in the US, community-dwelling women aged 65 years or older with incident breast cancer in 2003 were sampled from Medicare administrative claims data and invited to participate using an opt-out approach.[117] Participation was 70% initially for women with traceable contact information (2005–2006), and participation did not differ by socioeconomic status, health status, type of cancer treatment or race/ethnicity, although older women and those living in New York State were less likely to take part.[117] An opt-out approach to screening

for antibiotic resistance among patients with urinary tract infections achieved high participation (85.5%) and no significant differences between participations and non-participants in terms of age, gender or whether the urine sample was positive or not.[175] In a comparison of three methods of patient recruitment to a colorectal RCT, an investigator-initiated opt-out strategy (the *Call* method) had the highest accrual rate (35.4%) and afforded minimal selection bias.[104] The accrual rates in the alternative provider-led opt-in approaches (the *Letter* and *Click* methods) were too low (2.1% and 16.7%, respectively) to allow for an examination of selection bias.[104]

Although there is considerable variation across the studies reviewed, the opt-out approach generally appears to achieve a higher rate of participation than the opt-in approach. When planning a study, it is often hard to predict the participation rate that might be achieved when using the opt-in approach, as it relies on the research setting and population group under study, the nature of the illness, the methods employed and the effort expended. Selection biases commonly occur when using the opt-in approach; however, further research is required to characterise the direction and the magnitude of the effect.

2.3.10 Randomised controlled trials of consent options

There are no RCTs comparing the numbers and characteristics of participants enlisted in a data linkage study under opt-in and opt-out conditions. Five RCTs[21-25] relating to other aspects of medical research have shown that the opt-out approach yields higher participation rates than opt-in consent. These five trials are reviewed in detail in Chapter 3, Table 3.1. In these trials, the extent of participation ranged widely from 48%–85% in the opt-in arm and 59%–100% in the opt-out arm and all but one[23] had a small sample size or flawed methodology. Only two of the RCTs have some applicability to data linkage, in that participation was passive and did not involve clinic visits or screening tests.[21,25] Four of the five trials[22-25] reported that there was evidence of selection bias in the clinical and socio-

demographic characteristics of participants in the opt-in arm when compared with participants in the opt-out arm, but comparisons to the target population in each arm (external validity) were limited because of the small number of characteristics available for all eligible patients: either age and sex alone,[23,25] or additionally, area-based socioeconomic status.[24] Overall, there was no clear pattern in the direction or magnitude of the selection biases observed across the four trials.

2.3.11 Research justification

The literature review has demonstrated that data linkage used in the arena of health and medical research is a relatively new and rapidly expanding field. Data linkage has strong privacy preserving features through the use of a best practice protocol which assures the anonymity of pre-linked data to researchers. It holds much value for use in postmarketing vaccine safety surveillance, which is currently limited to passive (voluntary) reporting systems that have serious deficiencies, including not being able to establish whether there are causal relationships between vaccines and adverse events, particularly for rare events.

Although Australia's legislation presents no explicit barrier to the use of data linkage for vaccine safety surveillance, the complexity and varying interpretation of the dual federal and state/territory legislative framework by key government bureaucrats, data custodians and HRECs often leads to conservative, risk-averse decisions, so that opt-in consent is mandated for use in data linkage for health and medical research in circumstances where a waiver of consent is appropriate.

The ACIR, as a statutory register, has a specific release mechanism allowing release of identifiable data to researchers or others if the Federal Health Minister (or an appropriate delegate) decides an exemption is in the public interest as the benefits of the activity under review substantially outweigh any potential risks. The reality is that the process of obtaining an exemption can take several years due to bureaucratic delays at the federal

government level, at great cost to researchers and undermining their ability to meet often federally funded milestones, which are the conditions of the original funding agreement.

The current regulatory emphasis on privacy and consent has been informed by mostly flawed population surveys that do not provide the contextual background of intended societal benefits and privacy safeguards and costs of seeking consent in relation to the finite budget for public health. Most of these studies have found the public wants to be given the opportunity to opt in to research. There are only a handful of RCTs that have compared the performance of the opt-in and opt-out approach to seeking consent, and none involve data linkage.

The topic of this thesis is the design, conduct and results of an RCT of parental opt-in and opt-out consent to data linkage for the purpose of vaccine safety surveillance, followed by two telephone surveys: one of parents enrolled in the trial and the other of the general SA public. The primary outcome of the RCT is a comparison of the participation rates in each arm.

For the two consent approaches, the telephone interview of parents will explore:

- The reasons for participation and non-participation and parents' underlying intentions;
- Recall and understanding of the study purpose to evaluate the level of informed consent achieved;
- Socio-demographic characteristics among participants and non-participants in each arm for evidence of selection bias and an examination of the practical implications;
- Consent preferences and whether opinions change after the context of the public benefits of the research and the costs of seeking consent are described;
- Support and trust in data linkage for vaccine safety surveillance;
- Opinions on vaccine safety and effectiveness; and
- Parental vaccination practices in relation to the newborn.

The generalisability of parental opinions will be compared using select questions repeated in a community telephone survey in SA.

The findings of this thesis should fill a gap in knowledge about the level of public support and trust in data linkage for postmarketing safety surveillance of childhood vaccines. It will report on the findings from parental and general community consultation about whether there should be any requirement for consent. The relative performance of the opt-in and opt-out approaches to seeking consent will be thoroughly assessed, for the first time, in the context of a data linkage study. Together, these findings will fill important gaps in knowledge and inform future epidemiological study design and conduct.

3 Publication — A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage: study protocol

3.1 Preface

This chapter contains the first of four articles contributing to this thesis, all of which have been accepted for publication in peer reviewed journals. This article has been published in *Trials* and outlines the study protocol for the randomised controlled trial (RCT).[176]

RCTs are considered to be the gold standard for the evaluation of health care interventions, as long as they are properly designed, conducted and reported.[177] The Consolidated Standards of Reporting Trials (CONSORT) statement is a set of recommendations on the specific information to include in the report of an RCT to demonstrate the internal and external validity of its findings.[177,178] The CONSORT statement comprises a checklist of essential items to be included in the report, including enrolment procedures, intervention details, randomisation strategy, allocation concealment, blinding after assignment to interventions, sample size calculation, outcome assessments, statistical methods and a diagram for depicting the flow of participants through the trial.[177,178] The protocol of the RCT follows the CONSORT statement; peer reviewers for the *Trials* journal referred to the checklist when assessing the paper for suitability for publication.

3.2 Statement of authorship

Berry JG, Ryan P, Braunack-Mayer AJ, Duszynski KM, Xafis V, Gold MS, the Vaccine Assessment using Linked Data (VALiD) Working Group. A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage: study protocol. *Trials* 2011;12:1, doi: 10.1186/1745-6215-12-1.

By signing below, the authors declare that they give consent for this paper to be presented by Jesia Berry towards examination for the Doctor of Philosophy.

Jesia Berry (Candidate)

Developed the trial protocol and randomisation schedule, co-authored the study invitation material, designed the telephone survey questions, conducted interviews, collected the data, reviewed the literature and drafted the manuscript.

Signed: …… Date: 22/2/13

Philip Ryan

Contributed to the conception and design of the study, procured funding, designed the statistical analysis for the trial, provided statistical advice, helped design the study invitation material and telephone survey, and reviewed the manuscript.

Signed: …… Date: 22-2-13

Annette Braunack-Mayer

Contributed to the conception and design of the study, procured funding, helped design the study invitation material and telephone survey, and reviewed the manuscript.

Signed: …… Date: 01.02.2013

Katherine Duszynski

Contributed as trial coordinator to leading the design and direction of the study, co-authored the study invitation material, helped design the telephone survey, applied for ethical approval, and reviewed the manuscript.

Signed: …… Date: 20/02/2013

Vicki Xafis

Contributed to the design of the study invitation material and telephone survey, and reviewed the manuscript.

Signed: …… Date: 21/2/13

Michael Gold

Contributed to the conception and design of the study, procured funding, helped design the study invitation material and telephone survey, and reviewed the manuscript.

Signed: …… Date: 20/2/13

3.3 Article

3.3.1 Abstract

Background: The Vaccine Assessment using Linked Data (VALiD) trial compared opt-in and opt-out parental consent for a population-based childhood vaccine safety surveillance program using data linkage. A subsequent telephone interview of all households enrolled in the trial elicited parental intent regarding the return or non-return of reply forms for opt-in and opt-out consent. This paper describes the rationale for the trial and provides an overview of the design and methods.

Methods/Design: Single-centre, single-blind, randomised controlled trial (RCT) stratified by firstborn status. Mothers who gave birth at one tertiary South Australian hospital were randomised at six weeks post-partum to receive an opt-in or opt-out reply form, along with information explaining data linkage. The primary outcome at 10 weeks post-partum was parental participation in each arm, as indicated by the respective return or non-return of a reply form (or via telephone or email response). A subsequent telephone interview at 10 weeks post-partum elicited parental intent regarding the return or non-return of the reply form, and attitudes and knowledge about data linkage, vaccine safety, consent preferences and vaccination practices. Enrolment began in July 2009 and 1129 households were recruited in a three-month period. Analysis has not yet been undertaken. The participation rate and selection bias for each method of consent will be compared when the data are analysed.

Discussion: The VALiD RCT represents the first trial of opt-in versus opt-out consent for a data linkage study that assesses consent preferences and intent compared with actual opting in or opting out behaviour, and socioeconomic factors. The limitations to generalisability are discussed.

Trial registration: Australian New Zealand Clinical Trials Registry

ACTRN12610000332022

3.3.2 Background

Options for consent that are available for health and medical research involving human subjects are: no consent, using either identifiable or non-identifiable data; opt-in consent, where each person is informed about the research and their consent is sought; and opt-out consent, where each person is informed about the research and included unless they indicate an unwillingness to participate.[110] A request for consent may be either project-specific, extended (for future research projects) or broad authorisation for research use.[9] Under the opt-in approach, the subject's failure to act leads to non-inclusion; but 'non-participation' may not stem from a meaningful decision and may reflect a lack of contemplation or intention.[112] Under the opt-out approach, inclusion in research may largely depend on individuals' inertia; therefore, the true proportion of people who do not wish to participate may be understated.[179]

In Australia, the *National Statement on Ethical Conduct in Human Research*[9] guides Human Research Ethics Committees (HRECs) to require opt-in consent under most circumstances. However, health information can be used in the conduct of specific activities (including research of various types) without a subject's permission 'provided an assessment is made by an HREC that the research and other activities are, on balance, substantially in the public interest'.[6] Data linkage is one such specific activity,[9] defined as 'the bringing together, from two or more different sources, data that relate to the same individual, family, place or event'.[26]

The development in recent decades of integrated electronic administrative health care databases has enabled sophisticated and powerful population-level data linkage studies on the factors influencing health and wellbeing, and health services evaluation.[39,44,107,180]

Privacy advocates have perceived these developments as a potential threat to privacy, sparking an increase in the rigour and complexity of the privacy framework in Australia and associated regimens of HREC submissions.[6,39,100,181-183] Threats to privacy are minimised when data linkage adheres to the best practice protocol,[5] whereby strict separation of individual demographic identifiers from clinical health information is maintained during and after the linkage process, ensuring researchers never receive personal identifiers and data custodians never exchange identifiable health data.[5,26] Despite the availability of privacy-conserving linkage protocols, some data custodians still require each individual's opt-in consent for release of data,[13,100] with severe adverse consequences for the quality and validity of research. Holman (2001) suggests that when a system of consent leads to participation rates of less than 90%, the information available for the research becomes biased.[100]

Several cross-sectional surveys and focus groups conducted internationally[148,149,151,155-157] and in Australia[6,160] have shown that the public has a strong preference to be asked for consent for health and medical research, including for data linkage studies.[6,148,157] There are some notable exceptions: in two cross-sectional surveys conducted in the United Kingdom[163] and Australia,[115] the majority of the public did not consider the inclusion of identifiable health data in a cancer registry and birth defects registry without consent to be an invasion of privacy and expressed support for statutory case registration. In terms of consent to data linkage, there are no studies that have compared the numbers and characteristics of participants enlisted under opt-in and opt-out conditions using a well-designed Randomised Controlled Trial (RCT). While there are RCTs that relate to other aspects of medical research,[21-25] the extent of participation has varied widely, ranging from 48%–85% in the opt-in arm and 59%–100% in the opt-out arm, and all but one[23] had a small sample size or flawed methodology (Table 3.1).[21,22,24,25]

Table 3.1: RCTs of opt-in and opt-out consent

Study population and purpose	Parents in a health district of the UK were asked for consent for inclusion of low birth-weight infants on a register for the purpose of monitoring disability in children[21]	Mothers in the US were asked for consent for inclusion of infants at high risk to participate in a clinical trial of primary follow-up care[22]	Angina patients in two general practices in the UK were asked for consent to be involved in clinical research[23]	Patients aged 50–74 years in a general practice in Australia were asked to consent to testing decision aids for the screening of colorectal cancer[24]	Cancer patients in the Netherlands who had undergone primary surgery were asked for consent for the storage of excised tissue for future research purposes[25]
Sample size randomised (n)	Opt-in: 39 Opt-out: 30	Opt-in: 32 Opt-out: 25 (3 were excluded as they did not receive the allocated intervention)	Opt-in: 252 Opt-out: 258	Opt-in: 92 Opt-out: 60	Opt-in: 60 'Opt-out plus': 73 Control group (standard opt-out): 131
Mode of invitation	Verbal information, letter and reply slip given by a nurse prior to an infant's discharge from hospital	Verbal information and reply form given by a nurse within 24–48 hours of delivery. The opt-out form was shortened to include only specific disclosures that are appropriate for low risk research	Letter, information leaflet and reply card sent from a doctor	Letter sent from a doctor (plus reply card for the opt-in arm only)	Verbal information, specific information leaflet and reply form given by a doctor/nurse. The control group was only given a routine hospital leaflet and did not receive verbal information
Mode of response	Reply-paid slip	Reply form was collected from the mother	Reply card or telephone	Telephone or email (or reply-paid card for the opt-in arm)	Reply-paid form. The control group leaflet instructed patients to opt out by informing their doctor

Table 3.1 (Continued)

Study population and purpose	Parents in a health district of the UK were asked for consent for inclusion of low birth-weight infants on a register for the purpose of monitoring disability in children[21]	Mothers in the US were asked for consent for inclusion of infants at high risk to participate in a clinical trial of primary follow-up care[22]	Angina patients in two general practices in the UK were asked for consent to be involved in clinical research[23]	Patients aged 50–74 years in a general practice in Australia were asked to consent to testing decision aids for the screening of colorectal cancer[24]	Cancer patients in the Netherlands who had undergone primary surgery were asked for consent for the storage of excised tissue for future research purposes[25]
Reminder letter	No	No	After two weeks for the opt-in arm only	No	No
Time to respond	Not stated	Prior to discharge from hospital. Once a mother reached a decision, an interview occurred within the next 24 hours (usually 2 hours)	Opt-in: Not stated Opt-out: patients could opt out verbally when telephoned after two weeks	Not stated	One month
Participation rate	Opt-in: 79% Opt-out: 97%	Opt-in: 75% Opt-out: 91%	Opt-in: 48% Opt-out: 59%	Opt-in: 51% Opt-out: 90%	Opt-in: 85% Opt-out plus': 97% Standard opt-out: 100%
Recruitment rate	Not applicable	Face-to-face interview Opt-in: 81% Opt-out: 82%	Clinic attendance Opt-in: 38% Opt-out: 50%	Telephone survey Opt-in: 47% Opt-out: 67%	Postal and telephone survey Opt-in: 93% and 52% 'Opt-out plus': 93% and 51% Standard opt-out: 88% and 47%

Table 3.1 (Continued)

Study population and purpose	Parents in a health district of the UK were asked for consent for inclusion of low birth-weight infants on a register for the purpose of monitoring disability in children[21]	Mothers in the US were asked for consent for inclusion of infants at high risk to participate in a clinical trial of primary follow-up care[22]	Angina patients in two general practices in the UK were asked for consent to be involved in clinical research[23]	Patients aged 50–74 years in a general practice in Australia were asked to consent to testing decision aids for the screening of colorectal cancer[24]	Cancer patients in the Netherlands who had undergone primary surgery were asked for consent for the storage of excised tissue for future research purposes[25]
Evidence of selection bias	Not stated	Modest differences were found. Subjects recruited in the opt-in arm were older, more likely to be married and undergo a vaginal delivery than subjects in the opt-out arm	Subjects recruited in the opt-in arm were healthier and had less risk factors for coronary disease than subjects in the opt-out arm	Subjects recruited in the opt-in arm were more likely to prefer an active role in decision making than subjects in the opt-out arm	Subjects recruited in the opt-in arm were similar in age, sex, education and type of cancer to the 'opt-out plus' arm. The control group was similar, except that women were over-represented
Design flaws	Small sample size, non-random allocation and no mention of whether blinding was used	Small sample size and the collection of reply forms is resource-intensive and impracticable on a large scale	None evident	Small sample size and non-parallel design	Small sample size and no mention of whether blinding was used

Only two RCTs[21,25] are relevant to data linkage in that participation required no effort on the part of the subject in terms of clinic attendance or involvement in disease screening, and there were no follow-up reminders, which are not economically or logistically feasible for large population-level studies.[100]

There has been relatively little research on non-participants in RCTs because of problems in obtaining ethical approval.[108,184] Only two RCTs have elicited the intent behind the return or non-return of forms for subjects in the opt-in and opt-out trial arms by means of a face-to-face interview,[22] or postal and telephone survey.[25] We designed a large RCT of opt-in and opt-out consent for a proposed data linkage study into adverse events following immunisation. All eligible subjects were included in the RCT without their prior consent being sought, which necessitated a consent waiver from the approving HREC. Our justification for not obtaining consent was that if prior consent were sought it would lead to a selection bias in the study sample. In order to study reasons for participation and non-participation, we followed up the trial with a telephone interview aimed at all randomised subjects, whether or not they had indicated consent to the data linkage study.

Purpose

Primary objective and hypotheses

To determine which method of obtaining parental consent (opt-in or opt-out) provided the highest participation rate for a population-based childhood vaccine safety surveillance program using data linkage.

The following Null hypotheses will be tested:

(1) There is no difference in the participation rate for the opt-in and opt-out method, that is, the proportion of parents who opt in by return of a reply form (or telephoning or email) and the proportion who do not opt out.

(2) Neither the opt-in nor opt-out method of consent will result in parental participation greater than 90%.

Secondary objective and hypotheses

To examine consent preferences, and attitudes and knowledge about vaccine safety, data linkage and vaccination practices by means of a structured telephone interview of all randomised subjects.

The following Null hypotheses will be tested:

(1) There are no differences in the motivations and barriers given for the return/non-return of the reply form by subjects who consented, or did not consent, in the opt-in arm compared with subjects in the opt-out arm.

(2) There are no differences in consent preferences, and attitudes and knowledge about vaccine safety, data linkage, vaccination practices and socio-demographics of subjects who consented, or did not consent, in the opt-in arm compared with subjects in the opt-out arm.

3.3.3 Methods and design

Study design and flow

This was a single-centre, stratified (firstborn versus subsequent births), single-blind, parallel-group RCT conducted in the Women's and Children's Hospital (WCH), a tertiary referral centre in metropolitan Adelaide, the capital city of South Australia (SA) with a population of about 1.19 million in 2009.[185] Approximately 25% of all South Australian babies are delivered at the hospital.[186] The study population consisted of parent(s) of every consecutive child born in a three-month period: from July 27, 2009, to October 25, 2009, inclusive. Data listings of eligible live births were provided by the SA Department of Health (SA Health) utilising the electronic patient management system (*HOMER*™). The RCT received ethical approval from the Children, Youth and Women's Health Service

(CYWHS) HREC (Reference: REC2087/7/11) who granted a waiver of the usual requirement of individual, fully informed consent to participate in an RCT and allowed the limited disclosure to subjects of the true purpose of the trial.

Inclusion and exclusion criteria

Selection of subjects was based on the hospital records of mothers who met the study eligibility requirements (Table 3.2). Further exclusions were made on a case-by-case basis if an audit of the medical record revealed that the mother was incarcerated, mentally incapacitated, or the baby had been adopted or placed into foster care. Since infant (and maternal) deaths following a mother's discharge are not routinely captured in the hospital's patient management system, the South Australian Births, Deaths and Marriages Registration Office was engaged to conduct weekly searches to identify any deaths which might have occurred prior to randomisation and, where identified, the mother was excluded from the trial. Weekly searches for deaths continued until parents exited the interview. The flow of subjects in this study is shown in Figure 3.1.

Sample size

The primary outcome of interest was a comparison of the parental participation rate in each arm. To detect an effect size difference of 10% (assuming 80% in the opt-out arm and 70% in the opt-in arm) using a two-tailed test at the 5% level with power of 80% we required 313 subjects in each arm (total 626 subjects). A further 10% inflation allowed for the stratified design of randomisation for the prespecified confounder of firstborn status. Thus, the sample size for the primary outcome required 344 subjects in each arm: a total of 688 subjects. However, important secondary outcomes of interest related to the recruitment of parents for the subsequent telephone interview. The sample size required for the secondary outcome was 544 subjects in each arm: a total of 1088 subjects.

Table 3.2: Eligibility criteria and rationale

Criterion	Rationale
Inclusion criteria	
Mothers who had a live and surviving birth at the WCH	A birth must be viable and surviving to enable data linkage of immunisation encounters at two months and hospital admissions after birth
Mother's age was equal or above 18 years	This is the age accepted by HRECs where informed consent can be given by an individual
Mother was a resident of SA	The data linkage will involve only South Australian children whose immunisation encounters will be linked with admissions to a South Australian hospital. Cross-jurisdictional migration will be unaccounted for, i.e. if a family moves interstate after the birth or an infant is admitted to an interstate hospital
Exclusion criteria	
Maternal death, stillbirth or neonatal death. In the instance of twins or triplets, if one died, the mother was excluded	To avoid causing distress to a bereaved family
Infant stays in the NICU of 2 weeks or longer	To avoid causing distress to a family dealing with issues of infant illness and prematurity
Home births and births that occurred at other hospitals and were subsequently managed at the WCH	To ensure each mother had received the same type of care prior to discharge and data were available in the hospital patient management system for all variables of interest

Randomisation and blinding

The unit of randomisation was the mother who was randomly allocated, by date order of confinement, to the opt-in and opt-out arm in the ratio 1:1. The randomisation schedule was stratified by firstborn status (first live and surviving birth versus subsequent births). It used randomly permuted blocks of sizes 2, 4, 6 and 8 and was created using the program ralloc[187] in Stata statistical software.[188] We stratified on firstborn status because we judged that a parent's likelihood of participating in a data linkage study of childhood vaccine safety, and their attitudes towards vaccination and vaccination practices, could be

influenced by previous experience of infant immunisation, especially if an adverse event occurred following immunisation.

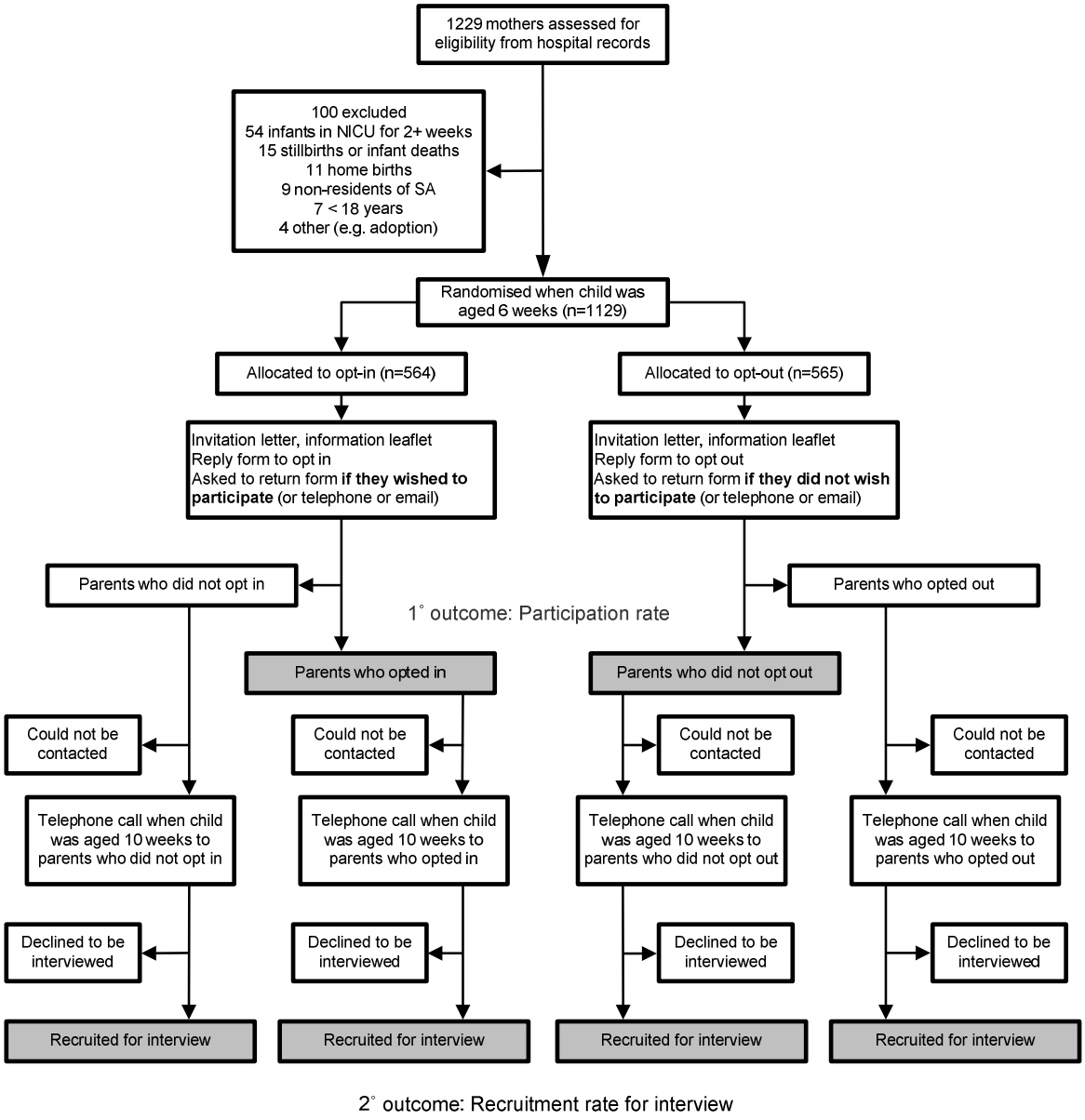
The trial was single-blinded: parents were unaware that two types of consent were being compared, but were aware of the data linkage study. Blinding was not appropriate for the two researchers [JGB, JW] who conducted interviews since the interview structure required knowledge of whether the parent had, or had not, returned the reply form. For the analysis and reporting, the primary outcome will be assessed by one researcher who will be blind to allocation.

Interventions and follow-up

All households received a cover letter (addressed to the mother), an information leaflet and a reply-paid form, with different formats according to allocation to the opt-in or the opt-out arm (Figure 3.1). The study material invited parents to be part of a 'Vaccine Data Linkage Study' in order to investigate data linkage as a new way of checking for rare reactions to vaccines by looking at large numbers of children. Parents were asked for permission to link infants' two-month vaccination records with any hospital visits occurring in the month following vaccinations. The study invitation was mailed after randomisation at six weeks post-partum; its arrival was timed to advise parents of the study one to two weeks prior to the scheduled two-month vaccinations. Parents in the opt-in arm were instructed to return a reply form to signal willingness to participate in data linkage; whereas parents in the opt-out arm were informed they would be included unless they returned a reply form to refuse consent. Telephone or email response was also accepted. No follow-up reminder letters were sent, to make the participation rate – the response to one invitation – relevant to large population data linkage studies. The cut-off time for data to be included in the estimation of the participation rate at 10 weeks post-partum included the first day of the 11th week to allow for internal hospital postal delays, giving all parents four weeks to respond. The

telephone interview occurred when infants reached 10 weeks of age, corresponding with one to two weeks after administration of the two-month vaccinations to enable data collection on vaccination practice and experience of adverse events.

Figure 3.1: Flow diagram of opt-in compared with opt-out trial



Data management

All data collection and interviews occurred at the study centre. A database was developed to manage the study flow and follow-up of subjects, the mail-out of study invitation material, and transcription of telephone interview responses from paper booklets into electronic format. All data were kept securely on a non-networked computer. File back-ups and associated paperwork were stored in a locked filing cabinet, as required by relevant guidelines for the ethical conduct of research.

Outcome assessment

The primary outcome at 10 weeks post-partum was the proportion of parental participation in each arm, as indicated by the respective return or non-return of a reply form (or via telephone or email response). Secondary outcome data, including socio-demographic characteristics, were captured from the hospital's patient management system and at the subsequent telephone interview at 10 weeks post-partum. These included: 1) the interviewee's age, gender, marital status, country of birth, main language at home and level of education; 2) the mother's age, marital status, country of birth, Indigenous status and firstborn status of the infant; and 3) the household size, composition, annual income, Socio-Economic Indexes For Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD)[45] and location (major cities or other). The IRSD and location measures were derived from postcode of usual residence.

The study invitation material and telephone survey were designed and administered according to recommended principles.[189,190] They were initially piloted on a small number of academic staff, and then further modified and refined through piloting on a convenience sample of 20 subjects similar to the study's target group: parents of young children. The pilot groups were re-utilised by the study team for training purposes to develop skills in the delivery of the telephone interview. The survey collected information on the parent's recall

of the study and its purpose, reasons for the return or non-return of the reply form, consent preferences, understanding of data linkage and the level of trust in its protection of privacy. The survey also canvassed attitudes towards vaccination in terms of its public health benefit, safety, and effectiveness; vaccination practices; experiences of minor and serious infant illness and the likelihood of being vaccine-related; and socio-demographics measures. Questions relating to consent preferences[148] and perceptions about the safety and effectiveness of vaccines[191] were derived from published telephone surveys to assist in comparison with similar studies.

The interview schedule was designed to be pragmatic to optimise response rates. While the researchers endeavoured to interview the parent (either mother or father) who had opted in or opted out as identified by name on the reply form, this was not always possible even with multiple call-backs. In such instances, the other parent, if available, was interviewed as a proxy. For households who neither opted in nor opted out, the interviewers had no knowledge of which parent, if any, had read the study invitation material. The first parent to answer the telephone was invited, as there was no basis for preferentially interviewing one parent over the other.

Analysis plan

All analyses will be performed on an intention-to-treat basis. The primary outcome, consent to participate, will be compared using a chi-square test, modified appropriately (Mantel-Haenszel method) to account for the permuted block randomisation. The Type I error level is set at 0.05 (two-tailed). There are no prespecified confounders for the primary analysis. Comparisons of socio-demographic characteristics between those consenting in the two arms will use chi-square tests, t-tests or Wilcoxon rank sum tests appropriate to the scale of measurement. The secondary outcomes for the study arms will be compared using simple tests (as above) and adjusted for socio-demographic characteristics where

appropriate using generalised linear models. Missing data are likely and, if missingness is considered to be either at random or completely at random, multiple imputation will be used. A total of 50 imputed datasets will be generated using the package mi in Stata statistical software.[188] Depending on the pattern of missing values, we will use sequential univariate conditional distributions or a multivariate normal method, using socio-demographic and other background variables as predictors. The quality of the imputations will be evaluated by checking how reasonable the imputed data are and testing the fit of the missing-data models.

Recruitment

Procurement of subject lists was straightforward and timely, with exclusions readily identifiable from existing data fields (Figure 3.1). Six ineligible mothers were included in the trial as a result of recording errors in the data fields (e.g. mothers whose infants had had an extended Neonatal Intensive Care Unit (NICU) stay or mothers who were non-residents of SA). An additional five mothers included in the trial would have been excluded had it been possible to audit all the medical records prior to randomisation. Examples were mothers who were incarcerated, mentally incapacitated, or whose baby was placed into foster care. If the mother's exigent circumstances were discovered upon audit of the medical record (to follow-up returned mail or non-contacts for the telephone interview), no further contact was attempted.

Implementation of phone interviews

Households were initially contacted on the day the infant reached 10 weeks of age. A minimum of three calls was made at varying times of the day (morning, afternoon, evening) before a household was classified as non-contactable. Interview recruitment was high: 1026 parents were interviewed (91%), of whom 925 (82%) completed the interview and 101 (9%) partially completed the interview. A partially completed interview was

usually one where the parent answered one question only: the reason why they did or did not return the reply form. There were 57 non-contactable households (5%) despite repeated attempts and a connected telephone number. A further 13 households (1%) were non-contactable due to disconnected or wrong telephone numbers recorded in the hospital system, while 28 (2%) were non-English speaking and 5 (<1%) refused to be interviewed.

3.3.4 Discussion

This is the first RCT of opt-in and opt-out parental consent for a population-based childhood vaccine safety surveillance program using data linkage. It featured a parallel design, adequate power for the primary outcome and thorough follow-up of subjects to determine attitudes to consent, data linkage and other important issues.

The comprehensive list of socio-demographic variables included in the hospital's patient management system provided basic information on a range of socio-demographics for all mothers: age, marital status, country of birth, Indigenous status, household location (major cities or other) and IRSD. It will, therefore, be possible to determine the presence of selection bias in the participation rate, irrespective of whether a subject answered the socio-demographic questions in the interview. The previous RCTs of opt-in versus opt-out consent[21-25] did not show such comparisons,[21,22] or were restricted by the small number of socio-demographic characteristics for which data were available for all eligible patients: either age and sex alone (which gave no insight),[23,25] or age, sex and the IRSD (which gave limited insight).[24]

The recruitment rate for the interview was high for a number of reasons. Firstly, SA Health's data listings recorded a mother's mobile and landline telephone number and often a spouse or de facto's mobile number, enabling parents to be contacted even if they had changed residence. Secondly, the interviewers were persistent in the follow-up of returned mail and non-contacts for the interview, and optimised contact through auditing medical

records to find valid residential addresses and telephone numbers. Thirdly, parents usually had a good rapport with the hospital as recent recipients of its health services and were willing to participate in the research for altruistic reasons.

This trial focused on parental attitudes towards using data linkage in one context: childhood vaccine safety surveillance. Although there will be some overlap in motivators and barriers to participation, some important determinants of participation among parents may not be relevant for data linkage studies in other health-related areas. The portfolio of evidence on the public's preferences for consent and attitudes towards the intrinsic value of data linkage, levels of trust in its protection of privacy in different population/patient groups and in different health areas requires expansion.

The cut-off time for data to be included in the estimation of the participation rate was chosen *a priori* to allow parents sufficient time to immunise their infants, and for adverse events to be captured, and to balance the potential for recall bias against potential for late returns. Every parent had four weeks to respond to the study invitation material and did not receive follow-up reminders. Based on findings from previous surveys,[189,190] we anticipate that the number of parents who opted in or opted out may be half those attained if follow-up mailings had been implemented. We accepted reply forms that were received within a week of the interview at 10 weeks post-partum, which prompted a small number of crossovers. For example, a parent in the opt-in arm may have answered in the interview that they had been too busy to send back the reply form, but the process of being interviewed reminded them to do so. In this instance, it is unlikely the parent would have returned the reply form of their own volition.

The interviews may have been subject to respondent bias, in that parents may not have honestly reported motivations and barriers to the return or non-return of reply forms in a telephone conversation with a ‘stranger’ affiliated with the trial. While qualitative

methodology may be more successful in revealing true motive, facilitated by developing rapport with interviewers and/or focus group members through in-depth exploration of reasons underlying participation and non-participation, fewer parents could have been studied in the same time.

We did not engage interpreter services for non-English speakers. While the number of parents who had no English comprehension was smaller than anticipated (2%), we encountered parents with varying levels of English proficiency, ranging from the ability to comprehend and answer a small number of questions in the interview (usually only questions related to vaccination practices and episodes of infant illness) to answering all questions, but with some uncertainty as to their understanding. The interviewers flagged the interviews in which they perceived the parents' English to be limited, and this can be used as a covariate in the analysis, in addition to the socio-demographic variables that provide information on country of birth and main language spoken at home.

Informed consent is generally regarded as an essential component of health research. Low participation rates in health and medical research can lead to selection bias and compromise statistical precision. Therefore, consent procedures should aim to reduce bias and improve participation rates. VALiD is the first RCT to compare opt-in with opt-out parental consent for a population-based childhood vaccine safety surveillance program using data linkage. This study fills a gap in the literature in that it will not only assess the participation rate and selection bias for each consent option but, through a subsequent telephone interview of all households, will also assess consent preferences and intent compared with actual opting in and opting out behaviour, and socioeconomic factors. The findings will have relevance to all stakeholders and policy makers and will stimulate public debate about what it means to protect patients' interests.

End of published article

3.4 Additional discussion

This paper describes the rationale for the trial, and its design, conduct and proposed analysis in accordance with the CONSORT statement.[177,178] Documentation of approval from the appropriate HREC for the conduct of the RCT is included in Appendix 2. Ethical approval for the weekly process of screening for infant and maternal deaths in the cohort of mothers prior to randomisation is included in Appendix 3. The study invitation materials sent at six weeks post-partum to all households enrolled in the opt-in and opt-out arm are included in Appendices 4 and 5, respectively. The telephone survey conducted at 10 weeks post-partum with a parent from each enrolled household (if contact was made) is included in Appendix 6. The interviews were identical for parents in the opt-in and opt-out arm, except for variations in the introductory material and the question (Q.7) regarding their reasons for the return or non-return of the form. Question 7 differed in wording and context depending on whether the parent had participated or not in the respective arm.

The approving HREC granted a consent waiver to enable all eligible subjects to be included in the RCT without their prior consent. The HREC also allowed the researchers to provide limited disclosure of the study's purpose to parents. Although parents were aware they were being asked to consent to data linkage, they did not know that they were enrolled in an RCT of two consent approaches. The *National Statement's* guidelines on limited disclosure in its Chapter 2.3.1 recommends in part (e) that after participation has ended, participants be 'provided with information about the aims of the research and an explanation of why the omission or alteration was necessary; and offered the opportunity to withdraw any data or tissue provided by them'.[9] Although it was not possible or appropriate for participants to withdraw from the trial after its conclusion, all households enrolled in the trial were sent a letter outlining the study's results and reasons for masking the study's purpose. The letter is included in Appendix 7.

4 Publication — A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage

4.1 Preface

This chapter contains the first of two articles presenting the results of the RCT. This article has been published in the *Journal of Medical Ethics*.[192] It presents the primary outcome, that is, a comparison of whether the opt-in or opt-out approach to gaining parental consent provided the highest participation rate for a program of childhood vaccine safety surveillance using data linkage.

The article also presents the first of a number of secondary outcomes; the remainder are presented in Chapter 5. The secondary outcomes included in the article are an examination of the socio-demographic differences between participants and non-participants in each arm, and parental reasons for participation and non-participation. The analysis of socio-demographic differences provides evidence for whether selection biases occur when using either of the two consent methods, that is, whether those participating differ in important ways from those who do not. The analysis of reasons for participation and non-participation allows for an examination of the attitudes of parents to the two consent approaches. Parents' behaviours upon receiving (or not receiving) the invitation to participate in the data linkage study are compared with their underlying intentions, or lack of such, regarding participation in the surveillance program.

4.2 Statement of authorship

Berry JG, Ryan P, Gold MS, Braunack-Mayer AJ, Duszynski KM, the Vaccine Assessment using Linked Data (VALiD) Working Group. A randomised controlled trial to compare opt-in and opt-out parental consent for childhood vaccine safety surveillance using data linkage. *J Med Ethics* 2012;38(10):619-25.

By signing below, the authors declare that they give consent for this paper to be presented by Jesia Berry towards examination for the Doctor of Philosophy.

Jesia Berry (Candidate)

Developed the trial protocol and randomisation schedule, co-authored the study invitation material, conducted interviews, collected the data, performed analyses, interpreted the results, reviewed the literature and drafted the manuscript.

Signed: …… Date: 22/2/13

Philip Ryan

Contributed to the conception and design of the study, procured funding, designed the statistical analysis for the trial, provided statistical advice, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 22-2-13

Michael Gold

Contributed to the conception and design of the study, procured funding, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 20/2/13

Annette Braunack-Mayer

Contributed to the conception and design of the study, procured funding, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 21.02.2013

Katherine Duszynski

Contributed as trial coordinator to leading the design and direction of the study, co-authored the study invitation material, applied for ethical approval, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 20/02/2013

4.3 Article

4.3.1 Abstract

Introduction No consent for health and medical research is appropriate when the criteria for a waiver of consent are met, yet some ethics committees and data custodians still require informed consent.

Methods A single-blind parallel-group randomised controlled trial: 1129 families of children born at a South Australian hospital were sent information explaining data linkage of childhood immunisation and hospital records for vaccine safety surveillance with four weeks to opt in or opt out by reply form, telephone or email. A subsequent telephone interview gauged the intent of 1026 parents (91%) in relation to their actions and the socio-demographic differences between participants and non-participants in each arm.

Results The participation rate was 21% (*n*=120/564) in the opt-in arm and 96% (*n*=540/565) in the opt-out arm [χ^2 (1df) = 567.7, *P*<0.001]. Participants in the opt-in arm were more likely than non-participants to be older, married/de facto, university educated and of higher socioeconomic status. Participants in the opt-out arm were similar to non-participants, except males were more likely to opt out. Substantial proportions did not receive, understand or properly consider study invitations, and opting in or opting out behaviour was often at odds with parents' stated underlying intentions.

Conclusions The opt-in approach resulted in low participation and a biased sample that would render any subsequent data linkage unfeasible, while the opt-out approach achieved high participation and a representative sample. The waiver of consent afforded under current privacy regulations for data linkage studies meeting all appropriate criteria should be granted by ethics committees, and supported by data custodians.

Clinical trial registration number Australian New Zealand Clinical Trials Registry ACTRN12610000332022

4.3.2 Introduction

There is a debate about the circumstances under which there is an ethical requirement to seek consent for the use of stored personal information in health research.[142,193] Research using medical records must be considered by a Human Research Ethics Committee (HREC), except for audits.[9] Australia's National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research* guides HRECs to require opt-in consent under most circumstances.[9] However, specific activities (including research of various kinds) can proceed without a subject's permission provided an HREC assesses that the activity is, 'on balance, substantially in the public interest'.[6] Qualifying criteria for a waiver of consent include: the research is low risk (i.e. where the only foreseeable risk is one of discomfort or inconvenience); the benefits from the research justify any risks of harm associated with not seeking consent; it is impracticable to obtain consent; there is no known reason for thinking that participants would not have consented if they had been asked; there is sufficient protection of an individual's privacy; an adequate plan to protect data confidentiality; and the waiver is lawful.[9] Data linkage is one activity that qualifies,[9] defined as 'the bringing together, from two or more different sources, data that relate to the same individual, family, place or event'.[26] Even so, researchers have reported inconsistencies in decisions made by HRECs and data custodians,[12,142,193,194] where some have ruled that each individual's opt-in consent is required to link administrative health records.[13,14]

There are two approaches to obtaining consent, whereby people are informed about the research and included if they actively signal willingness to participate (opt-in) or included by default unless they indicate an unwillingness to participate (opt-out).[23] The opt-in

approach is deemed ethically more defensible, as it is consistent with public expectations[6,148,159] (though there are notable exceptions[115,163]) and it implies an autonomous decision is made.[23] However, seeking consent by either means for large epidemiological studies can be prohibitively expensive when potential participants need to be individually informed either by mail or personal approach.[110,142] This is the case for postlicensure surveillance of national immunisation programs, where often millions of people are required to characterise the full safety profile of vaccines, as prelicensure clinical trials alone are insufficiently powered.[50] Data linkage of immunisation registers to hospitalisations, emergency department visits, outpatient visits and mortality data is routinely conducted in limited jurisdictions,[50] but only recently piloted in Australia.[76] Data linkage is able to determine causal relationships between vaccinations and rare adverse events, and is used to systematically investigate vaccine safety concerns raised through passive reporting systems, which are unable to do so.[50]

There are no randomised controlled trials (RCTs) comparing the numbers and characteristics of participants enlisted in a data linkage study under opt-in and opt-out conditions. While five RCTs relating to other aspects of medical research have shown that the opt-out approach yields higher participation rates than opt-in consent (reviewed in Berry et al.[176]), the extent of participation ranged widely from 48%–85% in the opt-in arm and 59%–100% in the opt-out arm, and all but one had a small sample size or flawed methodology. We designed a large RCT of the opt-in and opt-out consent processes for a proposed data linkage study examining adverse events following immunisation. All eligible subjects were included without their consent to avoid introducing selection bias in the study sample. The local institutional HREC granted a waiver of the usual requirement for consent and allowed the limited disclosure to subjects of the true purpose of the trial [Children, Youth and Women's Health Service (CYWHS) reference number: REC2087/7/11].

4.3.3 Methods

Design and participants

The study protocol of this single-centre, stratified (firstborn *vs* subsequent births), single-blind, parallel-group RCT has been published.[176] Mothers eligible for inclusion were aged 18 years and over, resided in South Australia (SA), and gave birth at the Women's and Children's Hospital, a tertiary referral centre in the capital city of Adelaide, where ~ 25% of South Australian babies are delivered.[176] Exclusion criteria were stillbirth, neonatal death or maternal death, Neonatal Intensive Care Unit (NICU) stay of two weeks or longer, home birth, inward transfer of a newborn from another hospital, and any identified maternal hardship — for example, incarceration, mental illness, or the baby had been adopted or placed into foster care. The study was disclosed on http://www.anzctr.org.au/ and assigned the identifier ACTRN12610000332022.

Randomisation and blinding

Mothers were randomly allocated at six weeks post-partum, by date order of confinement, to the opt-in and opt-out arm in the ratio 1:1, using randomly permuted blocks of sizes 2, 4, 6 and 8, stratified by firstborn status (first live and surviving birth *vs* subsequent births). Allocation was concealed by computer-automated merging of electronic data listings of eligible mothers with the randomisation schedule (created by JGB using the Stata program ralloc). The trial was single-blinded: parents were informed about the data linkage, but unaware that two consent procedures were being compared. Blinding was not appropriate for the interviewers [JGB, JC] since the interview structure required knowledge of a parent's opting in or opting out behaviour. The primary outcome was analysed by a researcher who was blind to allocation.

Objectives

The primary objective was to determine whether the opt-in or opt-out approach to gaining parental consent provided the highest participation rate for a program of childhood vaccine safety surveillance using data linkage. The secondary objectives were to examine socio-demographic differences between participants and non-participants in each arm, and reasons for participation and non-participation.

Sample size

For the primary outcome, using a two-tailed test at the 5% level with power of 80%, we required a sample size of 313 subjects in each arm to detect a difference in participation of 10% (assuming a participation rate of 80% in the opt-out arm and 70% in the opt-in arm). However, important secondary outcomes of interest related to the recruitment of parents for the subsequent telephone interview; this required a sample size of 544 subjects in each arm: a total of 1088 subjects.

Interventions and follow-up

At 1–2 weeks before the infant's scheduled vaccinations at two months of age, the household received a cover letter (addressed to the mother), an information leaflet and a reply-paid form, with different formats according to randomised allocation to the opt-in or the opt-out arm (Figure 4.1). The letter was signed by a paediatrician [MSG], and his affiliations as an employee at the hospital and a title holder at the university were included, along with the logos of the hospital and its governing state health authority. Parents were invited to be part of a 'Vaccine Data Linkage Study' and permission was sought to link infants' two-month vaccinations with any hospital visits occurring in the month afterwards to check for adverse events following immunisation. Parents were directed to a dedicated website for detailed information on the process of data linkage and how personal information is kept private (http://health.adelaide.edu.au/paediatrics/research/valid/) and

instructed to telephone the HREC secretariat if they had any concerns or complaints. Parents in the opt-in arm were instructed to return a reply form, telephone, or email to signal willingness to participate in data linkage. Parents in the opt-out arm were informed they would be included unless they refused consent by the same means. All parents were given four weeks to respond. No follow-up reminder letters were sent.

Outcome assessment

The primary outcome at 10 weeks post-partum was the parental participation rate in each arm. Mothers' baseline characteristics were captured from the hospital's patient management system and secondary outcome data, including socio-demographic characteristics, at the subsequent telephone interview at 10 weeks post-partum. The researchers attempted to interview the parent (either mother or father) who had opted in or opted out. When this was not possible, the other parent, if available, was interviewed as a proxy. For households that did not opt in or opt out, the first parent to answer the telephone was invited to be interviewed. The secondary outcomes reported in this paper are: parents' recall of study invitation material and reasons volunteered for the return or non-return of the reply form.

Statistical analysis

Analyses were based on intention-to-treat. The primary outcome was compared using an extended Mantel-Haenszel χ^2 test to account for the permuted block randomisation and stratification by firstborn status. There were no prespecified confounders for the primary analysis.

We used multiple imputation to 'fill-in' missing data for covariates collected at the interview and required for analysis of secondary outcomes.[195] Variables used in the imputation were the primary outcome and mothers' baseline characteristics, for which there were no missing data, and the secondary outcomes (i.e. interview responses), which

were affected by missing data. We used the Stata mi ice add-on to implement the procedure and obtained 50 imputed datasets. Full details on this procedure are supplied in online appendix A, including evaluations of the missing data and the quality of the imputed data (online appendix A, Figure 4.3). Comparisons of socio-demographic characteristics between the two arms used log-binomial regression models, and expressed treatment effects as relative risks (RRs). Free-text reasons for participation and non-participation were classified into seven binary variables, in which multiple responses were possible, and the proportions of parents in each arm were compared. Analytic results were produced by combining estimates from the imputed datasets using the mi suite of commands in Stata version 11.2, to generate a single set of estimates with valid standard errors that incorporate the uncertainty about the imputed values.[195]

4.3.4 Results

Figure 4.1 shows the flow of parents through the trial. A total of 1129 mothers were enrolled over a three-month period: from 27 July to 25 October 2009. We randomly assigned 564 mothers to the opt-in arm and 565 to the opt-out arm. The socio-demographic characteristics were comparable in the two groups (Table 4.1), except that fewer Aboriginal and Torres Strait Islander mothers were enrolled in the opt-in arm. At baseline, the cohort was ethnically diverse (40% born overseas), predominantly urban-dwelling (92%), represented a broad range of socioeconomic groups, included single mothers (23%), and had a median age of 30.6 years.

Figure 4.1: Flow diagram of opt-in compared with opt-out trial

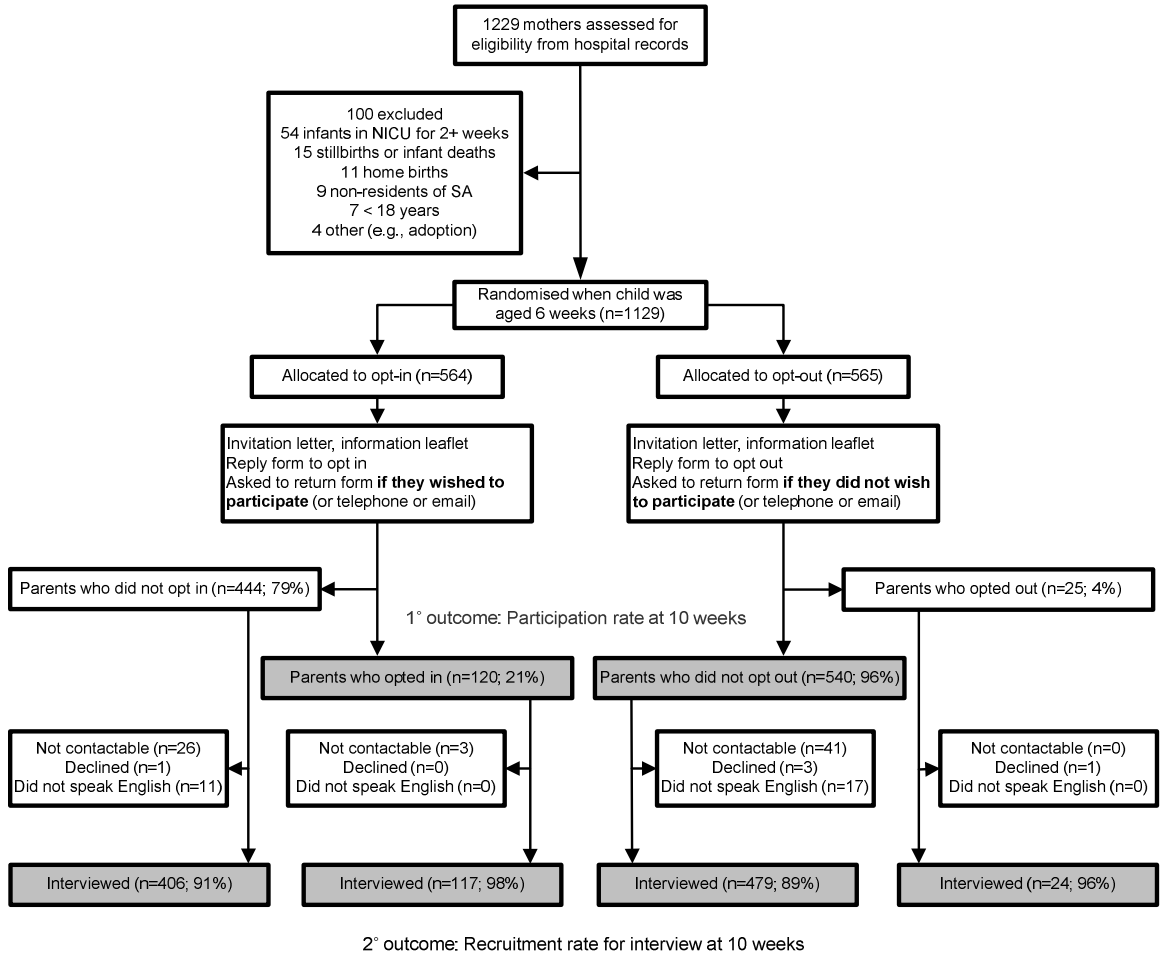


Table 4.1: Baseline characteristics of mothers at trial entry (complete cases)

Maternal factors	Opt-in (*n*=564)	Opt-out (*n*=565)	Total (*n*=1129)
Firstborn child	252 (44.7)	252 (44.6)	504 (44.6)
Median (IQR) age (years)	30.5 (26.5– 34.6)	30.7 (26.3–34.7)	30.6 (26.4–34.7)
Aboriginal or Torres Strait Islander origin	13 (2.3)	25 (4.4)	38 (3.4)
Living with partner	443 (78.6)	429 (75.9)	872 (77.2)
Australian born	346 (61.4)	332 (58.8)	678 (60.1)
Metropolitan residence	509 (90.3)	525 (92.9)	1034 (91.6)
Has private health insurance	60 (10.6)	45 (8.0)	105 (9.3)
Socioeconomic quintile[a] 1 (Least disadvantaged)	78 (13.8)	73 (12.9)	151 (13.4)
2	111 (19.7)	112 (19.8)	223 (19.8)
3	86 (15.3)	87 (15.4)	173 (15.3)
4	108 (19.2)	116 (20.5)	224 (19.8)
5 (Most disadvantaged)	181 (32.1)	177 (31.3)	358 (31.7)

Values are numbers (percentages) unless stated otherwise.

[a]Socioeconomic indexes for areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data.

Within four weeks, 120 reply forms (21%) were received from the 564 parents in the opt-in arm, and 24 reply forms and one telephone message (4%) from the 565 parents in the opt-out arm. The participation rate, defined as the proportion of parents who opted in and the proportion who did not opt out, was 21% in the opt-in arm and 96% in the opt-out arm [χ^2 (1df) = 567.7, P<0.001]. No complaints were made to the HREC about the opt-out reply form or the use of a verbal opt-out for the telephone interview.

In total, 1026 parents (91%) were interviewed (Figure 4.1), and 912 (81%) had complete data or were missing data for only one variable used in the substantive analysis (online appendix A, supplemental results Table 4.5). Five refused to be interviewed (<1%), 28 were non-English speaking (2%), and 70 were non-contactable (6%), including 13 with disconnected or wrong numbers recorded. In the first six weeks after birth, 56 families had changed residence (5%), as identified from mail returned undelivered or at the interview. In the opt-in arm, participants were more likely than non-participants to be older, married or in a de facto relationship, university educated, and in the highest annual household income bracket (Table 4.2). None of the 13 Aboriginal or Torres Strait Islander parents opted in. The socio-demographic characteristics of participants and non-participants in the opt-out arm were similar, except that men were less likely than women to participate (87% *vs* 97%). Only one of 25 Indigenous parents opted out.

Four-fifths of parents remembered receiving the study invitation material, with similar recall in the opt-in arm (81%) and the opt-out arm (83%); P=0.345. Figure 4.2 shows the proportion of parents who gave each reason by randomised allocation (opt-in or opt-out) and outcome (participation or non-participation).

Table 4.2: Demographic characteristics of participants and non-participants in data linkage for vaccine safety surveillance with missing data imputed by multiple imputation

	Opt-in arm (*n*=564)				Opt-out arm (*n*=565)			
	Participant (*n*=120)	Non-participant (*n*=444)	RR (95% CI)	*P* value	Participant (*n*=540)	Non-participant (*n*=25)	RR (95% CI)	*P* value
Age (years)								
18–24	7 (5.6)	75 (16.9)	1.00		75 (13.8)	3 (12.0)	1.00	
25–29	20 (16.7)	115 (25.9)	1.81 (0.77 to 4.25)	0.174	144 (26.6)	7 (28.0)	0.99 (0.94 to 1.05)	0.776
30–34	45 (37.7)	138 (31.0)	3.02 (1.38 to 6.61)	0.006	168 (31.1)	5 (20.0)	1.01 (0.96 to 1.06)	0.703
35–39	34 (28.4)	90 (20.2)	3.36 (1.52 to 7.44)	0.003	114 (21.1)	5 (20.3)	1.00 (0.94 to 1.06)	0.889
40+	14 (11.7)	27 (6.1)	4.16 (1.77 to 9.81)	0.001	40 (7.3)	5 (19.7)	0.93 (0.83 to 1.04)	0.180
Sex								
Female	114 (94.8)	399 (89.8)	1.00		488 (90.4)	17 (68.0)	1.00	
Male	6 (5.2)	45 (10.2)	0.54 (0.25 to 1.17)	0.119	52 (9.6)	8 (32.0)	0.90 (0.81 to 0.99)	0.035
Firstborn child								
Yes	55 (45.8)	197 (44.4)	1.00		245 (45.4)	7 (28.0)	1.00	
No	65 (54.2)	247 (55.6)	0.95 (0.69 to 1.31)	0.775	295 (54.6)	18 (72.0)	0.97 (0.94 to 1.00)	0.077
Marital status								
Separated/divorced/never married	5 (4.2)	66 (14.8)	1.00		77 (14.2)	2 (8.0)	1.00	
Married/de facto	115 (95.8)	378 (85.2)	3.30 (1.39 to 7.80)	0.007	463 (85.8)	23 (92.0)	0.98 (0.94 to 1.02)	0.272
Country of birth								
Australia	69 (57.5)	283 (63.6)	1.00		322 (59.7)	12 (46.9)	1.00	
Other	51 (42.5)	161 (36.4)	1.22 (0.89 to 1.68)	0.218	218 (40.3)	13 (53.1)	0.98 (0.94 to 1.02)	0.230
Main language spoken at home								
English	84 (70.1)	326 (73.4)	1.00		390 (72.2)	15 (61.4)	1.00	
Other	36 (29.9)	118 (26.6)	1.13 (0.80 to 1.61)	0.480	150 (27.8)	10 (38.6)	0.98 (0.93 to 1.02)	0.304

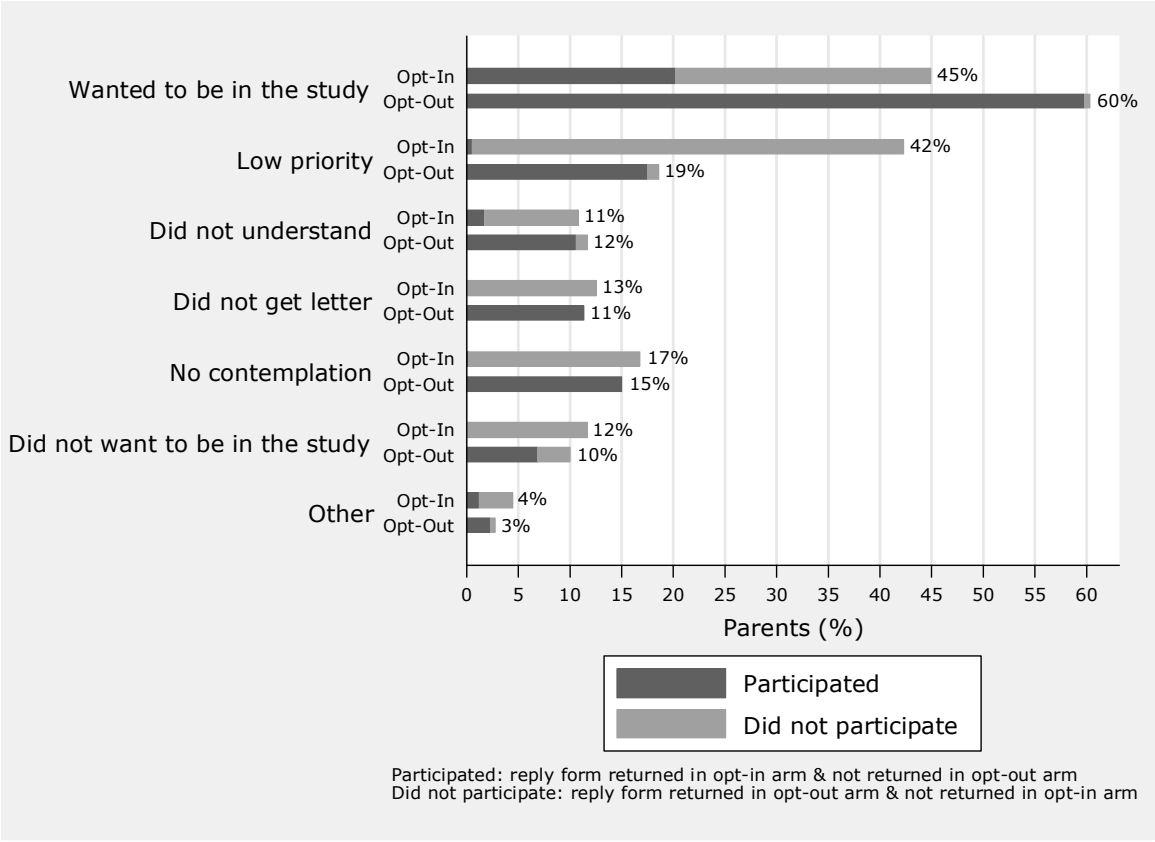
Table 4.2 (Continued)

	Opt-in arm (*n*=564)				Opt-out arm (*n*=565)			
	Participant (*n*=120)	Non-participant (*n*=444)	RR (95% CI)	*P* value	Participant (*n*=540)	Non-participant (*n*=25)	RR (95% CI)	*P* value
Educational attainment								
Up to year 10 (~16 years old)	6 (4.9)	57 (12.9)	1.00		60 (11.0)	4 (14.7)	1.00	
Up to year 12 (~18 years old)	16 (13.4)	88 (19.8)	1.68 (0.64 to 4.36)	0.291	122 (22.6)	4 (16.4)	1.03 (0.95 to 1.11)	0.484
Trade or certificate	32 (26.9)	152 (34.3)	1.90 (0.79 to 4.58)	0.155	159 (29.5)	8 (32.6)	1.01 (0.94 to 1.09)	0.797
University or higher	66 (54.9)	146 (33.0)	3.37 (1.46 to 7.81)	0.005	199 (36.9)	9 (36.3)	1.02 (0.94 to 1.09)	0.683
Annual household income ($A)[a]								
<$20,800	12 (9.8)	64 (14.4)	1.00		101 (18.7)	6 (25.6)	1.00	
$20,800–$41,599	21 (17.8)	138 (31.1)	0.87 (0.40 to 1.85)	0.708	129 (24.0)	7 (29.5)	1.01 (0.93 to 1.09)	0.875
$41,600–$83,199	46 (38.0)	153 (34.4)	1.49 (0.78 to 2.82)	0.226	185 (34.3)	7 (28.5)	1.02 (0.96 to 1.10)	0.487
$83,200+	41 (34.4)	90 (20.2)	2.04 (1.08 to 3.87)	0.029	124 (23.0)	4 (16.4)	1.03 (0.96 to 1.10)	0.397
Residence								
City	108 (90.0)	401 (90.3)	1.00		501 (92.8)	24 (96.0)	1.00	
Other	12 (10.0)	43 (9.7)	1.03 (0.61 to 1.74)	0.917	39 (7.2)	1 (4.0)	1.02 (0.97 to 1.08)	0.427
Socioeconomic quintile								
1 (Least disadvantaged)	19 (15.8)	59 (13.3)	1.00		67 (12.4)	6 (24.0)	1.00	
2	24 (20.0)	87 (19.6)	0.89 (0.52 to 1.50)	0.658	105 (19.4)	7 (28.0)	1.02 (0.94 to 1.11)	0.619
3	15 (12.5)	71 (16.0)	0.72 (0.39 to 1.31)	0.278	80 (14.8)	7 (28.0)	1.00 (0.91 to 1.10)	0.968
4	27 (22.5)	81 (18.2)	1.03 (0.62 to 1.71)	0.920	114 (21.1)	2 (8.0)	1.07 (1.00 to 1.15)	0.065
5 (Most disadvantaged)	35 (29.2)	146 (32.9)	0.79 (0.49 to 1.30)	0.357	174 (32.2)	3 (12.0)	1.07 (1.00 to 1.15)	0.059

All data are based on analysis of 50 imputed datasets. For the opt-in and opt-out arms, data are the number averaged across datasets and expressed as number (%) and the RR (95% CI) estimated by the model.

[a]1$A= £0.66; €0.79; US$1.05.

Figure 4.2: Parental responses when asked about the return or non-return of the reply form with missing data imputed by multiple imputation



Examples of the classification of parental responses are shown in online appendix A, supplemental results Table 4.6. In the opt-in arm, 45% of parents stated that they wanted to participate, but only about half opted in (20%). Common reasons for not opting in were: higher priorities (42%), no contemplation (17%), non-receipt of letter (13%), no desire to be in the study (12%), or lack of understanding (9%). About 2% of parents opted in although they did not understand the letter. Fewer parents in the opt-out arm thought the study was a low priority (19%) and more wanted to participate (60%), including three parents (0.5%, one was Indigenous) who misunderstood the instructions and opted out. However, similar proportions to the opt-in arm had not given the study any contemplation (15%), did not understand the letter (12%), did not receive the letter (11%), or did not want to be in the study (10% — although 7% did not elect to opt out).

4.3.5 Discussion

We have shown, that in the context of a program of vaccine safety surveillance using data linkage, the opt-in method of consent yielded a very low participation rate (21%). Our RCT is one of few to explore reasons for participation and non-participation, and fills an important gap in the literature.[106,108] Mothers recently discharged from hospital were identified from medical records and sent study invitations by mail, along with instructions on convenient means of opting in or opting out (e.g. telephone, email, post). Overall, about one in eight parents claimed not to have received the invitation, one in six paid no attention to it, and one in ten did not understand it. A clear distinction emerged in parental opinions regarding the opt-in and opt-out approaches. The most common reason for not opting in was respondent burden: 42% viewed the study as a low priority, resulting in only half of those who wanted to participate (45%) opting in (20%). Fewer parents in the opt-out arm viewed the study as a low priority (19%) and a larger proportion (60%) wanted to participate. Overall, about one in ten parents did not want to participate; this figure included parents with privacy concerns, but also those who mistakenly thought they did not qualify for inclusion. No parents were included against their wishes in the opt-in arm, since they did not opt in. However, in the opt-out arm, 7% of parents were included against their wishes because they failed to opt out.

This trial confirms that opt-in consent for data linkage studies using administrative health records is impracticable due to information constraints when seeking consent (e.g. when a patient is untraceable or deceased) and insufficient economic resources.[100] In less than two months after discharge from hospital, 5% of families had relocated. As mail is usually the only HREC-endorsed method of first contact for patients identified from medical records, these patients had become untraceable. In addition, some letters were returned to the hospital opened and presumably read by someone other than the intended recipient,

indicating that a breach of an individual's privacy had occurred through the very act of trying to respect it. Longer time lapses after discharge from hospital are particularly problematic; one data linkage study found that up to 50% of families relocated within 3.5 years.[196] Even with follow-up reminders (e.g. repeat mailings or telephone calls), potentially increasing the participation rate to about 30% for the opt-in arm,[197] the data linkage study would still be insufficiently powered to gather any meaningful data to enable the detection of adverse events following immunisation, despite the extra effort, costs and time delays.

This trial also confirms that the statistical precision and external validity of results is compromised when opt-in consent is required for the use of linked administrative health records. A common strategy to compensate for the loss of power from non-response is to inflate the sample size.[14,198] However, this does not guard against selection bias, which delivers distorted and invalid results if the relationship between the exposure (vaccination) and outcome (adverse events) is systematically different between those who opt in and the population at risk, or the distribution of predictors of the outcome (e.g. socioeconomic status) differs between the two. A strategy that identifies if selection bias is present, and provides an imprecise measure of how distorted the results are, is to collect (without individual consent) a minimum dataset of key prognostic variables for the population at risk,[106] subject to HREC approval. Nonetheless, utilising no consent or an opt-out approach from the outset effectively avoids the problem.

High recruitment for the interview (91%) and the use of multiple imputation for missing data enabled us to assess for the presence of selection bias among those participating compared to the target population in each arm (external validity). The five previous RCTs of opt-in and opt-out consent processes either did not show such comparisons (reviewed in Berry et al.[176]), or were limited in insight by the small number of characteristics available

for all eligible patients: either age and sex alone, or, additionally, area-based socioeconomic status. The study was limited to one context: parental consent to using data linkage for childhood vaccine safety surveillance. The opt-in and opt-out participation rates, and associated motivations and barriers, may differ by subject area and also by population/patient group. Interviews may have been subject to respondent bias, in that parents may have been reluctant to divulge the true reasons for their actions in a telephone conversation with a stranger affiliated with the trial. Qualitative face-to-face interviews and/or focus groups may be more successful in developing rapport and revealing true motive, but fewer parents could have been studied in the same time. We did not engage interpreter services for non-English speakers because of resource constraints. However, English language proficiency did not impact on the likelihood of opting in or out.

Opt-in consent has resulted in low participation rates for two Australian data linkage studies of national significance: the Australian Longitudinal Study on Women's Health (49.4% of 39 883 women who had previously opted into the cohort study from a sample of 106 000 invited women)[13,199] and the 45 And Up Study (17.9% of almost 1.5 million men and women).[14] The statistical precision and generalisability of these, and other, important epidemiological studies have been compromised by ethics committees' and data custodians' preference for opt-in consent, in circumstances where the criteria for waiver of consent are met, or an opt-out approach would suffice.[108] Our study confirms that the opt-out approach is well-accepted and results in high participation rates and a representative sample, whereas low participation and selection bias is evident when opt-in consent is used. The selection bias we observed concurs with Stanley's assertion that 'generally the people who are excluded from studies are the most marginalised…(such as young, disadvantaged, Indigenous, disabled people or those with particular risks).'[200]

Neither the opt-in nor opt-out approach was effective in achieving informed consent, as substantial proportions of parents did not receive, understand or properly consider study invitations and opting in and opting out behaviour was often at odds with parents' stated underlying intentions. Both approaches, therefore, were suboptimal in their capacity to respect participant autonomy, although the opt-out approach did appear to better reflect the wishes of those who actually wanted to participate. The absence of complaints about the opt-out reply form perhaps indicates that it is a generally acceptable method of patient recruitment. So, also, may be the use of a verbal opt-out for telephone interviews. The small number that refused outright to answer any questions supports the proposition that patients 'may not consider, for example, a brief telephone call after a letter explaining the proposed research to be an unjustifiable invasion of their privacy if there seems to be a good reason for the call and their privacy is in all other respects protected.'[108]

Some argue that the opt-out approach is a valid default strategy for studies that pose a low risk to patients because it enhances study rigour, providing evidence for cost-effective health services and policy decisions that are based on externally valid population samples.[23,108,110,113,114] It was clear from this study that the opt-out approach was much more successful than the opt-in approach at obtaining a high participation rate because it placed less of a burden on parents to participate. However, there is considerable opposition to an opt-out approach, because it does not appear to offer people adequate choice to participate or not.[118] The relative loss of choice is related to the fact that people may not receive, contemplate, or understand the invitation to opt out. For the latter reasons, it has been argued that 'it is difficult to see how (the opt-out approach) can reasonably fulfil the moral function of informed consent'.[118] However, in our study, it was also the case that some parents who did not opt in did so because they also did not receive, contemplate or understand the invitation. This finding suggests that opt-in consent does not necessarily always perform the moral function of respecting autonomy that is expected of it.[124]

A number of strategies may help to enhance respect for autonomy when the opt-out approach is being used. When health organisations provide upfront declarations and opt-out clauses to patients about the use of personal information for electronic health records,[141] clinical registries,[114,142] health research,[108] and the possibility they may be invited to take part in clinical trials,[137] it can circumvent the need to obtain opt-in 'consent for consent', an approach that impedes participation and equitable access to research.[108] Participation in RCTs is generally with opt-in consent; although there are exceptions (research involving incompetent, unconscious or incapacitated patients and cluster RCTs).[118,135] Nevertheless, the feasibility of aspects of a trial's conduct may necessitate HREC approval of a waiver of consent or an opt-out approach — for example, accessing medical records to identify potentially eligible subjects; complete follow-up of all randomised participants, both within the trial period and in the long-term; central coordination and study conduct; and potential secondary uses of trial data.[137]

Widespread education aimed at HRECs, data custodians, clinicians and researchers is required to clarify the conditions under which studies can proceed without consent, or when the opt-out approach may be permissible. Changes to policy and relevant legislation may be required to achieve consistent outcomes across HRECs and data custodians.[12,100] The waiver of consent afforded under current privacy regulations for data linkage studies meeting all appropriate criteria should be granted by ethics committees, and supported by data custodians.

4.3.6 Online appendix A

Methods for dealing with missing data in the VALiD trial of parental consent

There were no missing data for the primary outcome (parental participation) or for the baseline characteristics of the mother. In order to increase precision and minimise selection bias we used multiple imputation to 'fill-in' missing data for the secondary outcomes, namely the interview responses collected at 10 weeks post-partum. We chose the fully conditional specification (FCS) rather than multiple imputation based on the multivariate normal distribution (MVNI) because it is more flexible in application[201]; yet, it performs comparably.[202] Imputations were performed separately for each treatment arm with the common set of predictor variables, which included all variables to be used in the analysis model and potential predictors of missing data. We used switching regression,[203-205] as performed by the mi ice add-on in Stata version 11.2, to generate 50 imputed datasets at sampling intervals of 10 cycles. To generate a single set of estimates with valid standard errors that incorporate the uncertainty about the imputed values,[195,206] we used the Stata mi suite of commands to average results over the 50 datasets using Rubin's rules.

Our survey contained 40 main items, many of which contained missing data, and complexities arose from the skips patterns and logical constraints that needed to be observed. Van Buuren et al.[203] recommend 15-25 variables as optimal for inclusion in an imputation model. Therefore, we imputed the dataset in stages using four imputation models. The two models related to analyses reported in the present paper were:

Imputation Model 1: variables used to impute sex for parents who were not interviewed

Imputation Model 2: variables used to impute missing socio-demographic and interview responses about the topic of consent for all parents in the trial

Tables 4.3 and 4.4 in the supplemental results section of this appendix (see below) list the variables included in the missing data prediction models 1 and 2 respectively, the amount

of missing data each variable contains, and how the variables were imputed in the models. [Not shown are the missing data prediction models 3 and 4; these models were subsequently estimated to impute missing interview responses regarding the topics of parental opinions about data linkage, vaccine safety and effectiveness, vaccination practices, and experiences of adverse events following immunisation – subject matter which is not the topic of this paper.] Table 4.5 shows the most frequent patterns of missing data. Of the 1129 parents in the trial, 730 (64.7%) had complete data on all variables used in the substantive analysis and 182 (16.1%) had complete data apart from one missing variable – mostly annual household income (179 parents; 15.9%).

Multiple imputation assumes normality for continuous variables. In order to avoid biases that can arise when skewness in a continuous variable is ignored,[202] we used a log transformation with an offset in Stata using the *lnskew0* command to transform parents' age at time of interview. We then performed the imputation for unobserved values, and then back-transformed to obtain values on the original scale. It was also necessary to define customised prediction equations for the nominal variables in model 2 (and the associated skips) by excluding some variables from the imputation models to avoid multicollinearity problems and improve the overall quality of the model.[201]

The imputation procedure assumes that data are missing at random (MAR), i.e. missing cases differ from non-missing cases, but the pattern of missingness is discernable from other observed variables in the dataset.[195] Unfortunately, it is impossible to validate this assumption without access to complete data, in which case there would be no need for multiple imputation.[195] A recourse is to undertake sensitivity analyses that test various assumptions about the distribution of missingness in order to examine biases caused by data that are missing not at random (MNAR), i.e. the missing data depend on events or items that the researcher has not measured.[195] However, we did not do so in our trial

because we reasoned that, since all eligible mothers were enrolled in the trial (without consent) and we had a comprehensive list of baseline socio-demographic characteristics for every enrolled mother, the pattern of missingness is likely to be more satisfactorily imputed from the measured variables. Furthermore, the results from the complete case analysis (i.e. including only those parents with complete data on all variables used in any analyses) did not differ substantially from the multiple imputation results. There was one exception: for the complete case analysis of the opt-in arm, the relative risk estimate for participation in the highest income bracket ($83,200+) compared to the reference category of the lowest income bracket (<$20,800) did not reach statistical significance (RR=1.84; 95% CI: 0.90 to 3.75; *P*=0.093), whereas it did in the imputed data analysis (RR=2.04; 95% CI: 1.08 to 3.87; *P*=0.029). Parents of lower socioeconomic status were harder to contact for the interview, and the effect of multiple imputation was to better represent such groups by scaling up the proportion of parents in lower income brackets and the proportions of lone parent households (Figure 4.3). For other variables that had little influence on the likelihood of a parent being contacted for interview, such as age or the proportion of parents that were born in Australia, the observed and imputed values were similar. Thus, the imputed values appeared to be reasonable, even for the variable with the highest fraction of missing: annual household income (35%). Complete case results are not shown, but are available from the author on request.

Supplemental results for the VALiD trial of parental consent

Table 4.3: Imputation Model 1: variables used to impute sex for parents who were not interviewed

Variable	Data missing *n* (%)	Type of variable	Model used to predict missing data in this variable
Imputation Model 1			
Participation	0	Binary	N/A no missing
Mothers' baseline characteristics			
- Firstborn status	0	Binary	N/A no missing
- Age	0	Continuous	N/A no missing
- Indigenous status	0	Binary	N/A no missing
- Married/de facto	0	Binary	N/A no missing
- Australian born	0	Binary	N/A no missing
- Has private health insurance	0	Binary	N/A no missing
Household characteristics			
- Metropolitan residence	0	Binary	N/A no missing
- Socioeconomic quintile	0	Ordinal (5 categories)	N/A no missing
Interviewed parents' sex[a]	57 (5)	Binary	Logistic regression

[a]No interviews were conducted for the subset with missing values for parents' sex. Thus a two-step approach was taken where model 1 was specified to impute only one variable – parent's sex – based on all the available predictors and, subsequently, model 2 was specified to impute plausible values for missing data in the interview responses. For missing observations that were imputed as female in model 1, socio-demographics asked at interview were replaced with the relevant known baseline socio-demographics.

Table 4.4: Imputation Model 2: variables used to impute missing socio-demographic and interview responses about the topic of consent for all parents in the trial

Variable	Data missing *n* (%)	Type of variable	Model used to predict missing data in this variable
Imputation Model 2			
Participation	0	Binary	N/A no missing
Mothers' baseline characteristics			
- Firstborn status	0	Binary	N/A no missing
- Age[a]	0	Ordinal (5 categories)	N/A no missing
- Indigenous status	0	Binary	N/A no missing
- Has private health insurance	0	Binary	N/A no missing
Household characteristics			
- Metropolitan residence	0	Binary	N/A no missing
- Socioeconomic quintile	0	Ordinal (5 categories)	N/A no missing
- Number of children	206 (18)	Ordinal (integers)	Ordinal logistic regression
- Number of adults	206 (18)	Ordinal (integers)	Ordinal logistic regression
- Annual income	392 (35)	Ordinal (4 categories)	Ordinal logistic regression
Interviewed parents' characteristics			
- Age	210 (19)	Continuous	Linear regression
- Sex	0	Binary	N/A imputed in Model 1
- Married/de facto	207 (18)	Binary	Logistic regression
- Australian born	205 (18)	Binary	Logistic regression
- English language spoken at home	204 (18)	Binary	Logistic regression
- Lone parent status	202 (18)	Binary	Logistic regression
- Highest educational attainment	207 (18)	Ordinal (4 categories)	Ordinal logistic regression
- Remembers receiving letter	75 (7)	Binary	Logistic regression
- Reasons for opting in or opting out[b]	60 (5)	Free text, classified into 22 binary flags	Logistic regression
- Consent preference[c]	202 (18)	Nominal (7 categories)	Multinomial logistic regression

Table 4.4 (Continued)

Variable	Data missing *n* (%)	Type of variable	Model used to predict missing data in this variable
Imputation Model 2			
- Preferred contact frequency for opt-in consent[c,d]	202 (18)	Nominal (3 categories)	Multinomial logistic regression
- Importance of having the option to opt out[c,d]	202 (18)	Ordinal (4 categories)	Ordinal logistic regression
- Competing priorities scenario about consent for vaccine safety surveillance[c]	205 (18)	Nominal (5 categories)	Multinomial logistic regression

[a]The inclusion of their spouse's age category in model 2 resulted in better age predictions for male parents whose age was missing.

[b]After multiple imputation, the 22 binary flags were summarised into 7 main categories.

[c]A customised prediction equation was defined by excluding some variables from the imputation models to avoid multicollinearity problems. The question about consent preference and the associated skips were repeated once after the competing priorities scenario and the repeat questions were imputed separately from model 2 using a customised prediction equation.

[d]A skip was applied for parents for whom the question was not relevant.

Figure 4.3: A comparison of observed and imputed values for selected variables

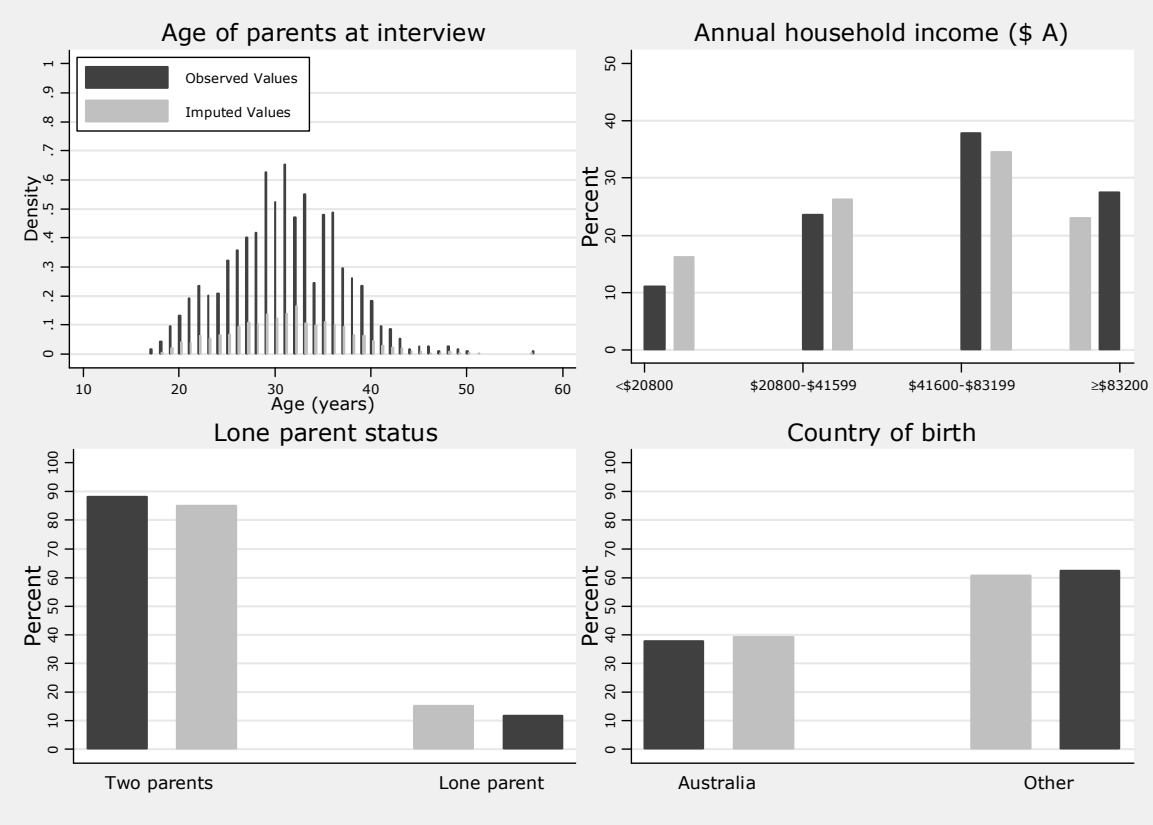


Table 4.5: Patterns of missingness of data for variables in substantive analysis

Participation outcome & baseline characteristics	Sex of parent at interview	Remembers letter	Reason for return/non-return of reply form	Consent preference/ Funding priorities scenario	Income	Other demographic characteristics	Parents *n* (%)	No. of missing variables
+	+	+	+	+	+	+	730 (64.7)	0
+	+	+	+	+	–	+	179 (15.9)	1
+	+	+	+	+	+	–	3 (0.2)	1
+	+	+	+	–	+	+	3 (0.2)	2
+	+	+	+	–	–	+	5 (0.4)	3
+	+	+	+	+	–	–	1 (<0.1)	3
+	+	+	+	+	–	–	11 (1.0)	4-10
+	+	+	+	–	+	–	1 (<0.1)	4-10
+	+	+	+	–	–	–	5 (0.4)	4-10
+	+	+	+	–	–	–	108 (9.6)	≥11
+	+	–	+	–	–	–	1 (<0.1)	≥11
+	+	+	–	–	–	–	8 (0.7)	≥11
+	+	–	+	–	–	–	13 (1.2)	≥11
+	+	–	–	–	–	–	4 (0.4)	≥11
+	–	–	+	–	–	–	9 (0.8)	≥11
+	–	–	–	–	–	–	48 (4.3)	≥11

Key: + = Complete, – = Missing

Table 4.6: Examples of key phrases used to classify parental responses in Figure 4.2 of the main paper

Classification	Examples
Wanted to be in the study	'I want to be in the study' 'include me' 'like records linked' 'good for baby's future' 'good to be involved' 'I want to support' 'important for data to be linked' 'willing to help out' 'I am fine about the study' 'it's for the greater good' 'to help out all future kids' ' no issue with the study' 'I am okay about you collecting data on my baby' 'posed no threat to my baby'; Opt in arm: 'meant to return form' 'all ready to go' 'everyone needs to return the form' 'intended to send it back'; Opt-out arm: 'agreed with study so did not send form back' 'did not have to do anything to be in the study, so I did not' 'did not object' 'didn't mind'
Low priority	'too much going on' 'too busy' 'bad timing' 'hectic' 'pile of things to do' 'didn't have time' 'overwhelmed' 'flat out' 'slipped my mind' 'got distracted' 'forgot' 'didn't think it was that important' 'bottom of my to-do list' 'could not be bothered' 'not high on my priority list' 'didn't take much notice' 'busy with sick child' 'in and out of hospital' 'complications with my newborn' 'baby-brain' 'lazy' 'disorganised'
Did not understand	'poor English' 'don't speak/no English' 'interpreter please' 'could not understand' 'cannot read or write' 'difficulty understanding the language of the letter' 'thought you might want me to come in' 'did not have any idea what the letter and data linkage was about'; Opt in arm: 'not aware that there was a need to return the form'
Did not get the letter	'didn't get the letter' 'moved house' 'moved interstate' 'went overseas' 'shifted addresses' 'don't have a proper place to live' 'homeless'
No contemplation	'I haven't considered it' 'out of sight, out of mind' 'thrown out by accident' 'probably binned it' 'did not open' 'did not get time to read the letter' 'in a pile of things to read' 'do not recall' 'don't remember it' 'lost' 'misplaced' 'not able to think'
Did not want to be in the study	'rather not participate' 'not interested' 'prefer not to' 'I don't want to' 'my husband/wife doesn't want it' 'like to keep our records private and don't want it shared' 'it is our responsibility to look after our baby' 'concerned about how the information was going to be used' 'would rather not have baby's records linked' 'do not have enough time to be part of the study' 'didn't want to be bothered with phone calls' 'did not feel it was relevant' 'did not think I would be a good candidate for the study' 'best not to be in the study as moving' 'did not think it is worth being part of the study as not vaccinating child'
Other	'husband/wife makes all those decisions' 'I thought I had to send it back' 'doctor told me to return form' 'does not look after the child' 'currently institutionalised' 'prefer not to say' 'didn't have a reason'

End of published article

4.4 Additional discussion

The results from the analyses in this article demonstrate that the opt-in approach resulted in very low participation and yielded a biased sample, with the implication being that an opt-in approach would not be feasible for a program of childhood vaccine safety surveillance using data linkage. In contrast, the opt-out approach achieved high participation and a representative sample and was generally well-accepted by parents.

Neither the opt-in nor opt-out approach was effective in achieving informed consent, as a considerable proportion of parents in each arm stated they did receive, understand or properly consider study invitations. Also, parental intentions and behaviour were often mismatched, with many parents who wanted to be in the data linkage study neglecting to opt in and some accidentally opting out. Likewise, a small proportion of parents who did not want to participate neglected to opt out and some parents opted in although they did not understand the study's purpose.

In the next chapter, I delve into parents' recall and understanding of the study invitation material and their attitudes towards data linkage for vaccine safety surveillance and opinions on the requirement for consent. A small body of literature demonstrates that informed consent is an ideal that is often unattainable among researcher volunteers in clinical trials involving therapeutic procedures[127-133]; however, there is a paucity of research in relation to data linkage studies. Informed consent may be easier to obtain for data linkage studies as they do not involve any direct participation on behalf of the volunteer and, therefore, do not require a detailed understanding of a procedure's risks and benefits. Chapter 5 reports on these findings.

5 Publication — Parent perspectives on consent for the linkage of data to evaluate vaccine safety: a randomised trial of opt-in and opt-out consent

5.1 Preface

This chapter contains the second of two articles presenting the results of the RCT. In particular, it presents the secondary outcomes of the RCT. This article has been accepted for publication in *Clinical Trials*. The article investigates whether it is possible to achieve informed consent using either the opt-in or opt-out approach as a strategy to invite parents by mail to participate in data linkage for childhood vaccine safety surveillance. Parental recall and understanding is compared between the opt-in and opt-out arms at four weeks following receipt of a mailed study invitation. Factors which may impact on parental comprehension, including the readability of the study invitation material and the educational attainment of the parent are examined.

The article also addresses gaps in the literature on community consultation by gauging parental attitudes towards data linkage for postmarketing surveillance of childhood vaccine safety and opinions on the requirement for consent. Furthermore, parental attitudes towards vaccination in terms of its public health benefit, safety, and effectiveness and vaccination practices in relation to the newborn are examined. In Chapter 6, these questions are repeated in a population-based sample survey of adults of all ages from South Australia, including respondents with and without children, and the generalisability of the findings between the two samples is examined in Chapter 7.

5.2 Statement of authorship

Berry JG, Ryan P, Duszynski KM, Braunack-Mayer AJ, Carlson J, Xafis V, Gold MS, the Vaccine Assessment using Linked Data (VALiD) Working Group. Parent perspectives on consent for the linkage of data to evaluate vaccine safety: a randomised trial of opt-in and opt-out consent. *Clinical Trials* (accepted 1/2/2013).

By signing below, the authors declare that they give consent for this paper to be presented by Jesia Berry towards examination for the Doctor of Philosophy.

Jesia Berry (Candidate)

Developed the trial protocol and randomisation schedule, co-authored the study invitation material and the telephone survey, conducted interviews, collected the data, performed analyses, interpreted the results, reviewed the literature and drafted the manuscript.

Signed: …… Date: ….22/2/13……

Philip Ryan

Contributed to the conception and design of the study, procured funding, designed the statistical analysis for the trial, provided statistical advice, helped design the study invitation material and telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: ….22-2-13..

Katherine Duszynski

Contributed as trial coordinator to leading the design and direction of the study, co-authored the study invitation material, helped design the telephone survey, applied for ethical approval, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: ……20/02/2013……

Annette Braunack-Mayer

Contributed to the conception and design of the study, procured funding, helped design the study invitation material and telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 21.02.2013

Jillian Carlson

Contributed to the design of the study invitation material and telephone survey, conducted interviews, collected the data, and reviewed the manuscript.

Signed: …… Date: 25-02-2013

Vicki Xafis

Contributed to the design of the study invitation material and telephone survey, and reviewed the manuscript.

Signed: …… Date: 21/2/13

Michael Gold

Contributed to the conception and design of the study, procured funding, helped design the study invitation material and telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 20/2/13

5.3 Article

5.3.1 Abstract

Background: We examined parents' consent preferences and understanding of an opt-in or opt-out invitation to participate in data linkage for postmarketing safety surveillance of childhood vaccines.

Methods: A single-blind parallel-group randomised controlled trial: 1129 families of babies born at a South Australian hospital in 2009 were sent information at six weeks post-partum explaining data linkage of childhood immunisation and hospital records for vaccine safety surveillance, with four weeks to opt in or opt out by reply form, telephone or email. At 10 weeks post-partum, 1026 (91%) parents were followed up by telephone interview.

Results: In both the opt-in (n=564) and opt-out arms (n=565), four-fifths of the parents recalled receiving the information (81% *vs* 83%, P=0.35), three-fifths reported reading it (63% *vs* 67%, P=0.11), but only two-fifths correctly identified the health records to be linked (43% *vs* 39%, P=0.21). Parents who actively consented (opted in) were more likely than those who passively consented (did not opt out) to recall the information (100% *vs* 83%, P<0.001), report reading it (94% *vs* 67%, P<0.001), and correctly identify the data sources (60% *vs* 39%, P<0.001). Most parents supported data linkage for vaccine safety surveillance (94%) and trusted its privacy protections (84%). Most parents wished to have minimal or no direct involvement, preferring either opt-out consent (40%) or no consent (30%). A quarter (24%) of parents indicated opt-in consent should be sought; of these 8% requested consent prior to every use, 5% preferred to give broad consent just once and 11% preferred periodic renewal. Three-fifths of the parents gave higher priority to rapid vaccine safety surveillance (61%) rather than first seeking parental consent (21%) and one in seven was undecided (15%). Although 91% of parents reported that their babies were fully (76%)

or under (15%) immunised, and trusted vaccines as safe (90%), three-fifths (62%) were very or somewhat concerned about serious reactions.

Limitations: The context of data linkage is limited to vaccine safety surveillance. Only recall and understanding retained at one month post-enrolment were measured.

Conclusions: This trial demonstrates that informed consent for a population-based surveillance program cannot realistically be achieved using mail-based opt-in and opt-out approaches. While recall and understanding of the study's purpose were better among parents who actively consented (opted in) compared with parents who passively consented (did not opt out), participation was substantially lower (21% *vs* 96% respectively). Most parents appeared to have a poor understanding of data linkage for vaccine safety surveillance; nonetheless they supported data linkage. They preferred a system utilising opt-out consent or no consent to one using opt-in consent.

5.3.2 Introduction

Linked electronic administrative health care databases are a valuable resource that can be used for postmarketing surveillance of medicines and vaccines.[16,17,19,77] In the last two decades, many countries have amended or passed laws to tighten the protection of individual privacy,[6,103,137] so that, generally, data can be accessed for research uses only when prior informed consent has been obtained, or when data are anonymised so that there is no reasonable way of identifying the individuals involved, or when certain provisions for consent waivers are met and approved by a human research ethics committee (HREC) or institutional review board.[9,137] For example, if an HREC assesses that a proposed data linkage project is 'substantially in the public interest',[6] it can allow the disclosure of identifiable demographic information to an authorised data linkage unit, without individual consent, for the purpose of creating a master linkage key in accordance with the best

practice protocol.[5,9] Individual privacy is preserved as researchers receive only files of pre-linked data with no personal identifiers.[39,100]

Some argue that legislative complexity and the vagaries of defining the sufficiency of the public interest needed to counter a requirement for informed consent have had a negative effect on public health research because HRECs and data custodians lack sufficient guidance as to when a consent waiver is appropriate.[6,10-12,103,137,207] Lack of guidance can create an over-reliance on a requirement for opt-in consent for reassurance of the voluntariness of participation and to protect against litigation.

Surveys and focus groups conducted internationally[148-151,156] and in Australia[6,10,12] have shown the public to be supportive of research that improves quality of care and public health; however, most believe that some form of consent should be sought prior to use of their data for research.[6,148,149,151,155-162] Opt-in consent, either verbally or in writing, generally is preferred over opt-out consent.[148,157-159] Some studies,[12,155,156,160-162] but not others,[149,159] have found the majority of the public want opt-in consent for both the use of identifiable and de-identified data, although people usually are not well-acquainted with the concept of 'de-identified data'[12] or what health and medical research entails.[6,149,151] Often missing from the investigations has been the provision of a contextual framework regarding the intended societal benefits and privacy safeguards[115,163,164] and the costs of obtaining consent in relation to the finite budget for public health,[100] which enables people to weigh the societal benefits and potential harms in their decision-making. When this context is provided, the public has been more receptive to research without patient consent.[115,163,164]

Previous studies have demonstrated that informed consent is an ideal that is often difficult to attain.[127-133] For example, a randomised controlled trial (RCT) conducted with parents of 101 children undergoing an upper endoscopy procedure showed that informed consent

assessed using a tailored survey instrument was achieved in only 10% of parents when form-based consent was administered along with physician discussion, and in 33% of parents when the information was repeated in a sixth-grade level video module.[129]

In 2009, we conducted an RCT to examine the feasibility of obtaining parental consent from families of newborns for the linkage of data to evaluate childhood vaccine safety by comparing two approaches – opt-in and opt-out. Eligible families were sent information by mail six weeks after birth, with four weeks to opt in or opt out by reply form, telephone or email. The participation rates at 10 weeks post-partum were compared in the primary analysis. Participation was significantly lower in the opt-in arm (21%, n=120/564) compared with the opt-out arm (96%, n=540/565) and selection bias was evident in the opt-in arm, as participants were more likely to be older, married or living with a partner, university educated and of higher socioeconomic status than non-participants, whereas participants in the opt-out arm were representative of the target population.[192] In a subsequent follow-up interview, it was apparent from the reasons given by parents for participation and non-participation that opting in or opting out behaviour often did not match a parent's stated underlying intention.[192] In this article, we report parental recall and understanding of the study invitation, consent preferences, trust in the protections of privacy in data linkage, opinions on vaccine safety and effectiveness, and the level of vaccination uptake for the newborn.

5.3.3 Methods

Setting and participants

The Vaccine Assessment using Linked Data (VALiD) trial was conducted at the Women's and Children's Hospital in Adelaide, the capital city of South Australia (SA), where approximately 25% of the state's babies are delivered.[186] We provide a brief description of the study protocol here; full details are provided elsewhere.[176] The study was disclosed on http://www.anzctr.org.au/ and assigned the identifier ACTRN12610000332022. All eligible mothers aged 18 years and older who resided in SA when they gave birth at the hospital were included without their consent to avoid introducing selection bias in the study sample. The hospital HREC granted a waiver of the usual requirement for consent and allowed the limited disclosure to mothers of the true purpose of the trial [Children, Youth and Women's Health Service (CYWHS) reference number: REC2087/7/11]. Exclusion criteria were stillbirth, neonatal or maternal death, two weeks or longer spent in neonatal intensive care, home birth, inward transfer of a newborn from another hospital, and any identified maternal hardship, for example, incarceration, mental illness, or adoption of the baby or placement into foster care.

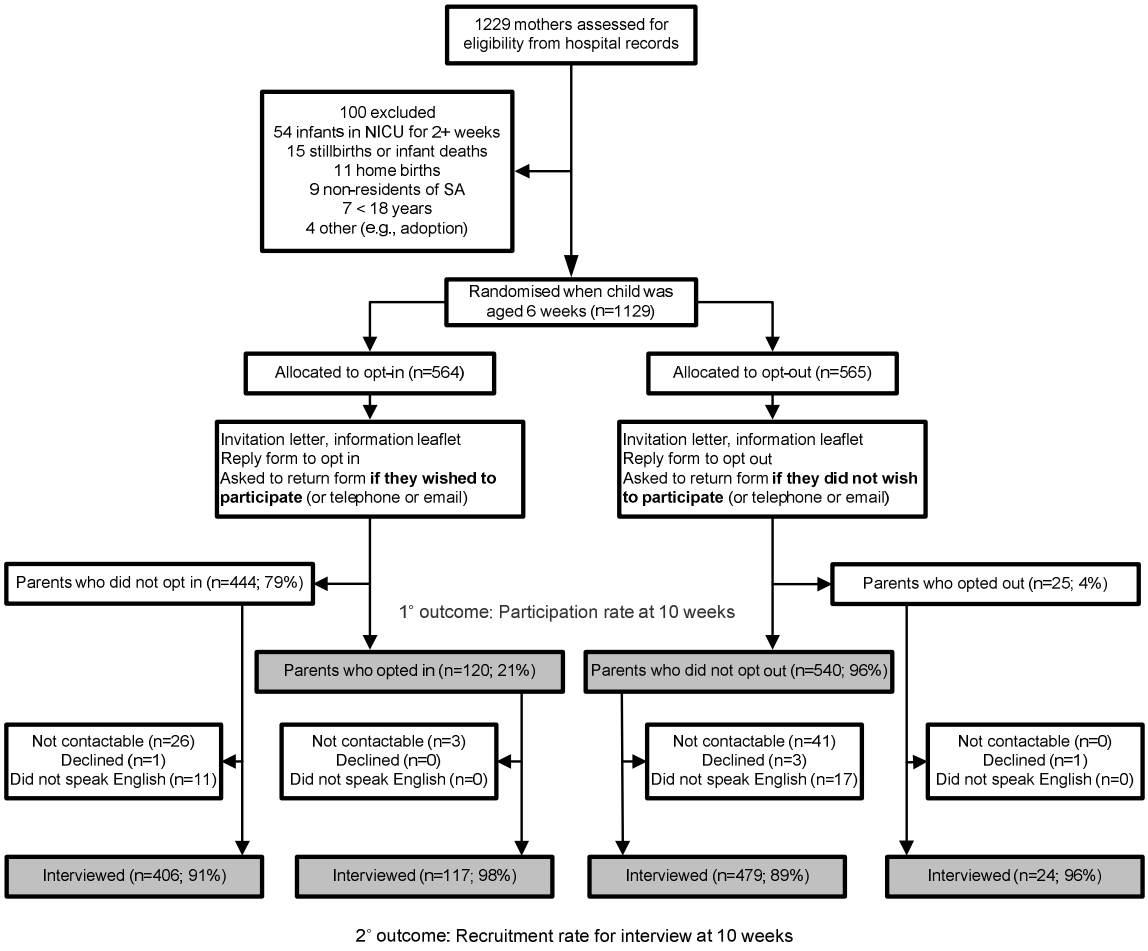
Randomisation and blinding

Mothers were allocated randomly at six weeks post-partum to the opt-in and opt-out arm in the ratio 1:1, using randomly permuted blocks of sizes 2, 4, 6 and 8, stratified by firstborn status (first live and surviving birth versus subsequent births). Allocation was concealed by computer-automated merging of electronic data listings of eligible mothers with the randomisation schedule (created using the Stata program ralloc[187]). The trial was single-blinded: parents were informed about the data linkage, but unaware that two consent approaches were being compared. The interviewers [JB, JC] were aware of the randomised allocation and participation status of the parents at the follow-up interview at 10 weeks post-partum.

Interventions and follow-up

One to two weeks prior to the infant's scheduled vaccinations at two months of age, the household received a cover letter (addressed to the mother), a two-page information leaflet and a reply-paid form, with different formats according to randomised allocation to the opt-in or the opt-out arm (Figure 5.1). Parents were invited to be part of a 'Vaccine Data Linkage Study' and permission was sought to link infants' two-month vaccinations with any hospital visits occurring in the month afterwards to check for adverse events following immunisation. Parents were directed to a dedicated website for detailed information on the process of data linkage and how personal information is kept private (http://health.adelaide.edu.au/paediatrics/research/valid/). Parents in the opt-in arm were instructed to return a reply form, telephone, or email to signal willingness to participate in data linkage. Parents in the opt-out arm were informed they would be included unless they refused consent by the same means. All parents were given four weeks to respond. No follow-up reminder letters were sent. At 10 weeks post-partum, attempts were made to interview, by telephone, the parent (either mother or father) who had opted in or opted out. When this was not possible, the other parent, if available, was interviewed as a proxy. For households that did not opt in or opt out, the first parent to answer the telephone was invited to be interviewed.

Figure 5.1: Flow diagram of opt-in compared with opt-out trial



Pilot study

Prior to commencement, the study invitation material and telephone survey were piloted on five academic staff and a convenience sample of 20 parents of young children in order to test the clarity, format and sequence of questions, which were designed and administered according to recommended principles.[189,190] According to the Flesch readability ease score, a standard and validated readability measure on a scale of 0 to 100,[208] most adults are able to read a document scoring 65 or above.[209] The letter scored 60 (standard/average) and the opt-in/opt-out forms scored 70 (fairly easy to read). The letter briefly explained the concept of data linkage for childhood vaccine safety surveillance and described the health records to be linked; these key points were repeated in the opt-in/opt-out forms. The two-page leaflet scored 49 (difficult to read); it comprised lengthier explanations on the process and

security measures used in data linkage, potential benefits and privacy risks, as well as HREC-prescribed legalese about patient confidentiality. According to the Flesch-Kincaid grade level (range, 0 to 12),[210] the academic grade a person would need to complete in order to read and comprehend these materials was 10 for the letter, 6 for the opt-in/opt-out form, and 12 for the leaflet.

Telephone survey

In the telephone interview, parents were asked general questions about the public health benefit, safety and effectiveness of vaccines (with some questions adapted from Gust et al.[191]). Parents were asked whether they had received and read the study invitation material and/or been exposed to other sources of information about data linkage, such as the VALiD study-specific website, other websites, newspapers, books, television and radio. Parents were tested on their understanding of the study's purpose by asking them to select the two sources of information about their baby's health that were to be linked from six possibilities that were read out to them: vaccination records, medication records, birth records, visits of the baby to hospital, visits of the baby to a general practitioner, and visits of the baby to a Child and Youth Health clinic.

The interviewer asked each parent why they did or did not participate in the VALiD study, as indicated by their opting in or opting out behaviour (these results are reported elsewhere[192]). Subsequently, a program of data linkage for childhood vaccine safety surveillance was described and each parent's consent preference was elicited using a six-point scale adapted from Willison et al.[148] Parents were then asked to choose between two priorities for Australian Government funding: performing rapid vaccine safety surveillance using data linkage without seeking consent or using some of this funding to seek parental consent first. The consent preference question was then re-asked, to see whether opinions had changed after the funding priorities scenario was presented. Parents subsequently were

asked to indicate their level of trust in the privacy protections used in data linkage. Further questions were asked about the vaccination status of each newborn in their care, enabling classification of the parent as having a baby or babies who were fully immunised, under immunised or unimmunised at two months of age according to the National Immunisation Program schedule. (For the exact wording of the telephone interview see Appendix 6.)

Sample size

A sample size of 544 in each randomised group was calculated to afford power of 90% to detect a difference of 0.1 in the proportions of binary responses to questions at interview using two-tailed tests at the 5% level of significance. In the absence of prior knowledge of response proportions, $\pi = 0.5$ was used for sample size estimation, as this yields the most conservative (largest) sample size. The reported *P*-values have not been adjusted for multiple testing.

Statistical analysis

We used multiple imputation to create 50 datasets in which the missing values in the survey responses were replaced by imputed values by applying the fully conditional specification (FCS) method,[202] as implemented using the mi ice add-on in Stata 11.2 software. Variables used in the imputation were the primary outcome (participation status) and mothers' baseline characteristics, for which there were no missing data, and the secondary outcomes (interview responses), which were affected by missing data. Full details of the imputation procedure are supplied in online appendix A. Statistical analyses consisted of tabulations of frequencies of responses to survey questions, with routines specifically designed to combine estimates from the imputed datasets to generate a single set of estimates with valid standard errors that incorporate uncertainty about the imputed values.[195] Small discrepancies in some table frequencies and percentage totals occur due to the effect of averaging across imputed datasets.

We used Wald tests to identify significant associations by randomised allocation in the response to questions. Consent preferences before and after presentation of the funding priorities scenario were compared using a Stuart-Maxwell test for association between matched pairs. Ordinal logistic regression analyses were used to examine the association between responses to questions regarding the safety and effectiveness of vaccines in relation to 1) randomised allocation and 2) parents' vaccination practices. Preliminary checks confirmed the proportional odds assumption.[211] Statistical tests were two-tailed, with a significance level of 5%.

5.3.4 Results

Figure 5.1 shows the flow of parents through the trial. A total of 1129 mothers were enrolled over a three-month period: from 27 July to 25 October 2009. We randomly assigned 564 mothers to the opt-in arm and 565 to the opt-out arm. The baseline sociodemographic characteristics were comparable in the two arms (Table 5.1).

Table 5.1: Baseline characteristics of mothers at trial entry (complete cases)

Maternal factors	Opt-in (*n*=564)	Opt-out (*n*=565)	Total (*n*=1129)
Firstborn child	252 (45)	252 (45)	504 (45)
Median (IQR) age (years)	31 (26–35)	31 (26–35)	31 (26–35)
Aboriginal or Torres Strait Islander origin	13 (2)	25 (4)	38 (3)
Married/de facto	443 (79)	429 (76)	872 (77)
Australian born	346 (61)	332 (59)	678 (60)
Metropolitan residence	509 (90)	525 (93)	1034 (92)
Has private health insurance	60 (11)	45 (8)	105 (9)
Socioeconomic quintile[a]			
Least disadvantaged (tiers 1–2)	189 (34)	185 (33)	374 (33)
3	86 (15)	87 (15)	173 (15)
Most disadvantaged (tiers 4–5)	289 (51)	293 (52)	582 (52)

Values are numbers (percentages) unless stated otherwise. IQR=interquartile range.

[a]Socioeconomic indexes for areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data.

In total, 1026 parents (91%) were interviewed; 810 (72%) had complete data or were missing data for only one variable used in the current analyses (online appendix A, supplemental results Table 5.8).

Parental recall and understanding of the study

Recall of the study's purpose and understanding of data linkage were similar in the opt-in and opt-out arms; all comparisons yielded probabilities of 0.11 or more (Table 5.2). The study invitation was recalled by 82% of parents and 65% reported that they had read the information; some also had been exposed to the VALiD study-specific website or other media (opt-in arm: 13%; opt-out arm: 15%). The study information had not been read by 35% of parents, though a few had gained some knowledge about data linkage from other sources (opt-in arm: 3%; opt-out arm: 4%). Only 41% of parents were able to identify correctly that the purpose of the VALiD study was to link their children's vaccination and hospital records. For 52% of the parents, one out of the two selected health records was incorrect, and 8% per cent of parents paired two incorrect options.

Parents with higher education had significantly higher levels of recall, reading and understanding of the information. There was a 15% difference in recall of receiving the information between the least educated quartile (attended up to year 10 of secondary school) and the most educated quartile (university educated) (72% *vs* 87%, $P<0.01$). Similarly, the proportions in the least and most educated quartile differed by 23% for those who read the information (49% *vs* 72%, $P<0.001$) and 13% for those who correctly identified the health records to be linked (30% *vs* 43%, $P=0.02$).

Table 5.2: Understanding of data linkage for childhood vaccine safety surveillance

Question	Opt-in arm, *n* (%)[a]				Opt-out arm, *n* (%)[a]			
		Returned reply form	Did not return reply form			Did not return reply form	Returned reply form	
	All, *n*=564	Participant, *n*=120	Non-participant, *n*=444	*P* value	All, *n*=565	Participant, *n*=540	Non-participant, *n*=25	*P* value
Recall study invitation								
Yes	457 (81)	120 (100)	337 (76)	<0.001[b]	470 (83)	446 (83)	24 (96)	<0.01
No	107 (19)	0 (0)	107 (24)		95 (17)	94 (17)	1 (4)	
Read the letter and information leaflet								
Yes	353 (63)	112 (94)	241 (54)	<0.001	381 (67)	361 (67)	20 (78)	0.24
No	211 (37)	8 (6)	203 (46)		184 (33)	179 (33)	5 (22)	
Identified the two health records to be linked								
Yes	240 (43)	72 (60)	168 (38)	<0.001	217 (39)	208 (39)	9 (38)	0.95
No, one correct	283 (50)	39 (32)	244 (55)	<0.001	300 (53)	289 (54)	11 (42)	0.32
No, both incorrect	41 (7)	9 (7)	32 (7)	0.91	48 (8)	43 (8)	5 (20)	0.18

[a]Averaged across 50 datasets, in which missing values were replaced by imputed values, and expressed as whole number (per cent).

[b]Interpret with caution as the estimation procedure led to predicted probabilities greater than 1 for some observations.

In the opt-in arm, parents who opted into data linkage (i.e. participants) were more likely than non-participants to recall and report that they had read the study invitation material, as well as correctly identify the health records to be linked (Table 5.2). In the opt-out arm, parents who opted out of the study (i.e. non-participants) were more likely to recall the material than participants, but were no more likely to say they had read the information or correctly to identify the health records to be linked (Table 5.2). Parents who actively consented (opted in) were more likely than parents who passively consented (did not elect to opt out) to recall the material (100% *vs* 83%, $P<0.001$), to say they had read it (94% *vs* 67%, $P<0.001$), and correctly to identify the health records to be linked (60% *vs* 39%, $P<0.001$).

Consent choice for linked children's health information

The majority (94%) of parents supported linking their children's vaccination and hospital records for the purpose of vaccine safety surveillance; very few were completely opposed (3%) or undecided (3%) (Table 5.3). The majority (70%) preferred minimal or no direct involvement: 40% would be satisfied with notification with the option to opt out and 30% preferred that their child's health information be linked without consent or notification. Among parents who favoured opt-out consent, 92% stated that the opportunity to opt out was either very or somewhat important. A quarter (24%) of parents indicated opt-in consent should be sought; of these 8% requested consent prior to every use and the remainder preferred to give broad consent, that is, to consent just once (5%) or at periodic intervals of their choosing (11%), with yearly intervals most preferred. Consent preferences were similar in the opt-in and opt-out arms, except for more undecided parents in the latter group (1% *vs* 4%).

Table 5.3: Opinions regarding consent to data linkage for childhood vaccine safety surveillance

We asked to join together your baby's vaccination records with any visits of your baby to hospital. Before your baby's records are linked, your baby's name and home address will be replaced by a unique number, which means that the researchers who look at the linked records will not be able to identify your baby.	Response, *n* (%)[a]		
	All subjects, *n* (%)	Opt-in, *n* (%)	Opt-out, *n* (%)
Which of the following statements best matches how you feel about your baby's health information being used for checking the safety of vaccines?			
Do not link	36 (3)	20 (4)	16 (3)
Opt-in consent			
Every time	90 (8)	46 (8)	44 (8)
Broad consent, renewing[b]	126 (11)	58 (10)	68 (12)
Broad consent once	59 (5)	36 (6)	23 (4)
Opt-out consent[c]	455 (40)	220 (39)	235 (42)
No consent	333 (30)	175 (31)	158 (28)
Undecided*	29 (3)	8 (1)	21 (4)
Total	1129 (100)	564 (100)	565 (100)
[b]Interval for renewing, *n* (column %)			
Every year	90 (71)	42 (71)	48 (71)
Once every five years	21 (16)	13 (22)	8 (12)
Some other period	15 (12)	4 (6)	12 (17)
Total	126 (100)	58 (100)	68 (100)
[c]Importance of option to opt out, *n* (column %)			
Very important	279 (61)	127 (58)	152 (65)
Somewhat important	141 (31)	76 (34)	65 (28)
Not too important	33 (7)	16 (7)	17 (7)
Not at all important	2 (1)	1 (1)	1 (1)
Total	455 (100)	220 (100)	235 (100)

[a]Averaged across 50 imputed datasets, in which missing values were replaced by imputed values, and expressed as whole number (per cent). **P*=0.03 in the comparison of proportions in the opt-in and opt-out arm.

Priorities for linked children's health information

Parents gave higher priority to Australian Government funding being allocated to enable rapid and comprehensive vaccine safety surveillance (61%) rather than first seeking parental consent to link their child's health information (21%) (Table 5.4). One in seven parents (15%) was undecided. There were no significant differences in parental priorities by randomised allocation; all comparisons yielded probabilities of 0.15 or more. When the consent preference question was repeated after the funding priorities scenario had been presented, there was a small, but significant, increase in the proportion of parents who chose opt-out consent and no consent (by 1 and 2.5 percentage points, respectively) and the proportion who selected opt-in consent declined by 5 percentage points ($P<0.001$). The majority (84%) of parents were either very or somewhat confident that the privacy of an individual's personal information would be protected by the security measures used in data linkage (Table 5.5).

Views on the safety and effectiveness of vaccines

Most parents (97%) supported childhood vaccination and agreed (90%) that the vaccines given to children in Australia are safe (Table 5.5). However, almost every parent (99%) agreed that it is important to check the safety of childhood vaccines, and many were very or somewhat concerned that a vaccine might cause a serious reaction (62%) or might be ineffective in preventing the targeted disease (42%). Vaccine safety concerns were cited as more pressing for parents who had reservations about both vaccine safety and the privacy protections in data linkage. Opinions were similar in the opt-in and opt-out arm.

Table 5.4: Opinions on the relative importance of obtaining consent or checking vaccine safety

The Australian Government has a set amount of money put aside for health and medical research. Spending money on one activity means there is less to spend on other things. I will read you two statements which describe different ways that time and money could be spent. With which statement do you most agree? If you cannot choose, just say so.	Response, *n* (%)[a]		
	All subjects	Opt-in	Opt-out
Asking parents for consent to link their baby's health information	242 (21)	110 (20)	132 (23)
Being able to perform quick, extensive and up-to-date checks on the safety of vaccines	683 (61)	348 (62)	335 (59)
Undecided	168 (15)	86 (15)	82 (14)
Do not link data	36 (3)	20 (4)	16 (3)
Total	1129 (100)	564 (100)	565 (100)

[a]Averaged across 50 datasets, in which missing values were replaced by imputed values, and expressed as whole number (per cent).

Table 5.5: General views on vaccine safety and surveillance

Question or proposition	Response, *n* (%)[a]					
	Total	Very confident	Somewhat confident	Undecided	Not too confident	Not at all confident
The usual measures for security in data linkage are to replace a person's name and home address with a unique number and store any personal information in a secure place. How confident are you that this will protect a person's identity?	All, 1129 (100)	333 (29)	619 (55)	44 (4)	120 (11)	14 (1)
	Opt-in, 564 (100)	171 (30)	301 (53)	18 (3)	65 (12)	9 (2)
	Opt-out, 565 (100)	162 (29)	318 (56)	25 (4)	55 (10)	5 (1)
	Total	Strongly agree	Agree	Undecided	Disagree	Strongly disagree
It is important to vaccinate children to prevent diseases such as polio, whooping cough and chicken-pox	All, 1129 (100)	851 (75)	240 (21)	11 (1)	18 (2)	8 (1)
	Opt-in, 564 (100)	427 (76)	120 (21)	1 (0)	12 (2)	4 (1)
	Opt-out, 565 (100)	425 (75)	120 (21)	10 (2)	6 (1)	5 (1)
It is important to check the safety of vaccines given to children in Australia	All, 1129 (100)	879 (78)	238 (21)	8 (1)	4 (0)	0 (0)
	Opt-in, 564 (100)	444 (79)	114 (20)	3 (0)	3 (0)	0 (0)
	Opt-out, 565 (100)	435 (77)	124 (22)	5 (1)	1 (0)	0 (0)
	Total	Very safe	Safe	Undecided	Unsafe	Very unsafe
In general, how safe do you think the vaccines are that are given to children in Australia?	All, 1129 (100)	403 (36)	613 (54)	76 (7)	33 (3)	5 (0)
	Opt-in, 564 (100)	204 (36)	307 (54)	34 (6)	17 (3)	2 (0)
	Opt-out, 565 (100)	199 (35)	306 (54)	42 (7)	16 (3)	2 (0)

Table 5.5 (Continued)

Question or proposition	Response, *n* (%)[a]					
	Total	Very concerned	Somewhat concerned	Undecided	Not too concerned	Not at all concerned
How concerned are you that a vaccine given to children might not work and they might still get the disease?	All, 1129 (100)	211 (19)	262 (23)	19 (2)	430 (38)	208 (18)
	Opt-in, 564 (100)	113 (20)	131 (23)	11 (2)	202 (36)	108 (19)
	Opt-out, 565 (100)	98 (17)	131 (23)	8 (2)	228 (40)	100 (18)
How concerned are you that a vaccine given to children might not be safe and might cause a serious reaction?	All, 1129 (100)	289 (26)	410 (36)	13 (1)	324 (29)	93 (8)
	Opt-in, 564 (100)	152 (27)	217 (39)	5 (1)	145 (26)	45 (8)
	Opt-out, 565 (100)	137 (24)	193 (34)	9 (2)	179 (32)	48 (9)
	Total	Privacy protection	Vaccine safety	Equal concern		
You have expressed some concerns about privacy protection in data linkage studies and also about vaccine safety. Which of your concerns is greater?[b]	All, 87 (100)	7 (8)	58 (67)	22 (25)		
	Opt-in, 48 (100)	5 (10)	31 (64)	12 (26)		
	Opt-out, 39 (100)	2 (4)	28 (72)	9 (24)		

[a]Averaged across 50 datasets, in which missing values were replaced by imputed values, and expressed as whole number (per cent).

[b]Asked of the subset of parents who indicated that they were not too confident or not at all confident in the security measures used in data linkage and very or somewhat concerned about serious vaccine reactions.

The majority of parents (91%, 95% CI: 89% to 93%) reported that their babies had been vaccinated by 10 weeks of age, 6% (95% CI: 5% to 8%) still intended to vaccinate, and 3% (95% CI: 2% to 4%) intended not to. Three-quarters (76%, 95% CI: 73% to 78%) of parents reported that their babies were fully immunised, 15% (95% CI: 13% to 17%) were under immunised, and 9% (95% CI: 7% to 11%) were unimmunised. Compared with parents of fully immunised babies, parents of unimmunised babies were more likely to view vaccines as unsafe (OR 4.6, 95% CI: 2.6 to 8.3) and have concerns about serious reactions (OR 2.9, 95% CI: 1.8 to 4.8) and vaccine effectiveness (OR 1.6, 95% CI: 1.04 to 2.5). For parents of under immunised babies, the corresponding cumulative odds ratio was significant for concerns that vaccines were unsafe (OR 1.5, 95% CI: 1.04 to 2.2), but not for concerns regarding serious reactions (OR 1.1, 95% CI: 0.7 to 1.6) or vaccine effectiveness (OR 0.9, 95% CI: 0.6 to 1.2).

[In the odds ratio results presented above, the original five categories in the Likert scale of parental vaccine safety concerns were used in the ordinal logistic regression analyses. Table 5.6 displays the results of analyses in which the original five categories for parental safety concerns were converted to three categories (e.g. 1 very safe/safe; 2 undecided; 3 unsafe/very unsafe; or 1 not at all/too concerned; 2 undecided; 3 somewhat/very concerned, as appropriate). These were the categories utilised in the ordinal logistic regression analyses displayed in Table 6.5 (Chapter 6), enabling direct comparisons to be made between the two studies, as is done in Chapter 7. Table 5.6 was not included in the published article in *Clinical Trials*.]

Table 5.6: Vaccine safety concerns and parental compliance with two-month immunisations by the age of 10 weeks for babies

	Response, *n*[a]				Parental concerns about vaccines: Odds Ratio (95% CI)[c]		
Vaccination status of babies	Opt-in	Opt-out	All	% (95% CI)	Unsafe	Serious reaction	Might not prevent disease
Fully immunised[b]	444	411	854	76 (73, 78)	1.00	1.00	1.00
Under immunised	75	96	171	15 (13, 17)	2.1 (1.2, 3.7)	1.1 (0.7, 1.6)	0.9 (0.6, 1.4)
Unimmunised	45	58	104	9 (7, 11)	7.3 (4.2, 12.9)	2.9 (1.4, 5.7)	1.5 (1.0, 2.5)
Total	564	565	1129				

[a]Averaged across 50 datasets, in which missing values were replaced by imputed values, and expressed as whole number (per cent).

[b]Reference category. Babies were classified as fully immunised if all of the two-month vaccinations had been administered: hexavalent vaccine (Infanrix hexa), pneumococcal conjugate vaccine (Prevenar) and oral rotavirus vaccine (RotaTeq). The hepatitis B vaccine (HB-Vax II) given at birth was excluded from the definition.

[c]Further exploration for potential confounders among the socio-demographic factors collected in the survey showed no evidence of any important confounding influences on the relationship between immunisation status and parental concerns about vaccines.

5.3.5 Discussion

Parental recall and understanding of the study's purpose showed incremental improvement with progressively higher levels of educational attainment. Parents who actively consented (opted in) were more likely than those who passively consented (did not elect to opt out) to recall (100% *vs* 83%) and have read the information (94% *vs* 67%) and correctly identify which health records were to be linked (60% *vs* 39%). Thus, parents who made an active decision to opt in were best placed to give truly informed consent. However, the drawback of using an opt-in consent system was a much lower participation rate than the opt-out approach (21% *vs* 96%) and selection bias toward participants of higher education and socioeconomic status.[192]

Five previous RCTs[21-25] (reviewed in Berry et al.[176]) have also found that the opt-out approach yielded higher participation rates than the opt-in approach, but the extent of participation in these trials varied widely from 48%–85% in the opt-in arm and 59%–100% in the opt-out arm. None of these trials were relevant to the context of data linkage; only two evaluated subject recall, understanding and reasons for (not) consenting,[22,25] and all but one[23] had a small sample size and flawed methodology.

Data linkage for postmarketing surveillance of vaccines was widely supported by parents (94%). Most trusted (84%) that their privacy would be protected through the use of pre-linked anonymised data by researchers and informational security safeguards. The majority also preferred minimal or no direct involvement in controlling the use of their baby's health information: opt-out consent (40%) and no consent (30%) were more popular than opt-in consent (24%). The proportion wanting some form of consent (either opt-in or opt-out) reduced to 21% when informed it would be at the expense of rapid and comprehensive vaccine safety surveillance, and twice as many (61%) gave precedence to the latter.

However, most parents reverted back to their original preference when re-asked which consent option they preferred.

Immunisation compliance at two months of age (76%) appears on course to reach the national target of 90% fully immunised at 12 months of age.[61] Nevertheless, similar to survey findings in the United States (US),[191,212] many parents expressed concerns about the likelihood of serious reactions and the effectiveness of vaccines. Such concerns were associated with suboptimal childhood vaccine uptake. These findings highlight the importance of improving vaccine safety surveillance for public reassurance and data linkage is a recommended strategy.[77]

Limitations

This trial was limited to one context: parental consent to using data linkage for childhood vaccine safety surveillance. Parental understanding of the study purpose, consent preferences, and opt-in and opt-out participation rates may differ by subject area and also by population/patient group. The eligible population was selected from hospital listings of births, sent an invitation by mail, and instructed to respond by email, telephone or post. We did not use reminders (e.g. repeat mailings or telephone calls) as they are impracticable for large population-level studies[100] and the likely gain in the opt-in arm to about 30% participation is modest.[197]

Some of the material required advanced reading skills. The level of informed consent may have been improved using strategies such as consumer consultation in document synthesis, incorporating discussion with immunisation providers, government media advertisements, and video presentations, but the gains do not appear to be substantial.[129,130,132] We measured recall and understanding of the consent forms retained at one month post-trial enrolment and not at the time they were first received by parents. We did not evaluate the adequacy of informed consent using a standardised instrument since those available are

directed at the gaining of consent for therapeutic procedures such as surgical or pharmacological interventions,[128,129,132] and are not relevant to low risk data linkage studies.

The participation rate may have been higher, mainly in the opt-in arm, if parents had been personally recruited by immunisation providers — for example, by integrating an opt-in or opt-out tick box for vaccine safety surveillance on Australia's national publicly funded health care (Medicare) web-based immunisation records system. The feasibility of doing so should be examined, since clinicians may be reluctant to take on the additional task of obtaining consent for surveillance activities in addition to their primary care responsibilities.[213]

The cross-sectional and fixed response nature of the survey did not permit exploration of whether parental opinions would change if parents had been presented with more information and had the opportunity to ask questions. Furthermore, the interviews may have been subject to respondent bias, as parents may not have revealed true opinions in a telephone conversation with a stranger affiliated with the trial. Since the interviewers were not blinded, biases in outcome assessment may have ensued from differential probing or obtaining answers to support preconceived notions. We did not engage interpreter services due to resource constraints.

5.3.6 Conclusion

This trial found that neither the opt-in nor opt-out approach was effective in achieving informed consent when parents were invited by mail to participate in a proposed data linkage program of childhood vaccine safety surveillance. Parents often did not receive, properly consider or understand the information, as evidenced by fewer than half being able to identify correctly the health records to be linked. Moderate gains in participant understanding were achieved by using the opt-in rather than the opt-out approach. However, the gains were at the expense of the integrity of research, as parents who opted in comprised a much smaller group of individuals of higher education and socioeconomic status. Even though many parents lacked a basic understanding of what data linkage for vaccine safety surveillance involved, the majority were supportive of the concept and trusted that their privacy would be protected. Parents were amenable to data linkage without informed consent when informed about the study's societal benefits and the monetary and time costs of obtaining consent.

5.3.7 Online appendix A

Methods for dealing with missing data in the VALiD trial of parental consent

Our survey contained 40 main items, many of which contained missing data. We imputed the dataset in stages using four imputation models:

Imputation Model 1: Variables used to impute sex for parents who were not interviewed

Imputation Model 2: Variables used to impute missing sociodemographic and interview responses about the topic of consent for all parents in the trial

Imputation Model 3: Variables used to impute missing interview responses about opinions on data linkage, vaccine safety and effectiveness, and vaccination practices for all parents in the trial

Imputation Model 4: Variables used to impute missing interview responses regarding parental reports of adverse events following infant immunisation

The imputation procedure is described in detail at: http://jme.bmj.com/content/38/10/619/suppl/DC1. [Included in this thesis as Section 4.3.6.] This link includes a description of Imputation Models 1 and 2. Table 5.7 in the supplemental results section of this Appendix lists the variables included in Imputation Model 3, the amount of missing data each variable contains, and how the variables were imputed in the model. [Not shown is Imputation Model 4; this model was subsequently estimated to impute missing interview responses for subject matter which is not the topic of this paper.] Table 5.8 shows the most frequent patterns of missing data. Of the 1129 parents in the trial, 541 (47.9%) had complete data on all variables used in the substantive analysis and 269 (23.8%) had complete data apart from one missing variable – mostly annual household income (129 parents; 11.4%).

Supplemental results for the VALiD trial of parental consent

Table 5.7: Imputation Model 3: variables used to impute missing interview responses about the topics of data linkage, vaccine safety and effectiveness, and vaccination practices for all parents in the trial

Variable	Data missing *n* (%)	Type of variable	Model used to predict missing data in this variable
Imputation Model 3			
Participation	0	Binary	N/A no missing
Mothers' baseline characteristics			
- Firstborn status	0	Binary	N/A no missing
- Age	0	Ordinal (5 categories)	N/A no missing
- Indigenous status	0	Binary	N/A no missing
- Has private health insurance	0	Binary	N/A no missing
Household characteristics			
- Metropolitan residence	0	Binary	N/A no missing
- Socioeconomic quintile	0	Ordinal (5 categories)	N/A no missing
- Number of children	0	Ordinal (integers)	N/A imputed in Model 2
- Number of adults	0	Ordinal (integers)	N/A imputed in Model 2
- Annual income	0	Ordinal (4 categories)	N/A imputed in Model 2
Interviewed parents' characteristics			
- Age	0	Continuous	N/A imputed in Model 2
- Sex	0	Binary	N/A imputed in Model 1
- Married/de facto	0	Binary	N/A imputed in Model 2
- Australian born	0	Binary	N/A imputed in Model 2
- English language spoken at home	0	Binary	N/A imputed in Model 2
- Lone parent status	0	Binary	N/A imputed in Model 2
- Highest educational attainment	0	Ordinal (4 categories)	N/A imputed in Model 2
- Remembers receiving letter	0	Binary	N/A imputed in Model 2
- importance of vaccinating children[a]	189 (17)	Ordinal (5 categories)	Ordinal logistic regression
- concern a vaccine might not prevent disease	192 (17)	Ordinal (5 categories)	Ordinal logistic regression
- belief in the safety of vaccines	193 (17)	Ordinal (5 categories)	Ordinal logistic regression
- importance of checking the safety of vaccines	194 (17)	Ordinal (5 categories)	Ordinal logistic regression
- exposed to sources about data linkage[a]	194 (17)	Nominal (4 categories)	Multinomial logistic regression
- identified health records to be linked[a]	395 (35)	Nominal (3 categories)	Multinomial logistic regression

Table 5.7 (Continued)

Variable	Data missing *n* (%)	Type of variable	Model used to predict missing data in this variable
Imputation Model 3			
- trust in the security measures used in data linkage	209 (19)	Ordinal (5 categories)	Ordinal logistic regression
- concern a vaccine might cause a serious reaction	205 (18)	Ordinal (5 categories)	Ordinal logistic regression
- concern is greater over privacy protection or vaccine safety[a,b]	212 (19)	Nominal (3 categories)	Multinomial logistic regression
Vaccination practices			
- baby received one or more vaccines	185 (16%)	Binary	Logistic regression
- parent intends to vaccinate baby[b]	188 (17%)	Binary	Logistic regression
- parent consulted immunisation book ('blue book')[b]	184 (16%)	Binary	Logistic regression
- baby received HB-Vax II[b]	195 (17%)	Binary	Logistic regression
- baby received Infanrix hexa/ Prevenar/ RotaTeq[b]	184 (16%)	Binary, classified into 3 binary flags	Logistic regression

[a]A customised prediction equation was defined by excluding some variables from the imputation models to avoid multicollinearity problems.

[b]A skip was applied for parents for whom the question was not relevant.

Table 5.8: Patterns of missingness of data for variables in substantive analysis

Participation outcome & baseline characteristics	Sex of parent at interview	Remembers letter	Reason for return/non-return of reply form	Understanding of data linkage /trust in its security	Consent preference /Funding priorities scenario	Vaccination practices /vaccine safety views	Income	Other demographic characteristics	Parents *n* (%)	No. of missing variables
+	+	+	+	+	+	+	+	+	541 (47.9)	0
+	+	+	+	+	+	+	–	+	129 (11.4)	1
+	+	+	+	–	+	+	+	+	138 (12.2)	1
+	+	+	+	+	+	+ /–	+	+/–	2 (0.2)	1
+	+	+	+	+ /–	+	+ /–	–	+	37 (3.3)	2
+	+	+	+	–	+	+ /–	+	+/–	6 (0.5)	2
+	+	+	+	+ /–	+	+ /–	–	+	3 (0.3)	3
+	+	+	+	+	+	+	–	–	1 (<0.1)	3
+	+	+	+	+	+	–	+	+	46 (4.1)	4-10
+	+	+	+	+ /–	–	+ /–	+	+	3 (0.3)	4-10
+	+	+	+	+ /–	+/–	–	–	+	13 (1.2)	4-10
+	+	+	+	+/–	+/–	+	–	–	9 (0.8)	4-10
+	+	+	+	+/–	+/–	+/–	–	–	4 (0.4)	≥11
+	+	+	+	–	–	–	–	+/–	111 (9.8)	≥11
+	+	+/–	+	–	–	–	–	–	17 (1.5)	≥11
+	+	+	–	–	–	–	–	–	8 (0.7)	≥11
+	+	–	–	–	–	–	–	–	4 (0.4)	≥11
+	–	–	+	–	–	–	–	–	9 (0.8)	≥11
+	–	–	–	–	–	–	–	–	48 (4.3)	≥11

Key: + = Complete, – = Missing

End of article

5.4 Additional discussion

The results from the analyses in this article demonstrate that neither the opt-in nor opt-out approach was effective in achieving informed consent. Only about 80% of parents in each arm recalled receiving the study invitation material and fewer than half (~40%) were able to correctly identify that the study's purpose was to link children's hospital and vaccination records. This was despite the letter and reply form being pitched at a level of readability that most adults could understand (although the information leaflet was more difficult to read). The ability of a parent to recall, read and understand the information was shown to be contingent on his or her level of education. The subset of parents who made an active decision to opt in demonstrated a higher level of understanding of the study's purpose (60%). However, the results from Chapter 4 demonstrate that this is a small and biased sample of individuals with higher educational attainment and socioeconomic status, and the participation rate in the opt-in arm was too low (21%) to be useful for vaccine safety surveillance.

These findings suggest that most parents have a poor understanding of data linkage for vaccine safety surveillance. Even so, most supported data linkage and a system utilising opt-out or no consent was preferred to one using opt-in consent. Although parents reported high compliance with childhood immunisations, and most trusted vaccines to be safe, three in five were concerned about serious reactions following immunisation and two in five expressed doubts about vaccine effectiveness. Suboptimal childhood vaccine uptake was more prevalent among parents with vaccine safety concerns. These findings highlight the importance of improving vaccine safety surveillance systems in Australia. Chapter 6 reports on the findings from the same or similarly worded questions asked of a population-based sample of South Australians.

6 Publication — Public perspectives on consent for the linkage of data to evaluate vaccine safety

6.1 Preface

This chapter contains the final of a series of four articles contributing to this thesis. The article has been published in *Vaccine* and outlines the findings from a population-based sample survey of South Australians on the topic of data linkage for the purpose of postmarketing vaccine safety surveillance.[214] The Health Monitor survey was conducted between March and May 2011, and the complete list of questions is included in Appendix 8.

Like Chapter 5, the article addresses current gaps in the literature on community consultation. The questions were the same or similarly worded to those asked of parents in the RCT to enable direct comparisons to be made between the two samples. Metropolitan and rural residents of South Australia of all ages, both with and without children, were asked about their attitudes towards data linkage for postmarketing surveillance of childhood vaccine safety and opinions on the requirement for consent. Further questions were asked about their attitudes towards vaccination in terms of its public health benefit, safety, and effectiveness. For a subset of the survey sample in which the respondents were legally registered parents, vaccination practices in relation to all children in their care were determined. The generalisability of the findings between the two samples is examined in Chapter 7.

6.2 Statement of authorship

Berry JG, Gold MS, Ryan P, Duszynski KM, Braunack-Mayer AJ, the Vaccine Assessment using Linked Data (VALiD) Working Group. Public perspectives on consent for the linkage of data to evaluate vaccine safety. *Vaccine* 2012;30(28):4167-74.

By signing below, the authors declare that they give consent for this paper to be presented by Jesia Berry towards examination for the Doctor of Philosophy.

Jesia Berry (Candidate)

Designed the telephone survey, performed analyses, interpreted the results, reviewed the literature and drafted the manuscript.

Signed: …… Date: …22/2/13……

Michael Gold

Contributed to the conception and design of the study, procured funding, helped design the telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: …20/2/13……

Philip Ryan

Contributed to the conception and design of the study, procured funding, provided statistical advice, helped design the telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: …22-2-13…

Katherine Duszynski

Contributed to the design of the telephone survey, applied for ethical approval, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 20/02/2013

Annette Braunack-Mayer

Contributed to the conception and design of the study, procured funding, helped design the telephone survey, assisted in the interpretation of results, and reviewed the manuscript.

Signed: …… Date: 21.02.2013

6.3 Article

6.3.1 Abstract

Introduction: We sought community opinion on consent alternatives when linking childhood immunisation and hospital attendance records for the purpose of vaccine safety surveillance.

Methods: We conducted computer-assisted telephone interviewing (CATI) of a sample of rural and metropolitan residents of South Australia in 2011.

Results: Of 2002 households interviewed (response rate 55.6%), 96.4% supported data linkage for postmarketing surveillance of vaccines; very few were completely opposed (1.5%) or undecided (2.2%). The majority (75.3%) trusted the privacy protections used in data linkage and most wished to have minimal or no direct involvement, preferring either opt-out consent (40.4%) or no consent (30.6%). A quarter of respondents (24.6%) favoured opt-in consent, but their preferences were divergent; half requested consent be sought prior to every use (11.4%) while the remainder preferred to give broad consent just once (3.4%) or renewed at periodic intervals (9.8%). Over half of the respondents gave higher priority to rapid vaccine safety surveillance (56.5%) rather than first seeking parental consent (26.6%) and one in seven was undecided (14.5%). Although 91.6% of respondents believed childhood vaccines are safe, over half (53.1%) were very or somewhat concerned that a vaccine could cause a serious reaction. Nevertheless, 92.4% of the parents in the sample (556/601) reported every child in their care as being fully immunised according to the National Immunisation Program schedule. Only 3.7% of parents (22/601) reported one or more children as under immunised, and 3.9% (23/601) reported that none of their children were immunised.

Conclusions: This survey demonstrates that data linkage for vaccine safety surveillance has substantial community support and that a system utilising opt-out consent or no consent was preferred to one using opt-in consent. These findings should inform public health policy and practice; data linkage should be established where feasible to address limitations in passive surveillance systems.

6.3.2 Introduction

Immunisation is one of the most important advances in health care of the last two centuries—with high levels of immunisation coverage, illness is prevented and many lives saved.[64] To ensure the public's trust in immunisation, it is essential that the risks and benefits of each vaccine are evaluated.[64] Prior to licensing, vaccines undergo strict evaluation of safety in clinical trials (phases I to III).[215] One of the limitations of these trials is the inability to detect rare or delayed reactions due to the limited follow-up period, small number of healthy volunteers, and rigid inclusion criteria.[19,215] Once vaccines are licensed and in widespread use, postmarketing surveillance can fill gaps left in the safety profile after clinical trials and safety is inferred if, for a particular vaccine, there is no increase in adverse reactions.[19,215]

Currently Australia, like many countries,[77] relies on a passive reporting system, which depends on health care providers, parents or vaccinees recognising and reporting suspected Adverse Events Following Immunisation (AEFI) to health authorities.[18,19] While passive reporting is useful in generating safety signals for further investigation,[50] important limitations include under-reporting and biased reporting which can result in a failure to detect early signals[18,72] and an inability to disentangle coincidental from causal events or to accurately determine the incidence of AEFIs due to unreliable numerator and, often, denominator figures.[18,19]

Recent federal[72] and state[71] reviews have identified that Australia's passive reporting system has been compromised by the limitations listed above, as well as slow information flows between state and federal health authorities. During the 2010 national seasonal trivalent influenza vaccination (TIV) program, the system failed to readily detect an increased incidence of febrile convulsions within 24 hours of receiving the TIV among children aged five years and under, and the program was subsequently suspended on April 23, 2010. Australia has a history of rapid uptake of new vaccines and, therefore, has the opportunity to contribute to global postmarketing data (e.g. TIV,[18] human papillomavirus[19]). Given the inadequacies of stand-alone passive surveillance systems, complementary active surveillance mechanisms provide for the best use of all available information for vaccine safety evaluation.

A limited number of countries, which include the United States (US),[50] the United Kingdom (UK),[74] and some Scandinavian countries,[30,75] use data linkage to test hypotheses about a potential causal association between an AEFI and vaccination and to calculate the risk compared with background rates (i.e. relative risk) and per total number of administered doses (i.e. absolute risk).[20,78] In addition, the Centers for Disease Control and Prevention (CDC) in the US has developed further capacity, through the Vaccine Safety Datalink (VSD) project, to undertake near real-time rapid monitoring of possible safety signals which may emerge after the introduction of newly licensed vaccines or changes to the immunisation schedule for existing vaccines. There are many examples where data linkage has provided the ability to refute a causal association between a reported safety signal and vaccination, such as autism and measles-mumps-rubella (MMR) vaccination[85] and intussusception following administration of the second-generation rotavirus vaccine,[50] or indeed to confirm an association, such as thrombocytopenic purpura[31] and febrile convulsions[84] after MMR vaccination. The VSD project has the ability to link and analyse data pertaining to an annual population of 8.8 million members (3% of the US population)

of its eight managed care organisations.[50] However, it may still not be possible to detect very rare reactions within a single country due to an insufficiently large population. There has been some interest in developing global capacity for linkage with potential for international collaborations using common protocols and data sharing.[31,77,83] Fifteen countries, including Australia, have electronic records of immunisations and health outcomes which could potentially be used for linkage.[20]

An Australia-wide program of data linkage is advocated by leading Australian researchers both in the evaluation of medicines[16,17] and vaccines.[18,19] Progress in achieving this aim has been slow because of privacy concerns, lack of political will, and barriers in access to, and linkage of, the various datasets across jurisdictions.[16,17] Data linkage for vaccine safety surveillance has been successfully piloted in one jurisdiction — South Australia (SA) — by linking the national Australian Childhood Immunisation Register (ACIR) with hospital inpatient and emergency data.[76] In this pilot study, obtaining authorisation for the release of identifiable demographic information for linkage purposes without individual consent (as required by national legislation governing the ACIR),[26,76] was protracted due to bureaucratic hurdles and privacy concerns.[12,17] The delays were despite the use of a best practice protocol which assured the anonymity of pre-linked data to researchers.[5] The process requires an exemption to privacy legislation and researchers are required to demonstrate that the exemption is in the public interest as benefits substantially outweigh any potential risks. However, little is known about public opinion regarding any requirement for consent when data linkage is used for vaccine safety surveillance. This article reports on a community survey undertaken in March 2011, in which we examined consent preferences, trust in the protection of privacy for data linkage, and attitudes towards vaccination in terms of its public health benefit, safety, and effectiveness.

6.3.3 Methods

Between March and May 2011, we conducted a computer-assisted telephone survey of randomly selected households in SA (population 1.6 million). The study was approved by the Human Research Ethics Committees of the South Australian Department of Health (SA Health) and the University of Adelaide. The University's Population Research and Outcomes Studies Unit conducted the survey as part of its Health Monitor program.[216] Households in both city and country areas were randomly selected from the SA electronic white pages telephone directory and a letter was sent introducing the survey. The person aged 18 years or over who last had their birthday was selected for interview; up to 10 call-backs were made to interview the identified person as selected persons were non-replaceable. Phone calls were made on every day of the week at different times of the day (and evening for weekdays only). In 2008, 68.7% of households in SA had a mobile and/or landline telephone listed in the Electronic White Pages directory.[217]

Prior to commencement, a pilot study of 50 randomly selected households was conducted in February 2011 in order to test the clarity, format and sequence of questions, which were constructed according to recommended principles.[189,190] Respondents were asked general questions about the safety and effectiveness of vaccines (with some questions adapted from Gust et al.[191]). Each respondent was asked if he or she was a parent or legal guardian and, if so, further questions were asked about the vaccination status of each child in his or her care, enabling classification of the respondent as having a child or children who were fully immunised, under immunised or unimmunised according to the National Immunisation Program (NIP) schedule.[53] Subsequently, a program of data linkage for childhood vaccine safety surveillance was described and each respondent's consent preference was elicited using a six-point scale adapted from Willison et al.[148]:

- The child's health information should not be used at all;
- The researchers should get your consent first, prior to every use;
- The researchers should get your general consent, with periodic re-contacting;
- The researchers should get your general consent once;
- The researchers should let you know the linkage is being done, with the option to opt out;
- There is no need to know about the linkage; just use the information.

Respondents were then asked to choose between two priorities for Australian Government funding: performing rapid vaccine safety surveillance using data linkage without seeking consent or using some of this funding to seek parental consent first. Respondents were subsequently asked to indicate their level of trust in the privacy protections used in data linkage. The complete list of questions is available from the corresponding author.

The survey data were weighted to be representative of the population of SA. First, individual data were weighted by the inverse of the individual's probability of selection and then reweighted to benchmarks derived from the Australian Bureau of Statistics' estimated resident population as at 30 June, 2009 (according to age, sex and geographic region) for SA.[216,218] We used the socioeconomic indexes for areas index of relative socioeconomic disadvantage as an area-based measure of socioeconomic status.[45]

We used Stata 11.2 software for statistical analyses which consisted of tabulations of frequencies of responses to survey questions, with routines specifically designed to analyse clustered, weighted survey data. Significant associations between demographic variables and consent preferences were examined with χ^2 tests. Ordinal logistic regression analyses were used to examine the association between parents' vaccination practices and responses to questions regarding the safety and effectiveness of vaccines. Responses were converted to three categories to avoid small cell counts (e.g. 1 very safe/safe; 2 undecided; 3

unsafe/very unsafe; or 1 not at all/too concerned; 2 undecided; 3 somewhat/very concerned, as appropriate). Preliminary checks confirmed the proportional odds assumption was not violated.[211] Statistical tests were two-tailed, with a significance level of 5%.

6.3.4 Results

Of the 4700 telephone numbers selected, 1100 were ineligible: either not residential numbers, disconnected, fax/modem numbers or corresponded to households located outside of SA. Of the remaining 3600 eligible numbers, 993 households refused to be interviewed, 275 were not contactable after six attempts, 229 were either not available or too sick and 101 spoke no English; yielding a total of 2002 conducted interviews, a participation rate among eligible households of 55.6%.

Table 6.1 summarises the demographics of the 2002 respondents, weighted for both numbers and proportions, compared with the population of SA. Survey respondents were similar to the SA population, although respondents who were married or in a de facto relationship, native English-speakers, post-secondary school educated, employed, and living in higher income households were overrepresented. The mean age of the household interviewees was 53.9 (95% confidence interval (CI) 53.1, 54.7), with a median age of 55 years and a range of 18–99 years. Within weighted households, the mean age of the interviewee was 47.6 years (95% CI 46.6, 48.6), with an almost equal proportion of men and women (Table 6.1). There were 1377 children younger than 18 years residing in 724 (36.2%) of the households interviewed. Of these households, 601 (83.0%) involved an interview with the parent or legal guardian, with the parent able to give details on the vaccination status of 1199 children in their care. The median number of children per parent was two, with a range of one to seven children.

Table 6.1: Household demographics of survey respondents (*n*=2002): South Australia, 2011

Respondent characteristics	Respondents, raw *n* (weighted)	Respondents, weighted %	SA population % (*n*=1 514 336) [a]
Age (years)			
18–24	169 (248)	12.4	9.2
25–34	154 (329)	16.4	12.3
35–44	282 (355)	17.7	14.5
45–54	353 (363)	18.1	14.3
55–64	435 (312)	15.6	11.7
≥65	609 (395)	19.7	15.4
Sex			
Male	808 (979)	48.9	48.6
Female	1194 (1023)	51.1	51.4
Residence			
City	1448 (1475)	73.7	73.7
Country	554 (527)	26.3	26.3
Country of birth[b]			
Australia	1540 (1571)	78.5	69.2
Other	461 (431)	21.5	24.7
Main language spoken at home[b]			
English	1935 (1921)	96.0	82.5
Other	66 (80)	4.0	13.0
Marital status[b]			
Married/de facto	1239 (1342)	67.4	55.9
Separated/divorced/widowed	450 (249)	12.5	21.6
Never married	303 (400)	20.1	22.5
Educational attainment[b]			
Secondary school/studying	898 (818)	40.9	52.8
Trade/certificate/diploma	672 (690)	34.5	24.8
Bachelor degree or higher	428 (490)	24.5	13.6
Annual household income ($A)[c, d]			
≤ 20,000 [SA population: ≤ 18,200]	277 (170)	8.5	17.0
20,001–80,000 [SA population: 18,200–88,399]	810 (741)	37.0	55.9
> 80,000 [SA population: ≥ 88,400]	539 (695)	34.7	17.1
Not stated	376 (396)	19.8	10.0

Table 6.1 (Continued)

Respondent characteristics		Respondents, raw *n* (weighted)	Respondents, weighted %	SA population % (*n*=1 514 336) [a]
Employment[b]				
Full or part time		1107 (1287)	64.3	57.2
Not in labour force		894 (715)	35.7	37.6
SEIFA IRSD[d,e]	Least disadvantaged (tiers 1–2)	721 (735)	36.7	35.9
	3	390 (385)	19.2	18.3
	Most disadvantaged (tiers 4–5)	891 (881)	44.0	45.9

[a]Australian Population Census, 2006, persons aged ≥18 years, Australian Bureau of Statistics (ABS), http://www.abs.gov.au/cdataonline. Some categories do not add to 100% due to proportions recorded as 'not stated/not applicable'.

[b]1 missing case for country of birth and main language spoken at home; 10 missing cases for marital status; 4 missing cases for educational attainment; 1 missing case for employment.

[c]The 2006 ABS Census income categories are not directly comparable in terms of income ranges.

[d]The categories relate to households and are not restricted to persons aged ≥18 years.

[e]Socioeconomic indexes for areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data.

Consent choice for linked children's health information

The majority (96.4%) of responders were supportive of the linkage of a child's vaccination and hospital records for the purpose of vaccine safety surveillance; very few respondents were completely opposed to the concept (1.5%) or undecided (2.2%) (Table 6.2). The majority (71.0%) preferred minimal or no direct involvement: 40.4% would be satisfied with notification with the option to opt out and 30.6% preferred that a child's health information be linked without consent or notification. Among people who favoured opt-out consent, 80.7% stated that the opportunity to opt out was either very (52.1%) or somewhat (36.9%) important. Of the 24.6% of respondents who indicated opt-in consent should be sought, views were split almost equally between those who preferred to give consent prior to every use (11.4%) and the remainder who preferred to give broad consent, that is, to consent just once (3.4%) or at periodic intervals of their choosing (9.8%). There was no clear consensus on the preferred interval for renewal.

Table 6.2: Opinions regarding consent to data linkage for childhood vaccine safety surveillance (*n*=2002)

Data linkage matches pieces of information about the child which come from different sources. If a child goes to hospital, the information about their illness can be linked to their vaccination records to see if a vaccination may have caused their illness. Before the linkage occurs, the child's identifying information is removed and replaced with a unique number. This prevents the researchers who look at the linked records from identifying any child.	Do not link data	Opt-in consent, *n* (%)			Opt-out consent	No consent	Undecided
	n (%)	Every time	Broad consent, renewing	Broad consent, once	*n* (%)	*n* (%)	*n* (%)
[a] Which of the following statements best matches how you feel about your child's health information being used for checking the safety of vaccines?[b]	29 (1.5)	228 (11.4)	197 (9.8)	68 (3.4)	808 (40.4)	612 (30.6)	44 (2.2)
Interval for renewing, *n* (column %)	Every year		90 (45.7)				
	Once every five years		81 (41.0)				
	Some other time period		17 (8.5)				
	Undecided		9 (4.7)				
	Total		197 (100.0)				
Importance of option to opt out, *n* (column %)	Very important				421 (52.1)		
	Somewhat important				298 (36.9)		
	Undecided				3 (0.3)		
	Not too important				72 (8.9)		
	Not at all important				14 (1.8)		
	Total				808 (100.0)		

Values are weighted numbers (percentages).

[a]An introductory phrase 'Imagine you have a child…' was used as required.

[b]16 refused to answer.

Priorities for linked children's health information

In this scenario, respondents were advised that resources were finite and they were asked to indicate their preference for allocation of the Australian Government's time and money (Table 6.3). Respondents gave higher priority to funding being allocated to enable quick, extensive and up-to-date checks on the safety of vaccines using data linkage (56.5%) rather than first seeking parental consent to link their child's health information (26.6%). One in seven respondents (14.5%) was undecided. Respondents who preferred opt-in consent to be sought prior to every use placed a higher priority on seeking parental consent over performing rapid vaccine safety surveillance (51.7 % *vs* 27.6%) than those who favoured broad consent to be sought just once (40.8 % *vs* 49.3%) or renewed at periodic intervals (34.5 % *vs* 49.4%), or preferred opt-out consent (30.4% *vs* 54.1%) or no consent (12.3% *vs* 81.8%); $P<0.001$. Table 6.3 shows that respondents who were parents, particularly those whose children were fully immunised, were more likely than respondents without children to select vaccine safety surveillance as a higher priority than obtaining parental consent. Respondents favouring vaccine safety surveillance were also more likely to be married or in a de facto relationship, aged between 25 and 44 years, employed, post-secondary school qualified and living in higher socioeconomic areas and higher income households. Three-quarters (75.3%) of respondents were either very (22.3%) or somewhat (53.0%) confident that the privacy of an individual's personal information would be protected by the security measures used in data linkage (Table 6.4).

Table 6.3: Opinions on the relative importance of obtaining consent or checking vaccine safety (*n*=2002)

When money is spent on one health activity, the Australian Government has less to spend on other things. These two statements describe different ways that time and money could be spent. With which statement do you most agree? If you cannot choose, just say so.	Response, weighted % (*n*)				χ^2 (*P*)
	Asking parents for consent to link their child's health information	Being able to perform quick, extensive and up-to-date checks on the safety of vaccines	Undecided	Do not link data	
Total sample[a]	26.6 (533)	56.5 (1130)	14.5 (290)	1.5 (29)	
Males	27.1	57.6	13.2	2.1	8.3 (0.134)
Females	26.7	56.5	16.0	0.8	
18–24 yrs	33.6	48.1	15.5	2.8	37.5 (0.018)
25–34 yrs	23.3	66.2	10.0	0.5	
35–44 yrs	19.6	63.5	15.3	1.6	
≥45 yrs	28.9	54.0	15.6	1.4	
Married/de facto	24.7	60.6	13.5	1.3	26.4 (0.009)
Separated/divorced/widowed	28.5	50.1	20.0	1.4	
Never married	33.3	49.5	14.8	2.4	
No children	29.6	52.9	15.8	1.8	32.9 (<0.001)
Have children	20.7	66.5	12.0	0.8	
Children unimmunised	36.0	38.9	15.7	9.4	27.3 (0.004)
Children under immunised	20.9	50.5	28.6	0.0	
Children fully immunised	20.0	68.3	11.2	0.5	
Secondary school/studying	31.6	49.8	16.4	2.3	36.1 (0.001)
Trade /certificate/diploma	25.1	59.6	14.3	1.1	
Bachelor degree or higher	21.6	65.3	12.2	0.8	

Table 6.3 (Continued)

When money is spent on one health activity, the Australian Government has less to spend on other things. These two statements describe different ways that time and money could be spent. With which statement do you most agree? If you cannot choose, just say so.	Response, weighted % (*n*)				χ^2 (*P*)
	Asking parents for consent to link their child's health information	Being able to perform quick, extensive and up-to-date checks on the safety of vaccines	Undecided	Do not link data	
Employed full or part time	24.0	61.3	13.1	1.6	28.9 (<0.001)
Not in labour force	32.1	49.3	17.3	1.2	
Household income ≤ 20 000	39.3	38.7	19.3	2.7	56.8 (<0.001)
20 001–80 000	27.9	58.2	12.0	1.9	
>80 000	20.7	67.8	11.1	0.4	
English spoken at home	26.4	57.7	14.3	1.5	12.2 (0.050)
Other language	38.0	40.2	21.8	0.0	
Australian born	26.6	57.9	14.1	1.4	3.4 (0.472)
Born elsewhere	27.7	53.7	16.6	1.9	
City residence	27.1	57.7	14.1	1.1	6.6 (0.199)
Country residence	26.4	55.0	16.1	2.5	
Least disadvantaged[b] (tiers 1–2)	26.4	60.9	16.3	0.5	18.9 (0.033)
Middle (tier 3)	23.7	57.5	15.9	2.5	
Most disadvantaged (tiers 4–5)	28.7	53.5	14.6	1.8	

[a]20 refused to answer.

[b]SEIFA IRSD quintiles.

Table 6.4: General views on vaccine safety and surveillance (*n*=2002)

	Response, weighted *n* (%)				
Question	Very confident	Somewhat confident	Undecided	Not too confident	Not at all confident
The usual measures for security in data linkage are to replace a person's name and home address with a unique number and store any personal information in a secure place. How confident are you that this will protect a person's identity?[a]	447 (22.3)	1061 (53.0)	30 (1.5)	314 (15.7)	148 (7.4)
	Response, weighted *n* (%)				
Question	Very safe	Safe	Undecided	Unsafe	Very unsafe
The next few questions are about the vaccination of children in Australia. In general, how safe would you say the vaccines given to children are?	1016 (50.7)	819 (40.9)	115 (5.8)	40 (2.0)	12 (0.6)
	Response, weighted *n* (%)				
Question	Very concerned	Somewhat concerned	Undecided	Not too concerned	Not at all concerned
How concerned are you that a vaccine given to children might not work and they might still get the disease?	222 (11.1)	572 (28.6)	39 (1.9)	742 (37.1)	428 (21.4)
How concerned are you that a vaccine given to children might not be safe and might cause a serious reaction?	429 (21.4)	634 (31.6)	37 (1.8)	617 (30.8)	286 (14.3)

[a]2 refused to answer.

Views on the safety and effectiveness of vaccines

The majority (91.6%) of respondents believed the vaccines given to children in Australia are safe (40.9%) or very safe (50.7%); however, many were very (21.4%) or somewhat concerned (31.6%) that a vaccine might cause a serious reaction (Table 6.4). Over a third of respondents were very (11.1%) or somewhat concerned (28.6%) that a vaccine given to children might be ineffective in preventing the targeted disease. Respondents with concerns about serious reactions to vaccines were less likely than those without concerns to select no consent (22.3% *vs* 41.2%) and more likely to favour opt-out consent (45.1% *vs* 36.6%) or opt-in consent (29.3% *vs* 18.9%), particularly prior to every use (15.0% *vs* 6.6%); $P<0.001$. Rapid vaccine safety surveillance was not prioritised as highly among respondents concerned about serious reactions to vaccines (53.0 % *vs* 63.3%; $P<0.001$) and more reported they were not too confident or not at all confident in the privacy protections used in data linkage (28.1% *vs* 17.3%; $P<0.001$) compared with respondents without concerns.

Likewise, respondents who believed a vaccine might be ineffective were less likely than those who did not share this belief to select no consent (22.3% *vs* 37.2%) and more likely to favour opt-out consent (44.3% *vs* 38.7%) or opt-in consent (30.0% *vs* 20.8%), particularly prior to every use (15.5% *vs* 8.3%); $P<0.001$. Rapid vaccine safety surveillance was not prioritised as highly among respondents who questioned the effectiveness of vaccines (51.6% *vs* 61.7%; $P=0.002$) and more reported they were not too confident or not at all confident in the privacy protections used in data linkage (28.1% *vs* 19.6%; $P=0.001$) compared with respondents without doubts about vaccine effectiveness.

When asked about coverage according to the vaccines recommended by the NIP, 92.4% of the parents surveyed reported every child in their care as being fully immunised, 3.7% reported that one or more children were under immunised, and 3.9% reported that none of

their children were immunised (Table 6.5). Compared with parents of fully immunised children, parents of unimmunised children were more likely to view vaccines as unsafe and have concerns about serious reactions to vaccines, but not about vaccine effectiveness, since the cumulative odds ratio of the latter, although elevated, did not reach statistical significance. The corresponding cumulative odds ratios for parents of under immunised children, while elevated, did not reach statistical significance.

Table 6.5: Vaccine safety concerns and vaccination practices among parents and guardians (*n*=601)

Vaccination status of all children in their care	Response (weighted)		Parental concerns about vaccines: Odds Ratio (95% CI)[b]		
	n	% (95% CI)	Unsafe	Serious reaction	Might not prevent disease
Fully immunised[a]	556	92.4 (89.3, 94.7)	1.00	1.00	1.00
Under immunised	22	3.7 (2.3, 6.0)	4.9 (1.0, 23.9)	1.7 (0.7, 4.4)	1.4 (0.6, 3.6)
Unimmunised	23	3.9 (2.3, 6.4)	59.2 (19.4, 180.6)	3.5 (1.1, 10.8)	1.9 (0.8, 5.0)

[a]Reference category.

[b]Further exploration for potential confounders among the socio-demographic factors collected in the survey showed no evidence of any important confounding influences on the relationship between immunisation status and parental concerns about vaccines.

6.3.5 Discussion

This study fills an important gap in research on community attitudes to data linkage for vaccine safety surveillance.[15] We found that this sample of the Australian public was supportive of data linkage for childhood vaccine safety surveillance with very few opposed. The use of pre-linked anonymised data by researchers and informational security safeguards appear to assuage public fears about potential breaches in privacy, as three-quarters of respondents reported reasonably high levels of confidence in these measures.

The majority of respondents (71%) preferred minimal to no direct involvement in controlling the use of their children's health information in vaccine safety surveillance. While two-thirds (65%) wished to exercise some degree of control over access to their children's health information through some form of consent, most commonly by opt-out

consent (40%), the proportion reduced to 27% when informed it would be at the expense of rapid and comprehensive vaccine safety surveillance, and twice as many (57%) chose the latter as having precedence. The segments of the population that showed the most support for rapid vaccine safety surveillance were those who may have had a better understanding of the need for such research and the most to gain from it. These were the tertiary educated and high socioeconomic groups and parents, particularly those of fully immunised children. Our findings concur with other studies which have shown that the marginalised, poorly educated and low socioeconomic groups are less likely to opt in to public health research.[12,200]

Participants' opinions about the safety of vaccines were somewhat contradictory. While vaccines were generally trusted by respondents, and there was high parental compliance with childhood immunisations, substantial proportions expressed concerns about the likelihood of serious reactions (53%) and the effectiveness of vaccines (40%). The 2003–2004 National Immunization Survey in the US yielded comparable proportions of parents with concerns about the likelihood of serious reactions (58%) and the effectiveness of vaccines (66%).[191] In a 2009 survey, half (54%) of the parents surveyed in the US strongly agreed or agreed to having concerns about serious adverse effects of vaccines.[212] Like Australia,[61] the US has immunisation coverage at near all-time high levels[60]; therefore, high immunisation compliance should not be used to infer an absence of vaccine concerns among parents.

Only a small number of parents did not immunise their children (3.9%); a figure consistent with national estimates (3.1%).[61] As may be expected, and consistent with studies internationally,[191,219] parents of unimmunised children were much more likely to express vaccine safety concerns than those of fully immunised children. International studies have also shown that vaccine-declining parents mistrust Government, health professionals and

officially-endorsed vaccine research, but trust media and non-official sources of information, including testimony from other parents.[219] Similarly, respondents in this survey who voiced concerns about the likelihood of serious reactions and the effectiveness of vaccines displayed mistrust in the privacy protections used in data linkage and wanted to act as gatekeepers in the use of their children's health information through the implementation of some form of consent. These observations are counter-intuitive to what one might expect; it would be reasonable to assume that parents with concerns about the safety and effectiveness of vaccines would want more scientific evidence, but this appears not to be the case. Future empirical research should investigate whether this reasoning is, in fact, motivated by avoidance of cognitive dissonance, whereby parents may recoil from information that contradicts deeply held beliefs. Such insights can help inform vaccine communication, social networking and public engagement strategies.[59,220]

These study results should be considered in light of potential limitations. The response rate was only 55.6%. People who are likely to have been under-represented in this survey because they tend not to have a mobile or landline telephone listed in the SA Electronic White Pages directory include those who are younger, never married, separated or divorced, not in the labour force, city dwellers, and from low socioeconomic areas.[217] Weighting the survey data by age, gender and geographical profile may compensate to some extent for this bias by ensuring the sample structure better represents the general population. Some differences remained even after the survey weighting was applied; respondents who were older, married or in a de facto relationship, native English speakers, post-secondary school educated, employed, and living in higher income households were over-represented compared with the SA population. Further, there is likely to be an under-representation of the more privacy-orientated members of the population, as 993 (27.6%) of the eligible population refused to be interviewed and 275 (7.6%) proved difficult to

contact after repeated attempts. Because of these factors, the results of our survey may not be fully generalisable to the whole SA population.

The cross-sectional and fixed response nature of the survey did not permit exploration of whether opinions would change if presented with more information and the opportunity to ask questions. Also, respondents received a verbal explanation of the process of data linkage and the concept may not have been fully understood. The framing of some questions may have influenced responses; for example, people may be more likely to express misgivings (or trepidation) when questioned about 'concerns'.[190] Qualitative face-to-face interviews, focus groups or citizens' juries are recommended to further investigate some of the inherent limitations of fixed response surveys.

While some countries have established privacy-preserving data linkage systems for vaccine postmarketing surveillance,[20,29,31,50,78] other industrialised countries, including Australia, lag behind,[16-18,76] as do low- and middle- income countries, which lack the appropriate e-health infrastructure and expertise.[77,78] This community survey has shown that the majority of the Australian public strongly supports data linkage for vaccine postmarketing surveillance and does not place personal privacy above societal benefits in this context, given appropriate privacy safeguards. To maintain high parental compliance with childhood immunisations, and to build public confidence in vaccine safety, Australia, along with many other countries, needs to move swiftly towards developing a national pharmacovigilance system that utilises data linkage in addition to passive surveillance. Such developments are integral to progressing adequate vaccine safety assessment on a global level.

End of published article

6.4 Additional discussion

The results from the population-based sample survey were very similar to the findings in the RCT. These similarities are discussed further in Chapter 7. Most South Australians supported data linkage and a system utilising opt-out or no consent was preferred to one using opt-in consent. Although most respondents trusted vaccines to be safe, one in two was concerned about serious reactions following immunisation and two in five expressed doubts about vaccine effectiveness. Among the subset of parents in the survey, compliance with childhood immunisations was high, but those with vaccine safety concerns were more likely to report suboptimal childhood vaccine uptake. In light of the findings, an argument is made for why data linkage should be established in Australia in order to address the limitations of the current passive surveillance system.

7 Generalisability of the findings

Generalisability, otherwise known as external validity or applicability, is the extent to which the findings from a study can be seen as having relevance to other populations, settings, or variables.[178,221] In the context of the VALiD RCT, assessing its generalisability involves asking whether the results can be generalised to other groups of individuals that may differ from those enrolled in the trial with regard to age, gender, socioeconomic status, and other characteristics.

In Chapters 3 to 5, I described the design, conduct, and analysis of the VALiD RCT and presented the findings regarding the feasibility of obtaining parental consent for childhood vaccine safety surveillance, and the attitudes of parents to methods of consent. In this chapter, firstly, I consider whether the VALiD RCT has internal and external validity in its own right, by considering the trial design and the study population of 1129 families of children born at a public hospital in metropolitan Adelaide. Secondly, I compare the findings of the RCT with those from a survey sample of metropolitan and rural South Australians, and consider whether the findings from the trial can be generalised to the South Australian population and, further, to the whole population of Australia.

7.1 The internal and external validity of the RCT

Before we consider the external validity of the trial, we must first assess its internal validity. As Moher et al.[178] explains: 'internal validity, the extent to which the design and conduct of the trial eliminates the possibility of bias, is a prerequisite for external validity'.

The VALiD RCT adhered to the CONSORT statement and demonstrated good internal validity by implementing a series of trial procedures that reduce bias. These included blinding, appropriate randomisation, allocation concealment, prespecified outcome

measurement, use of appropriate statistical analyses, achievement of a high level of follow up for the telephone interview (91%) and accounting for missing data through the use of multiple imputation.[177,178] Two strategies that may have further improved the internal validity of the trial would have been, first, to blind the interviewers to the identity of the group allocation of families (i.e. double blinding rather than single blinding) and, second, to have used a validated survey instrument in the telephone interview. However, there are good reasons why it was impractical to do so. First, if the interviewers had been blinded to study allocation, they would have been unable to ask parents about their reasons for participation and non-participation. Second, no relevant validated survey instrument exists. Although it is a reasonable premise to validate the survey instrument prior to use in the trial, it is a time-consuming and complex process involving repeated sampling and testing of the population of interest, and it would have been beyond the scope of this work.

Generalisability is a matter of judgement and critical appraisers do not always reach consensus.[222] Factors that potentially affect the generalisability of a trial are the setting, selection and characteristics of participants included in the trial, the nature of the interventions tested and the outcomes assessed.[223] Broad inclusion criteria, a large sample size, and conducting a multi-centre rather than a single-centre study are strategies that can improve the generalisability of the results.[178,222] The VALiD RCT was a single-centre study based at a public hospital that is the site of delivery for a quarter of South Australian babies each year. Eligible families were enrolled without seeking informed consent and the inclusion criteria were as broad as could be ethically justified; only death, infant illness, maternal hardship, and a limited range of other cases (home births, inward hospital transfers, non-residents of SA, and mother aged less than 18 years) were excluded. The trial was powered to answer all prespecified secondary outcomes. A strategy that may have further improved the generalisability of the trial to South Australian families would have been to conduct the VALiD RCT as a larger multi-centre study and include a mix of public

and private hospitals, across metropolitan and rural SA. However, it would have been beyond the scope of this work.

7.2 A comparison of findings in the RCT and population survey

This section provides a summary of the key findings of the RCT and the population survey from Chapters 3 to 6. As the tables, figures and survey questions are simplified for the purpose of illustration, the reader is advised to refer to the relevant chapters if further details are required.

Demographic characteristics

Those interviewed in the RCT were parents, predominantly female, mostly married or living with a partner, and with a mean age of 31 years (Table 7.1). In contrast, only about a third in the SA survey sample were parents, half were female, and only about two-thirds were married/living with a partner. The SA survey sample was older, with a mean age of 48 years. Respondents born in Australia, native English speakers and country residents were more prevalent in the SA survey than in the RCT. In terms of socioeconomic status, although there was a higher proportion of respondents with a university education in the RCT, household incomes appeared to be somewhat lower (although it is difficult to be sure due to the use of different income categories), and a higher proportion resided in the most disadvantaged areas compared with the SA survey. Since respondents in the RCT were parents of newborns, they were probably more likely to be in single income households, which could explain their relatively lower socioeconomic status. Also, the RCT is likely to be more inclusive of a range of socioeconomic groups than the SA survey, due to the hospital patient management system capturing most parents' mobile and landline telephone numbers, whereas low socioeconomic groups are under-represented in the SA Electronic White Pages directory.[217]

Table 7.1: Demographic characteristics of the interviewed parents and survey respondents

Characteristic	VALiD RCT[a]			SA survey[b]
	Opt-in (*n*=564)	Opt-out (*n*=565)	Total (*n*=1129)	Total (*n*=2002)
Legally registered parent	564 (100)	565 (100)	1129 (100)	601 (30)
Mean age (95% CI)	31 (31, 32)	31 (31, 32)	31 (31, 32)	48 (47, 49)
Female	513 (91)	505 (89)	1018 (90)	1023 (51)
Married/de facto	493 (87)	486 (86)	979 (87)	1342 (67)
Australian born	352 (62)	334 (59)	686 (61)	1571 (78)
Native English speaker	410 (73)	405 (72)	815 (72)	1921 (96)
Metropolitan residence	509 (90)	525 (93)	1034 (92)	1475 (74)
University educated	212 (38)	208 (37)	420 (37)	490 (25)
High income household[c]	131 (23)	128 (23)	259 (23)	695 (35)
Socioeconomic quintile[d]				
Least disadvantaged (tiers 1–2)	189 (34)	185 (33)	374 (33)	735 (37)
3	86 (15)	87 (15)	173 (15)	385 (19)
Most disadvantaged (tiers 4–5)	289 (51)	293 (52)	582 (52)	881 (44)

Values are numbers (percentages) unless stated otherwise.

[a]With missing data imputed by multiple imputation. [b]Weighted to be representative of the population of SA.

[c]Annual income ($A) of $83,200+ for the VALiD RCT and > $80,000 for the SA survey.

[d]Socioeconomic indexes for areas (SEIFA) area-based index of relative socioeconomic disadvantage (IRSD) derived from residential postcode and based on the Australian census data.

The two survey samples were quite different in demographic characteristics. The RCT sample was ethnically diverse and represented the spectrum of socioeconomic groups among predominantly urban-dwelling families attending a public hospital in a metropolitan city. The RCT findings are likely to be representative of the enrolled cohort as the response rate for the interview was high (91%) and the use of multiple imputation to estimate missing data compensated for refusals and non-response to the interview.

The response rate for the SA survey was only 55.6% and, as Chapter 6 describes, younger, single, urban, unemployed, low socioeconomic and privacy-orientated members of the population were likely to be under-represented. Although weighting the survey data compensated to some extent for the bias and yielded a sample representative of the SA population in terms of age, sex, geographical region and, consequently, area-based

socioeconomic status, differences remained. Compared to the general SA population, there was a higher prevalence of respondents who were older, married/living with a partner, native English speakers, employed and of higher educational and income status. The potential limits on generalisability to the whole SA population should be kept in mind when interpreting the results.

In the VALiD RCT, parental opinions for most of the questions about consent preferences and vaccine safety were similar in the opt-in and opt-out arm; therefore, for the following sections, I will consider the pooled totals of the two arms in the trial when making comparisons to the population survey.

Consent choice and priorities for linked children's information

As shown in Figures 7.1 and 7.2, opinions on the requirement for consent for the linkage of data to evaluate vaccine safety were remarkably similar when comparing the sample of parents enrolled in the RCT with the sample of the general population of SA.

Figure 7.1: Parent and public perspectives on consent for the linkage of data to evaluate vaccine safety

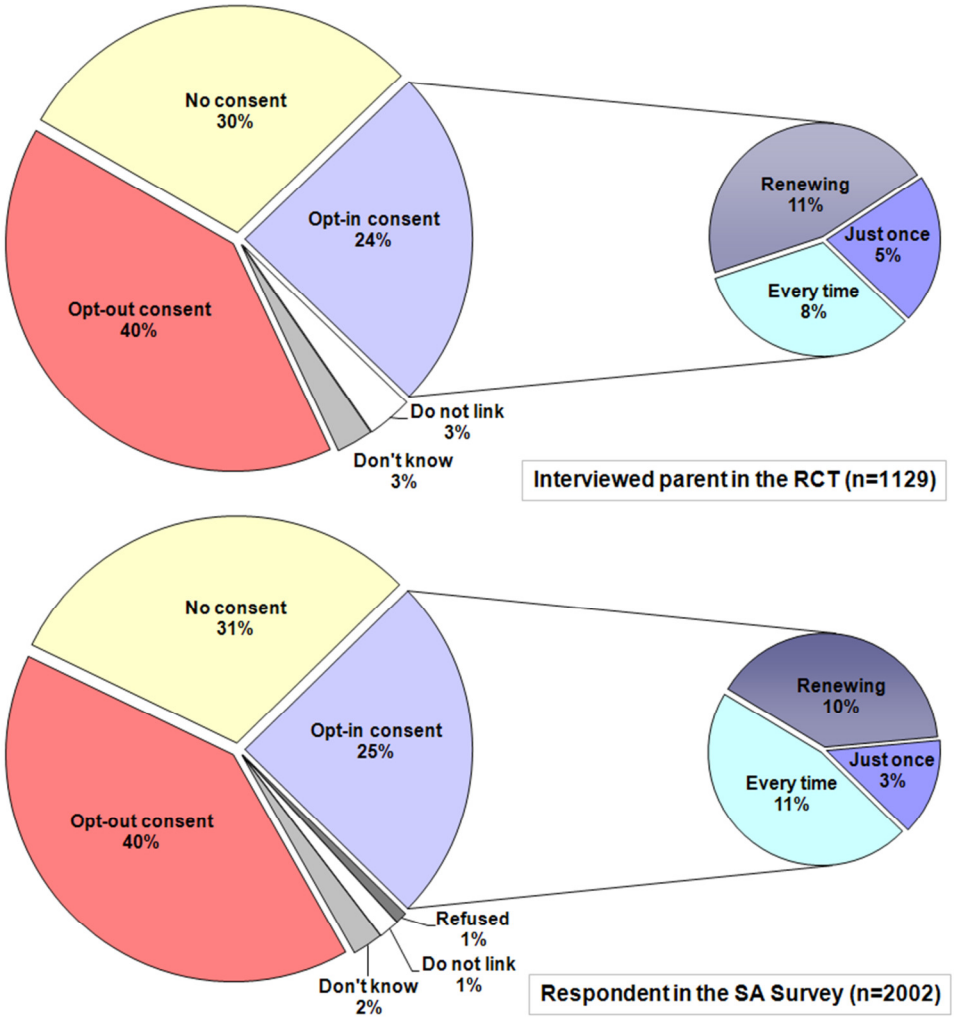
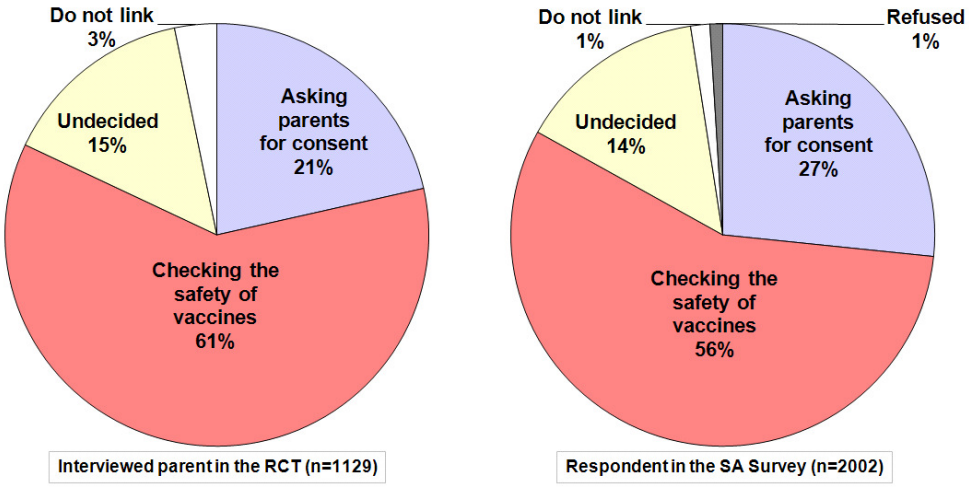


Figure 7.2: Parent and public opinions on the relative importance of obtaining consent or checking vaccine safety



Views on the safety and effectiveness of vaccines

As shown in Table 7.2, views on the safety and effectiveness of vaccines, and confidence in data linkage for vaccine safety surveillance, were remarkably similar when comparing the sample of parents enrolled in the RCT with the sample of the general population of SA.

Table 7.2: Parent and public perspectives on vaccine safety and surveillance

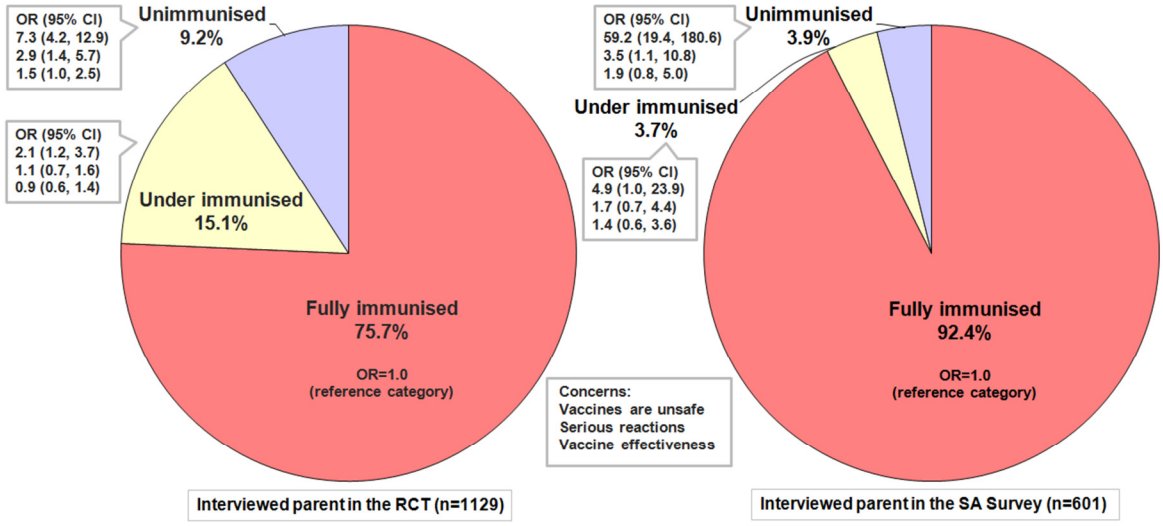
Question or proposition	VALiD RCT (*n*=1129)[b]			SA survey[c] (*n*=2002)		
	Yes *n* (%)	Unsure *n* (%)	No *n* (%)	Yes *n* (%)	Unsure *n* (%)	No *n* (%)
Are you confident data linkage will protect a person's identity?[a]	951 (84)	44 (4)	134 (12)	1508 (75)	30 (1)	462 (23)
Are vaccines given to children safe?	1016 (90)	76 (7)	38 (3)	1835 (92)	115 (6)	52 (3)
Are you concerned that a vaccine might not be effective?	472 (42)	19 (2)	638 (56)	793 (40)	39 (2)	1170 (58)
Are you concerned that a vaccine might cause a serious reaction?	699 (62)	13 (1)	417 (37)	1062 (53)	37 (2)	903 (45)

Values are numbers (percentages) unless stated otherwise. [a]2 refused to answer

[b]With missing data imputed by multiple imputation. [c]Weighted to be representative of the population of SA.

Figure 7.3 shows a similar pattern among parents in the RCT and the SA survey samples; parents who were concerned about the safety of vaccines were less likely than parents without concerns to fully immunise their children. Parents who expressed concerns about the effectiveness of vaccines tended towards being less likely than parents without concerns to fully immunise their children, but these observations did not reach statistical significance. The proportion of parents who reported their children to be fully immunised was lower in the RCT because the interviews were conducted in a narrow 1–2 week window after the two-month immunisations were due. Hence, some parents intended to vaccinate their children, but were delayed in doing so.

Figure 7.3: Vaccination practices and safety concerns among parents in the two studies



7.3 Summary

Despite the low response rate in the SA survey relative to the RCT, there was a very high concordance in the opinions of respondents in two studies with regard to consent preferences and levels of trust in data linkage for vaccine safety surveillance. Likewise, the two studies showed similar patterns of beliefs about the safety and effectiveness of vaccines in relation to child vaccination practices. These similarities were observed even though the two study designs were disparate in terms of the response rate achieved and the constituent socioeconomic groups.

The response rate in the RCT was high (91%) and the analysis accounted for missing data through the use of multiple imputation. The RCT comprised mainly urban dwelling families of ethnic diversity and a broad range of socioeconomic groups. In contrast, the SA survey had a low response rate (56%), and despite having an age, sex and urban/rural mix similar to the population distribution of SA, selection bias was evident as low socioeconomic groups and, potentially, privacy-orientated members of the public were under-represented. The results may, therefore, not be fully generalisable to the whole SA population. It would be presumptive to make an assertion about the generalisability of the

findings to the whole of Australia without some investigation into whether attitudes to data linkage for vaccine safety surveillance are likely to vary by jurisdiction of usual residence. To answer this question, a potential area for future research would be to repeat the Health Monitor survey questions in a sample taken from another jurisdiction.

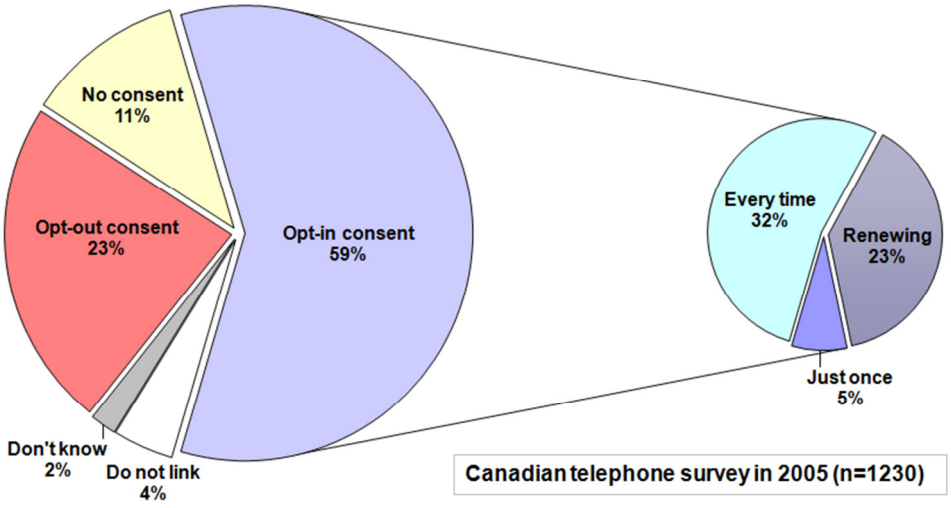
There are few relevant Australian studies with which to compare the findings of the RCT and SA survey. Apart from one pilot survey of immunisation providers and the SA population conducted as a precursor to this research,[15] and reviewed in Section 2.3.7, no other Australian study has examined parental consent preferences for childhood vaccine safety surveillance using data linkage, and the findings presented in this thesis are unique in this regard. Attitudinal research into the use of linked databases in other areas of health research in Australia and internationally is limited and has yielded mixed results. As discussed in Section 2.3.7, most of the studies conducted so far have concluded that the public prefers opt-in consent for health research, including for data linkage studies. However, several studies have shown that the public can become more receptive to the use of medical information without consent when educated about the intended societal benefits and privacy safeguards.

Attitudinal research into parental opinions on vaccine safety and effectiveness in Australia is piecemeal and limited in its scope. Most of the telephone surveys conducted so far have little direct relevance to the RCT and SA survey, for example, surveys restricted to parental attitudes among non-vaccinators only,[224] or to specific vaccines (e.g. varicella[225,226] and influenza[227]) or to the influenza and NIP vaccines following the suspension of the 2010 national seasonal trivalent influenza vaccination (TIV) program.[228,229] The most relevant information has been collected in New South Wales (NSW) Child Health Survey, which forms part of an annual telephone survey of about 15,000 people from all over NSW.[230] However, only two questions about immunisation were included in the 2007-08 and 2009-

10 surveys, limiting the comparisons that could be made.[230] The 2001, 2003-04 and 2005-06 surveys were of even less relevance as their focus was mainly to do with meningococcal C vaccine. Nevertheless, similar to the findings of the RCT and SA survey, the majority of parents and carers in the NSW survey trusted vaccines as safe; 93.1% strongly or generally supported childhood immunisation in 2009-10, although the level of support had declined from 97.4% in 2001.[231] Parents and carers in the NSW survey also reported high levels of compliance with childhood immunisation; 94.6% thought their child was completely up-to-date with their childhood immunisation in 2009-10, a figure that remained stable from 2007-08 (94.1%).[231] The concurrence in public opinion and vaccination practices in the surveys conducted in SA and NSW based on these similarly worded, albeit limited number of, questions suggest that the other findings of the RCT and SA survey might also have applicability across jurisdictions.

The opinions of respondents in the two settings (the RCT and SA survey) appear to be unaffected by differences in the distribution of characteristics such as age, marital status, English language proficiency, employment status, socioeconomic status and educational attainment. The remarkably similar results between the two samples, despite the heterogeneity of the study samples, indicate that the findings about respondents' consent preferences for the use of linked data to evaluate vaccine safety are consistent and reliable, even though the findings diverge from the previous studies reviewed in Section 2.3.7. In these studies, much larger proportions of the public wanted to be asked for opt-in consent, particularly prior to each use of their data. An example of one of these previous studies is a telephone survey of the Canadian population by Willison et al.[148]; its relevant findings are presented as a pie-chart in Figure 7.4, in order to provide a comparison with Figure 7.1.

Figure 7.4: Public perspectives on consent for the use of data from medical records



A reason why the telephone survey of the Canadian population[148] achieved such different results to the SA and RCT surveys might be the expansive and undifferentiated context provided when explaining what research entails. Respondents were first asked general questions about their attitudes towards privacy, health research and the relative importance placed on the two. When explained this simplistically, most people think about research in broad, general terms.[156] Both health research and privacy protection were strongly valued and most respondents were reluctant to see a compromise in either, although 68% conceded that they were willing to forgo privacy to allow health research that could be beneficial to people's health. Respondents were then queried about their level of support for a variety of types of research ranging from public health to market research. Support was higher for studying the quality of health care and communicable diseases (86% to 89%) relative to research for commercial purposes such as tailoring marketing to doctors and for profit (35% to 60%). When queried about their level of trust in various institutions, respondents were more trusting of data institutes, university researchers, hospitals and disease foundations (76% to 81%) than insurance industries, drug companies and government (35% to 54%). Subsequently, respondents were asked about their consent choices if information from their medical records were to be added to a database and used

for research that may improve disease treatment (Figure 7.4). Respondents were informed that directly identifying information such as their name, address and health insurance number would be removed prior to use of their information, making it difficult, although not impossible, to reidentify them. The preamble describing various types of research might have instilled confusion and uncertainty among Canadian respondents as to the exact research purposes the database would be used for, prompting a more cautious and restrictive attitude towards the use of their personal information. In contrast, the SA and RCT surveys thoroughly described the exact nature of the research to be undertaken, its privacy safeguards and intended societal benefits and this may have alleviated any concerns and elicited a more permissive attitude among respondents to the use of their personal information.

People whose health or treatment could be improved through progress in research may also view research more favourably. An RCT in the Netherlands examined the opt-in and opt-out approaches to seeking consent from 264 cancer patients for the use of their excised surgical tissue for future diagnosis, treatment or research uses.[25] Consent preferences among cancer patients differed somewhat to those of parents in the VALiD RCT, but were also generally permissive: 59% of the 239 respondents favoured the opt-out approach, either 'opt-out plus' (43%) or standard opt-out (16%), 34% preferred opt-in consent and 8% did not want to be given the opportunity to make a choice.[25]

Further, the topic of vaccine safety in the SA and RCT surveys engages most, if not all, of the public, as vaccines are universally recommended for all birth cohorts. Thus, the findings of this research regarding opt-in and opt-out participation rates, the presence/absence of selection bias, the level of informed consent achieved, consent choices, and attitudes towards data linkage could be particularly relevant for studies of very prevalent or universal health conditions.

8 Findings and conclusion

This thesis has explored the issue of consent in the context of postmarketing surveillance of vaccine safety using data linkage. The relative performance of the opt-in and opt-out approaches to seeking consent were thoroughly assessed, for the first time, in the context of a data linkage study using a well-designed randomised controlled trial (RCT).

In the trial, parents were invited to take part in a data linkage study to evaluate the safety of the two-month immunisations for their newborn infants by linking vaccination and hospital records during the month following immunisation. The primary outcome was a concurrent comparison of the participation rates achieved when using the opt-in and opt-out approach and the impact of each on the capacity of a data linkage system to detect adverse events following immunisation (AEFI). Secondary outcomes included an assessment for evidence of any selection bias by examining socio-demographics differences between participants and non-participants in each arm, and an assessment of the level of informed consent achieved by using the two consent approaches. The latter was examined by comparing parents' reasons for participation and non-participation in each arm, in relation to their underlying intentions, and by examining parental recall and understanding of the study purpose. The implications of these outcomes on the feasibility of the opt-in and opt-out approach were examined.

Further, parental and general community consultation were undertaken to canvass support and trust in data linkage for vaccine safety surveillance. Respondents were asked about their preference for any requirement for consent, opinions on vaccine safety and effectiveness, and the level of vaccination uptake for their children. This concluding chapter draws together key findings and contributions, outlines limitations of the research and suggests potential areas for future research.

8.1 Key findings and contributions

8.1.1 An RCT of the opt-in and opt-out approach to gain parental consent

The primary aim of the thesis was a comparison of the participation rates achieved when using either the opt-in and opt-out approach to invite parents to take part in a data linkage study to evaluate vaccine safety. In Chapter 2, a review of observational studies that used one of either approach to seeking consent for clinical or data linkage research identified that the opt-out approach generally yielded higher participation rates than the opt-in approach, although participation rates varied substantially across the included studies from 20%–97% for the opt-in method and 35%–99% for the opt-out method. In Chapter 3, a review of the literature identified only five RCTs that have assessed the relative performance of the opt-in and opt-out approach in terms of numbers and characteristics of participants enlisted to medical research, and all but one[23] had a small sample size and flawed methodology. Consistent with the findings from the observational studies reviewed in Chapter 2, the opt-out approach yielded higher participation rates than the opt-in approach, but the extent of participation in these trials varied widely from 48%–85% in the opt-in arm and 59%–100% in the opt-out arm.

None of the five RCTs were relevant to the context of a data linkage study. Three of the RCTs required more effort from the study sample than would be required in a data linkage study, as participation involved attending clinic,[23] undergoing screening tests,[24] and follow-up evaluations.[22] The burden of these requirements may have lowered the participation rate, which ranged from 48%–75% in the opt-in arm and 59%–91% in the opt-out arm. Two of the RCTs may have more applicability to a data linkage study since participation simply involved parents allowing child enrolment on a disability surveillance register,[21] or surgical cancer patients allowing excised tissue to be used in laboratory

research.[25] The relatively low impost may have optimised the participation rate, which ranged from 79%–85% in the opt-in arm and 97% –100% in the opt-out arm.

In order to assess the relative performance of the opt-in and opt-out approaches to seeking parental consent, we conducted a RCT in which 1129 families of children born at a South Australian hospital were sent information explaining data linkage of childhood immunisation and hospital records for vaccine safety surveillance, with four weeks to opt in or opt out by reply form, telephone or mail. A subsequent telephone interview of 1026 parents (91%) allowed for an examination of the secondary outcomes. Chapter 3 describes the study protocol for the RCT in detail, and Chapters 4 and 5 present the results for the primary and secondary aims.

We have shown that, in the context of a program of data linkage to evaluate vaccine safety, the opt-in method of consent yielded a very low participation rate (21%) compared with the opt-out method (96%), such that the data linkage study would be unable to gather enough meaningful data to enable the detection of adverse events following immunisation. Participation in the VALiD RCT did not involve clinic attendance, screening tests or follow-up evaluations, apart from one telephone interview at 10 weeks post-partum. Nonetheless, there was a much lower propensity among people in the VALiD trial to opt in to research compared with all five previous RCTs, the reasons for which are unknown. In contrast, the participation rate in the opt-out arm was comparable to the other RCTs, in which participation rates of 90% or greater were achieved, except for one trial which required patients to attend clinic (59%).[23] It may be that patients or people with vested interests, for example, parents of low birth-weight infants[21] and cancer patients,[25] may be more motivated to participate in research than parents of generally healthy newborns. The trial of cancer patients assessed subject recall, understanding and reasons for (not) consenting,[25] and its findings lend support to this idea as 'the primary reason for

respondents to provide consent was a desire to contribute to improving treatment for future patients' and to benefit relatives that might also develop cancer.[25]

There was clear evidence of selection bias in the opt-in arm, with an over-representation of parents who were older, married or in a de facto relationship, university educated and of high socioeconomic status, and an exclusion of the most marginalised people, including Indigenous parents and those of low socioeconomic status. In contrast, there was no evidence of selection bias in the opt-out arm, as high participation yielded a representative sample, except men were a little less likely to participate than women.

Two systematic reviews, one of prospective observational studies and the other of data linkage studies, both using the opt-in approach, found differences in the socio-demographics and health status of participants and non-participants, but no clear pattern in the direction and magnitude of the effect (Chapter 2). Unlike these systematic reviews, we found a clear pattern in the socio-demographic comparisons of participants and non-participants in the opt-in arm of the RCT. Our findings were more in line with other studies also reviewed in Chapter 2, in which people who opted in were more likely to be in better health and of higher socioeconomic status. When the opt-out approach was used, we found minimal differences in the socio-demographic profile of participants and non-participants, a finding consistent with other studies (Chapter 2).

Previous research, reviewed in Chapters 2 and 5, has established that informed consent is an ideal that is often difficult to attain. Aside from providing sufficient information, the other necessary components are outside the realm of the researcher's control as they involve the participant's ability to attend to the proposed research, adequately understand it, consider the implications of participation and to make a voluntary choice. In the RCT, we compared the level of informed consent achieved when using the mail-based opt-in and opt-out approaches by conducting a follow-up interview with a parent from each family.

Both consent methods were suboptimal, firstly, in gaining the attention and understanding of the target audience. Although four-fifths of parents who received either the opt-in or opt-out intervention remembered receiving the study invitation material (81% and 83%, respectively), substantial proportions in both arms claimed they did not receive the invite (13% and 11%), paid no attention to it (17% and 15%), or were unable to understand it (9% and 12%). Secondly, when considering the reasons given by parents in the interview for participation or non-participation, it became clear that opting in and opting out behaviour was often at odds with parents' stated underlying intentions. In the opt-in arm, respondent burden was the most commonly cited reason for non-participation (42%), resulting in only half of those who wanted to participate (45%) opting in (20%). A further small proportion of parents opted in (<2%) although they did not understand what was asked of them. Fewer parents in the opt-out arm reported that the study ranked low on their relative priorities (19%) and a larger proportion wanted to participate (60%), some of whom accidentally opted out (0.5%). Only about one in ten parents in each arm explicitly stated that they did not want to participate (12% and 10%) for a variety of reasons mainly to do with privacy concerns, but also including time constraints and misunderstandings about the study purpose and/or their eligibility.

No complaints were received about either the opt-in or opt-out approach, which may indicate that both methods were well-accepted, although parents were not specifically asked to provide such feedback. In terms of relative strengths and weaknesses, the opt-in approach did not include parents against their wishes, since they did not opt in; however, half of the parents who wanted to participate were excluded because they failed to opt in, and a substantial proportion did not have the opportunity to make a choice because they did not receive, contemplate or understand the invitation. The opt-out approach did appear to better reflect the wishes of those who actually wanted to participate; however, 7% of parents were included against their wishes because they failed to opt out, and similarly (as

found in the opt-in arm) a substantial proportion did not have the opportunity to make a choice because they did not receive, contemplate or understand the invitation. Both methods, therefore, were ineffective in achieving informed consent and suboptimal in their capacity to respect participant autonomy.

A further criticism of both consent methods is that parents demonstrated poor understanding of the study purpose, despite the one page cover letter and reply form being carefully constructed to outline all the essential information with an ease of comprehension that would be understood by most adults, as assessed by the Flesch readability ease score. The detailed two-page information sheet was considerably more difficult to read; however, it was intended as an additional source for those who wanted more information and it was not essential to read it in order to understand the study's purpose. About two-thirds of parents who received either the opt-in and opt-out intervention reported that they had read the letter and information sheet (63% and 67%, respectively). However, the proportions able to correctly identify the two health record sources to be linked (i.e. vaccination and hospital records) were considerably lower (43% and 39%). These findings are congruent with a small body of literature,[127-133] reviewed in Chapter 5, which demonstrates that the informed consent process is less than ideal among research volunteers in many RCTs.

Parental recall and understanding of the study's purpose showed incremental improvement with progressively higher levels of educational attainment. When comparing the participants in each arm, parents who made an active decision to opt in were better able to correctly identify which records were to be linked than those who passively consented, i.e. did not elect to opt out (60% *vs* 39%). However, the moderate gain in participant understanding that can be achieved by using an opt-in rather than an opt-out approach must be considered in relation to its drawbacks, which are a much lower participation rate and selection bias towards participants of higher education and socioeconomic status.

This work provides the most comprehensive comparison of the relative performance of the opt-in and opt-out approaches to seeking consent. Neither method achieved adequate informed consent. Each had its own unique flaws; the opt-in approach performed a little better in achieving informed consent, whereas the opt-out approach invoked minimal scientific losses in statistical precision and generalisability. These findings call into question the current reliance in ethical guidelines on opt-in consent to provide blanket assurance that research participants are willing to contribute to health and medical research.

8.1.2 Parent and public perspectives on consent for the linkage of data to evaluate vaccine safety

Chapter 2 reviewed the literature on prior community consultation, encompassing cross-sectional mail and telephone surveys, face-to-face interviews, and focus groups. Most of these international and Australian studies found that the majority of people want opt-in consent. The usual frame of these studies was simply to ask people about their attitudes with little or no elaboration about the societal benefits, privacy safeguards applied, and the costs of seeking consent. Unfortunately, these limited interpretations of public opinion inform Australia's current regulatory emphasis on privacy and consent.

In this thesis, public consultation was undertaken to examine whether people do or do not support the linkage of children's health information for the purpose of vaccine safety surveillance when considered in the light of potential public benefits and the privacy safeguards applied. In their decision-making regarding consent preferences, people were asked to consider the cost and time delays a requirement to seek parental consent would have on a vaccine safety surveillance program.

Data linkage for postmarketing surveillance of vaccines was widely supported by parents and the wider community (96% and 94%) and there was trust in its privacy protections

(84% and 75%). The majority also preferred minimal or no direct involvement: either opt-out consent (40% and 40%) or no consent (30% and 31%). Only a quarter preferred opt-in consent (24% and 25%), and fewer than half of them requested that consent should be sought prior to every use (8% and 11%). Over half of the parents and the wider community gave higher priority to rapid vaccine safety surveillance (61% and 56%) rather than first seeking parental consent (21% and 27%), while one in seven was undecided (15% and 14%). Despite generally vaccinating their children (91% and 96% of children) and trusting vaccines as safe (90% and 92%), many parents and community members were concerned that vaccines may be ineffective (42% and 40%) and may cause serious reactions (62% and 53%). Opinions were remarkably similar when comparing parents in the RCT with the sample of the general population of SA. As discussed in Chapter 7, these similarities were observed despite the diverse socio-demographic profiles of the two surveys and the differing response rates.

Both surveys demonstrate that data linkage for vaccine safety surveillance has substantial community support and that an informed public is more amenable to data linkage without individual consent. The consistency in our results about consent despite the heterogeneity of the study samples gives weight to our findings even though they diverge from most previous studies reviewed in Chapter 2. Our findings are more in line with two previous surveys which also provided a contextual framework to allow the public to weigh up individual privacy rights against the benefits arising from research.[115,163] The clear gap in public confidence regarding the safety of vaccines highlights a need for Australia to strengthen its current system of vaccine safety surveillance.

8.2 Limitations and future directions

The limitations of the RCT and the population-based survey and the implications for the generalisability of the findings have been discussed in the relevant chapters and will not be repeated here. Instead, this section will focus on the overall limitations of the approach taken and identification of areas for future research.

This thesis was necessarily limited to one topic of data linkage of the many possible scenarios that might be of interest. The particular topic, the safety of vaccines, is one in which the benefits of conducting research are easily recognised by most people. Universal immunisation is recommended for children, who comprise a particularly vulnerable group of the population, which may invoke people's protective instincts. Most people have an interest and an opinion on the safety of vaccines or otherwise, having heard stories through the media or through their social circles about adverse events following immunisation.

Further research is required to see if the high level of public support for data linkage that we observed in our consultation process would hold in another context, such as a data linkage study on a sensitive or controversial topic. Examples could include criminal justice, mental health, risk behaviours (e.g. licit/illicit drug-taking, self-harm and sexuality) or studies of particular religious, migrant, or socioeconomic groups. It is important to elucidate the spectrum of research uses of data linkage that the public values.

In the VALiD RCT, we examined a mail-based approach to seeking consent, and evaluated parents' attitudes, knowledge and understanding retained at one month post-trial enrolment and not at the time of first receipt of the study invitation material. We did not examine alternative and potentially more efficient means of recruitment, for example, by integrating an opt-in or opt-out tick-box for participation in vaccine safety surveillance on Australia's national publicly funded health care (Medicare) web-based immunisation records system. This is an area of potential future research, but would require commitment from Medicare

and immunisation providers to be involved in the administration of these extra surveillance activities, which may prove difficult to achieve.

We did not specifically examine or compare the cost implications of the mail-based opt-in and opt-out approaches in the Australian context. Nevertheless, it is clear that large population-level studies are required to detect rare adverse events following immunisation, and both mail-based opt-in and opt-out approaches would be impracticable on this scale. In the VALiD trial, it became evident that, in addition to the inefficiency and cost due to non-response, the low participation rate (21%) and selection bias in the opt-in arm would prevent reliable detection of even the most common adverse events. Although participation was much higher using the opt-out approach (96%), sending individualised mail to vast numbers of parents would involve substantial environmental and cost burdens, together with the problem of relocation of parents after birth (and the potential for privacy breaches from misdirected mail), which can reach up to 50% mobility in less than four years.[196] A cost-benefit analysis that took all these factors into account would be worthwhile.

The analysis of whether immunisation uptake is influenced by opinions on vaccine safety and effectiveness was based on parental recall of childhood immunisation, and could not be validated using the Australian Childhood Immunisation Register (ACIR) without a requirement for parental consent due to legislative constraints, or alternatively, approval for a consent waiver could be sought. Recall may be less problematic in the RCT as the interview usually occurred no more than 1–2 weeks after the two-month immunisations were administered. The recall of information about vaccination practices is likely to be less reliable for parents in the SA survey since parents were asked to indicate the level of overall compliance with the immunisation schedule across the age spectrum for all children in their care, which can involve quite lengthy time lapses for older children.

Not all of the questions in the RCT interview were analysed for the purpose of this thesis; the questions about parental experiences of AEFI in their newborn after immunisation are yet to be examined. This work is envisaged as part of post-doctoral studies.

8.3 Concluding remarks

This thesis began with a discussion of the applications of data linkage for population health research, including for the postmarketing surveillance of medicines and vaccines. The limitations in prelicensure clinical trials and Australia's current system of postlicensure surveillance through passive (voluntary) reporting of adverse reactions were outlined. A case was made for integrating data linkage into Australia's current system of pharmacovigilance, which may help to build public confidence in the safety of vaccines and medicines.

It was shown that Australia's legislative framework provides a release mechanism to allow data linkage studies to proceed without a requirement for individual opt-in consent. A properly constituted HREC can approve the release after assessing that the benefits of the research substantially outweigh the public interest in privacy; however, data custodians still retain the right of refusal for data release. The onus is on the researcher to convince the HREC of the public interest of the proposed research, and to provide empirical evidence of why the requirement for opt-in consent is impracticable due to logistical reasons and scientific losses.

Due to legislative complexity and the vagaries of defining the sufficiency of the public interest needed to counter a requirement for informed consent, HRECs and data custodians may lack sufficient guidance as to when a consent waiver is appropriate. Lack of guidance can create an over-reliance on a requirement for opt-in consent for reassurance of the voluntariness of participation and to protect against litigation. This work represents the first application of an RCT to investigate the feasibility and public acceptability of a

requirement for consent in the context of data linkage, within the particular area of vaccine safety surveillance.

The purpose of seeking informed consent is to achieve a 'reflection of a person's choice'.[110] However, in the RCT comparison of the mail-based opt-in and opt-out approaches, many people did not get the choice to consider taking part in the data linkage study as a result of not receiving, reading, considering or properly understanding the information, and this was the case for both consent methods. Even among people who did read the information, understanding was poor and depended on their level of educational attainment. The findings of the RCT suggest that, in many instances, a person's response (or lack of one) to a request for informed consent does not truly reflect their intention regarding participation or adequately express their personal autonomy.

A requirement for opt-in consent for the linkage of data to evaluate vaccine safety led to scientific losses, namely a loss of statistical precision leading to an underestimation of the incidence of AEFI, and selection bias through the exclusion of the most marginalised in society. In contrast, the opt-out approach achieved high participation with a minimal loss of statistical precision, and a representative sample.

We conducted two telephone surveys to gauge public attitudes to consent methods, one among parents enrolled in the RCT, and the other in a population-based survey sample of the general SA population. In both surveys, there was substantial support for the linkage of data to evaluate vaccine safety and a system utilising no consent or opt-out consent was preferred to one using opt-in consent. This shows that people are amenable to overriding individual autonomy for the public good when given enough information to enable them to see the benefits of the proposed data linkage study and be reassured about the privacy safeguards applied.

In data linkage, identifiable data are only used in the linkage stage in accordance with a strict separation principle, and the researchers never have access to the identifiable data. Hence, the data the researcher receives are essentially anonymous, or at least data in which a person's identity cannot reasonably be ascertained unless the researcher uses list-matching or some other illegal means to unmask identities.[99] In this case, the researcher's obligation to work ethically can be covered by the confidentiality agreements he or she signs as part of their contractual obligation, for which there are severe penalties if breached.

Since the linked data are anonymous, I argue that there is no legal impediment to data release to researchers without individual consent. However, if HRECs and data custodians are still inclined to err on the side of caution, then the results of this thesis demonstrate that the only viable options are notification (for population-level studies) or opt-out consent for smaller studies. The exception is when the research poses more than a low risk of harm to participants (e.g. for invasive interventions), and in such instances, opt-in consent is generally most appropriate. However, as described in the thesis, the use of any consent method, whether it be notification, opt-out consent or opt-in consent, provides no reassurance that informed consent has been gained, as communication attempts often fail to reach the target audience and are often met by widespread public apathy. Further, there are technical difficulties and unforseen ethical dilemmas in appropriately managing those who opt in or out.

In conclusion, I argue that the waiver of consent afforded under current privacy regulations for data linkage studies meeting all appropriate criteria should be granted by ethics committees, and supported by data custodians. These findings should inform relevant public health policy and practice. Specifically, this information may encourage policy makers, government bureaucrats, data custodians, HRECs, and researchers to work towards the establishment of data linkage for vaccine (and medicine) safety surveillance in Australia and internationally. More generally, the findings may also influence future epidemiological study design and conduct by demonstrating the shortcomings of a requirement for consent for population-level studies.

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Appendix 1 Vaccine Assessment using Linked Data (VALiD) Working Group

This work was supported by an Australian Research Council (ARC) Linkage Project grant [grant number LP0882394]. In-kind and financial support was provided by: the South Australian Department of Health (SA Health); Surveillance of Adverse Events Following Vaccination in Victoria (SAEFVic); New South Wales Health (NSW Health); and the Australian Paediatric Surveillance Unit (APSU).

Members of the Vaccine Assessment using Linked Data (VALiD) Working Group include:

- University of Adelaide, SA: Michael S Gold, Annette J Braunack-Mayer, Philip Ryan, Katherine M Duszynski, Jesia G Berry, Vicki Xafis, Jillian Carlson, Bernadette Richards and Jackie M Street.
- New South Wales Department of Health, NSW: Lee K Taylor.
- Royal Children's Hospital, Vic: Jim P Buttery.
- University of Melbourne, Vic: Cecily J Freemantle.
- Monash University, Vic: John J McNeil and Lisa L Demos.
- University of Wollongong, NSW: Colin Thomson.
- University of New South Wales, NSW: Glenda L Lawrence.
- The University of Sydney, NSW: Elizabeth J Elliot and Julie Leask.
- John Hunter Hospital, NSW: Rod Givney.
- Therapeutic Goods Administration, ACT: Gary Lacey.
- SA Health, SA: Tony Woollacott, Chris Gascoigne, Ann Koehler, Maureen Watson, Rebecca Horgan and Sarah Lawson.
- University of Western Australia, WA: Peter C Richmond.
- Medicare Australia, ACT: Sean Tarrant.
- University of South Australia, SA: Elizabeth E Roughead.

Appendix 2 Ethical approval for the Randomised Controlled Trial

Women's & Children's Hospital

Department of Allergy & Clinical Immunology
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August 18th 2009

Dr Tamara Zutlevics
Chair
Children, Youth and Women's Health Service (CYWHS)
Human Research Ethics Committee
72 King William Rd
NORTH ADELAIDE SA 5006

Dear Tamara,

RE: REC 2087/7/11 [Investigating the technical feasibility of obtaining consent for vaccine safety data linkage in Australia].

We write to update you on issues related to study REC 2087/7/11 particularly with respect to the modifications requested by the Human Research Ethics Committee detailed in your letter dated July 1st 2009. Furthermore we wish to inform the Committee of the completion of final arrangements in order to receive their approval for the study to proceed.

Previous communication to you (letter dated June 23rd 2009) has already clarified the strategy for addressing study modifications relating to recruitment and data linkage.

The third modification concerned an addition to the study introductory letter which detailed a mechanism in the introductory cover letter for study participants to opt-out from further communication from the study group. This mechanism involved contacting the Discipline of Paediatrics to inform them that they (the participant) wished no further contact from the University of Adelaide researchers. Following discussions involving members of the Project Executive Committee (A/Professor Annette Braunack-Mayer and Professor Philip Ryan) and yourself, where concerns regarding the confusion participants might experience regarding this modification and specific requests relating to requirements of the return/non-return of the study form, there was agreement that this sentence would not be included in the letter. As detailed in your email communication to Annette (dated Jul 8th 2009) detailing resolution of this matter, the omission of this sentence was on the proviso that, all (participant) interviews were to be conducted by CYWHS staff and that at time of interview request, the CYWHS staff-member re-stated that participation "*in the interview is completely voluntary and that a refusal will in no way affect any care they receive at the CYWHS now or in the future*". The two final (amended) study cover letters informing potential participants of the project is enclosed for your reference.

In accordance with these provisos we wish to inform you of the designation of two key project staff, Jesia Berry and Jillian (Jill) Carlson as CYWHS employees. This employment will ensure that any identified data are managed only by these project personnel. In addition, all study participant interviews will also be conducted only by Jesia and Jill. Confirmation of Jesia and Jill's employment are enclosed.

With respect to the final arrangements, enclosed are signed study Confidentiality Agreements and notification of Police Clearances for members of the study Project Executive Committee who are non-CYWHS employees and who are either based at, or visit the Women's and Children's Hospital campus. They are:

- A/Professor Annette Braunack-Mayer
- Professor Phil Ryan
- Katherine Duszynski and
- Vicki Xafis

Government of South Australia
SA Health

Confidentiality Agreements and Police Clearance notifications for Jesia Berry and Jill Carlson are also enclosed.

We look forward to receipt of an updated approval from the CYWHS Human Research Ethics Committee enabling commencement of the trial.

Sincerely,

Dr Michael Gold
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University of Adelaide, Discipline of Paediatrics
Women's and Children's Hospital
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Encl:
1. Study introductory cover letter - opt-in version
2. Study introductory cover letter - opt-out version
3. Employment contract – Jesia Berry
4. Employment contract – Jill Carlson
5. Study Confidentiality Agreement - A/Professor Annette Braunack-Mayer
6. Study Confidentiality Agreement - Professor Phil Ryan
7. Study Confidentiality Agreement - Katherine Duszynski
8. Study Confidentiality Agreement - Vicki Xafis
9. Study Confidentiality Agreement - Jesia Berry
10. Study Confidentiality Agreement - Jill Carlson
11. National Criminal History Record Check and Screening Assessment Letter - A/Professor Annette Braunack-Mayer
12. National Criminal History Record Check and Screening Assessment Letter - Professor Philip Ryan
13. National Criminal History Record Check and Screening Assessment Letter - Katherine Duszynski
14. National Criminal History Record Check and Screening Assessment Letter - Vicki Xafis
15. National Criminal History Record Check and Screening Assessment Letter - Jesia Berry
16. National Criminal History Record Check and Screening Assessment Letter – Jill Carlson

Cc:
A/Professor Annette Braunack-Mayer
Professor Philip Ryan
Katherine Duszynki

Government of South Australia
SA Health

Women's & Children's Hospital

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72 King William Road
North Adelaide SA 5006
Tel 08 8161 6521
Tel 08 8161 6390
Fax 08 8161 8177
www.cywhs.sa.gov.au

31st August 2009

Dr M Gold
University Dept of Paediatrics
CYWHS

Dear Mike

Re: Investigating the technical feasibility of obtaining consent for vaccine safety data linkage in Australia REC2087/7/11

I refer to your letter dated 18th August 2009 and advise approval of your response to the privacy and confidentiality issues raised in my letter dated 1st July 2009. I also advise approval of the study introductory cover letters, opt-in version and opt-out version.

[redacted]
CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Appendix 3 Ethical approval for maternal and infant death screening

Women's & Children's Hospital

Department of Allergy & Clinical Immunology
UNIVERSITY OF ADELAIDE, DISCIPLINE OF PAEDIATRICS
Level 2, Clarence Rieger Building

Postal address:
University of Adelaide
Discipline of Paediatrics
Women's and Children's Hospital
72 King William Road
North Adelaide SA 5006
Tel 08 8161 7266
Fax 08 8161 7031
ABN 64 021 748 126
www.wch.sa.gov.au

August 11th 2009

Dr Tamara Zutlevics
Chair
Children, Youth and Women's Health Service (CYWHS)
Human Research Ethics Committee
72 King William Rd
NORTH ADELAIDE SA 5006

Dear Tamara,

RE: REC 2087/7/11 [Investigating the technical feasibility of obtaining consent for vaccine safety data linkage in Australia].

I am writing to you with regard to one aspect of the study design for the above-mentioned randomised controlled trial (RCT). The protocol that was submitted to the CYWHS Human Research Ethics Committee incorporates the following exclusion criteria:

- still-births and infant deaths — and in the instance of twins, if one dies, the mother is excluded from the study;
- births where the infant has a length of stay in the Neonatal Intensive Care Unit of ≥ 2 weeks (that is, infants who are unwell and are not discharged as per standard birth protocol);
- births where the mother is less than 18 years of age;
- home-births; and
- births that occur at another hospital but are subsequently managed at the Women's and Children's Hospital (WCH).

Furthermore, mothers that are non-residents of South Australia will also be excluded from the study. In this way, safeguards are in place to minimise the possibility of a mother being included in the study if her infant is unwell, or at risk of dying.

Our study team has given further thought about how we would like to enhance the protocol to minimise the possibility of contacting a mother who is bereaved. We will coordinate with Jill Edwards, Systems Consultant, Health Informatics, Policy & Performance Outcomes (HIPPO) to receive the HOMER data extract of births at monthly intervals after the second week of each month has elapsed. This timing ensures that the HOMER data extract we receive will certainly be up-to-date with regard to any still-births and infant deaths that occur whilst in hospital. Our understanding is that a reciprocal data exchange occurs between HOMER and the Births, Deaths and Marriages Registration Office (BDM) located at Level 2, Chesser House 91-97 Grenfell Street, Adelaide SA 5000. The CYWHS personnel who manage HOMER provide BDM with notifications of births and deaths that occur at the Women's and Children's Hospital — births are notified weekly and deaths are notified every two days. Likewise, the CYWHS Patient Master Index (PMI) Coordinator is able to log-on to the BDM database to update HOMER with deaths that have been notified from other sources; the PMI Coordinator routinely updates the HOMER extract a month at a time. The process of receiving a HOMER extract at monthly intervals will capture deaths prior to discharge from hospital and, in most instances, deaths that occur whilst the hospital is still in communication with the mother after discharge, i.e. for billing purposes.

Government of South Australia
SA Health

We note that the precautions that we have in place will ensure the possibility of missing an infant death is very small. However, a window of time remains in which an infant death can occur, and potentially not be captured, since we will be enrolling infants into our study when they are six weeks of age — they will be randomised to the opt-in or opt-arm, and mail-out will occur on the day after randomisation. We propose that we could check for additional deaths that might occur in the several weeks prior to randomisation, by checking each birth record in the HOMER data extract against death notifications at the BDM. The BDM database is usually updated within 1–2 weeks of a death; once the paperwork is submitted by the respective funeral director. We have enquired with the Registrar, Ms Val Edyvean, as to how this could be done. The process would be undertaken by Jesia Berry or Jill Carlson, who are the designated CWYHS employees and the only team members who see identifiable data and conduct all the interviews with consenting participants.

The two possibilities are:

1. A project officer (Jesia or Jill) visit the BDM and log into a stand-alone computer and do a key-word search for the names on each birth record in the HOMER data extract. This would be done on a weekly basis, on the day prior to mail-out when a child reaches six weeks of age, for the duration of the study (3–4 months).

2. The BDM constructs syntax to allow an automated computer search of the BDM database to occur on a weekly basis. The project officer (Jesia Berry) sends an email to the BDM project officer, Mr Ian Neale, with an Excel data file containing only the minimum data needed for the search. The Excel data file includes the following details for the baby and mother: first name, surname, date of birth, and gender. The automated computer search is conducted, and any deaths are notified by Mr Ian Neale to Jesia Berry by return email. The benefit of this approach is that no list is physically taken off-site from the WCH campus by the project officer. The data files sent in correspondence would also be encrypted, to further protect confidentiality of the study participants.

We are seeking your advice on this enhanced protocol, as to whether you think the steps to check for infant deaths in the weeks prior to randomisation are warranted, and if so, what preference you have as to the two possible methods. I look forward to your response.

Sincerely,

Dr Mike Gold
University of Adelaide, Discipline of Paediatrics,
Women's and Children's Hospital
Email: michael.gold@adelaide.edu.au
Tel: +61 8 8161 7030
Fax: +61 8 8161 7031

Government of South Australia
SA Health

Women's & Children's Hospital

Research Secretariat
72 King William Road
North Adelaide SA 5006
Tel 08 8161 6521
Tel 08 8161 6390
Fax 08 8161 8177
www.cywhs.sa.gov.au

31st August 2009

Dr M Gold
University Dept of Paediatrics
CYWHS

Dear Mike

Re: Investigating the technical feasibility of obtaining consent for vaccine safety data linkage in Australia. REC2087/7/11

I refer to your letter dated 11 August 2009, regarding amendment of the process to minimise the possibility of contacting a mother who is bereaved. At its meeting on 26th August 2009, the CYWHS Human Research Ethics Committee sought further clarification regarding the two options outlined in your letter. Following my discussion with you, Jessie Berry and Katherine Duszynski at our meeting on September 1st 2009, I can now confirm approval of the second option, that is, that the BDM constructs syntax to allow an automated computer search of the BDM database to occur on a weekly basis.

At its meeting the Committee also requested advice on the proposed process if a bereaved mother is contacted despite your efforts to avoid this. This issue was also discussed at our meeting and I understand that you will forward your response to the Committee shortly.

I look forward to your response.

TAMARA ZUTLEVICS (DR)
CHAIR
CYWHS HUMAN RESEARCH ETHICS COMMITTEE

Women's & Children's Hospital

Department of Allergy & Clinical Immunology
UNIVERSITY OF ADELAIDE, DISCIPLINE OF PAEDIATRICS
Level 2, Clarence Rieger Building

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University of Adelaide
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Women's and Children's Hospital
72 King William Road
North Adelaide SA 5006
Tel 08 8161 7266
Fax 08 8161 7031
ABN 64 021 748 126
www.wch.sa.gov.au

September 1st 2009

Dr Tamara Zutlevics
Chair
Children, Youth and Women's Health Service (CYWHS)
Human Research Ethics Committee
72 King William Rd
NORTH ADELAIDE SA 5006

Dear Tamara,

RE: REC 2087/7/11 [Investigating the technical feasibility of obtaining consent for vaccine safety data linkage in Australia].

Thank-you for today's meeting to clarify our proposal related to enhanced checks for infant deaths in association with study **REC 2087/7/11**.

As a result of the discussion it was agreed that we would proceed with further verification for additional infant deaths that might have occurred in the intervening time following a mother's discharge after birth. As outlined in our letter dated August 18th this process would be undertaken with the assistance of the Adelaide Births, Deaths and Marriages Registration Office (BDM). The specific process would involve the second of the two options detailed whereby, the BDM would undertake an automated computer search of the BDM database, with searches conducted weekly. As suggested by you in today's discussion these weekly searches would be cumulative in nature. This would further identify any deaths which might occur following the initial mail-out of the study information but prior to contacting study participants for the voluntary interview. Cumulative searches would include all those names of children whose families were to be mailed that week or had been mailed in the preceding weeks with contact for interview still to be made. The list for searching comprising the first name and surname of the mother and baby (together with baby's date of birth and gender), would be forwarded to the BDM early on the day prior to mail-out and its return following review, anticipated to be later the same day. The list would be sent (and received) via CYWHS employee email in an encrypted format.

In the circumstance where a family receives correspondence from the research group and an infant death has occurred without our knowledge then, your advice will be sought on the most appropriate way to respond to this bereavement and any distress caused by the study invitation.

We now understand that all outstanding issues and clarification have been resolved for the proposed study allowing us to now proceed with commencing the formal component of the study. We thank the Committee's input in strengthening the privacy and confidentiality aspects of the study protocol and look forward to reporting on the study's results in due course.

Sincerely,

Dr Mike Gold
University of Adelaide, Discipline of Paediatrics,
Women's and Children's Hospital
Email: michael.gold@adelaide.edu.au
Tel: +61 8 8161 7030
Fax: +61 8 8161 7031

Government of South Australia
SA Health

Appendix 4 Study invitation material: opt-in arm

Consent trial OPT-IN Documentation

- Cover letter
- Information Sheet
- Study Form (two copies: first to be printed on yellow paper, the second on white paper)

Women's & Children's Hospital

Postal address:
VALiD Study
Discipline of Paediatrics
Clarence ieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

27 July 2009

<mothertitle> <motherfirstname> <mothersurname>
<motheraddressline1>
<mothersuburb> <motherstate> <motherpostcode>

Dear Parent(s),

Congratulations on the birth of your new baby. As a doctor at the Women's and Children's Hospital, I am pleased to invite you to take part in a study conducted by my team of researchers from the hospital and the University of Adelaide. In a couple of weeks, your baby will be due for their 2 month vaccinations. We would like to link your baby's vaccination records with any hospital visits that may occur in the month after they receive their vaccinations. This is so we can trial a new way of checking for rare reactions to vaccines by looking at large numbers of children: called data linkage.

Studies have shown that vaccines are safe and it is rare for serious reactions to occur. Data linkage joins together records from the national vaccination and hospital databases, to see if there is a connection between the reason a child has come to hospital and being recently vaccinated.

Even if you do not vaccinate your baby at 2 months, we are still interested to look at any visits of your baby to hospital in order to make comparisons with babies that are vaccinated.

A researcher will contact you when your baby is about 10 weeks of age to invite you to take part in a 15–20 minute telephone interview to find out your views about data linkage and vaccination.

To let us link your baby's records, **please sign both copies of the enclosed Study Form** and **return the yellow copy to us** in the reply paid envelope. Please keep the white copy for reference when we call.

It would be helpful if you could have your child's 'Personal Health Record' otherwise known as the 'Blue Book' nearby for when we call. Further information on the study is in the Information Sheet.

Participation in the study is voluntary and involves no visits to the Women's and Children's Hospital. Any information you provide will be maintained in confidence. You are free to withdraw from the study at any time; this will in no way affect any future treatment that you, or your baby, may have at the hospital. We would be happy to answer any questions you might have. Please call Jesia Berry on (08) 8161 7244.

Sincerely,

Dr Mike Gold
Discipline of Paediatrics
Women's and Children's Hospital & the University of Adelaide

Government of South Australia
SA Health

CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE (CYWHS)

INFORMATION SHEET

Vaccine Data Linkage Study

Scientific title: Vaccine Assessment using Linked Data (VALiD)

Researchers: Dr Michael Gold, Associate/Professor Annette Braunack-Mayer, Professor Philip Ryan, Ms Katherine Duszynski, Ms Jesia Berry, and Ms Vicki Xafis.

Why have you been sent this information?

You are invited to join a study on vaccinations being conducted by researchers at the Women's and Children's Hospital and the University of Adelaide. You have been selected because you recently had a baby at the Women's and Children's Hospital, and in a couple of weeks, your baby will be due for their 2 month vaccinations.

What is this study about?

There are two parts to the study. Firstly, we would like to link your baby's vaccination records with any hospital visits that may occur in the month after they receive their 2 month vaccinations. This is so we can trial a new way of checking for rare reactions to vaccines called data linkage. Even if you do not vaccinate your baby at 2 months, we are still interested to look at any visits of your baby to hospital in order to make comparisons with babies that are vaccinated. The second part of the study involves us contacting you when your baby is about 10 weeks of age to invite you to take part in a 15–20 telephone interview to find out your views about data linkage and vaccination.

What is data linkage and how is it used to check the ongoing safety of vaccines?

Studies have shown that vaccines are safe and it is rare for serious reactions to occur. All the vaccines used in Australia are carefully checked for safety and your vaccine provider can discuss the safety of individual vaccines with you further. In South Australia, any unexpected or serious reactions after a vaccination are reported to the SA Immunisation Coordination Unit. However, not all reactions are reported, so it is important to develop new ways to check the ongoing safety of vaccines.

Data linkage can **check for rare reactions to vaccines by looking at large numbers of children.** It is currently being used overseas, but it is new to Australia. If your baby is vaccinated, the vaccinations given to your baby and the date they are given are recorded on a national electronic database maintained by the Commonwealth Government — the Australian Childhood Immunisation Register (ACIR). If your baby goes to hospital, the reason for going to hospital is also recorded on a separate database.

Data linkage joins together records from the national vaccination and hospital databases, to see if there is a connection between the reason the baby has come to hospital and being recently vaccinated.

Eventually the aim will be to link all vaccination and hospital records for children in Australia. If we do this, we will be able to find out more quickly whether reactions to vaccines are occurring, and this will help health authorities to take appropriate action. It may also be possible for data linkage to be used in the future to check for milder effects arising from vaccination that would lead to a visit to a GP.

What health information will be collected for data linkage?

For each baby, their name, date of birth, gender, address, reason for hospital visit (if the baby goes to hospital) and vaccine details (if vaccination has occurred) will be collected. No other personal or health information will be collected.

How is your family's privacy protected?

Before your baby's vaccination records and hospital records are joined together, your baby's name and your home address will be replaced with a unique number, so that the researchers who look at the linked records will not be able to identify your baby. The steps taken to protect your privacy will include having special computer 'passwords' that only the researchers know, having computers in locked rooms, and the following of all State and Commonwealth privacy guidelines and laws.

Your personal details and answers to the telephone interview will be locked away and will only be looked at by the researchers. Your name and address will not appear in any way in relation to the results of this study. Your information, and your baby's, will remain confidential except in the case of a legal requirement to pass on personal information to authorised third parties. This requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare; however, we have an obligation to inform you of this possibility.

How can I find out more information on how my baby's information will be kept private?

For further details on how data linkage is done and how information is kept private, please visit the website http://health.adelaide.edu.au/paediatrics/research/valid/ or email any specific questions to valid.study@adelaide.edu.au

What do I need to do now?

If you give permission for your baby's vaccination records and any visits of your baby to hospital to be included in data linkage, please complete both copies of the enclosed Study Form as follows:

- Fill in your name and sign both copies of the Study Form
- Complete the other details on the **yellow copy** of the Study Form
- **Return the yellow copy** to us in the reply-paid envelope provided, and
- Keep the white copy for future reference when we call

Your baby's information will be included ONLY if you return the Study Form.

If the reply paid envelope is lost, please return the Study Form in an envelope to (*no stamp required*):
VALiD Study
Discipline of Paediatrics
Clarence Rieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

What happens now?

Regardless of whether you decide that your baby's information will be included in the data linkage or not, we will contact you when your baby is about 10 weeks of age.

The reason to do this is to invite you to take part in a 15–20 telephone interview to find out your views on data linkage and vaccination. Consent for the telephone interview will be obtained from you at the time and you will be free to decline the interview. It would be helpful if you could have your child's 'Personal Health Record' otherwise known as the 'Blue Book' nearby for when we call.

Additional information

The study has received ethics approval from the Women's and Children's Human Research Ethics Committee. If, at any time, you wish to discuss the ethical approval process, or have a concern or complaint, please contact the Secretary of the Committee (Ms Brenda Penny) on (08) 8161 6521.

If you have any questions about the study: about your baby's safety, or your rights, or wish to withdraw your consent to data linkage, please call:

PhD Candidate: Jesia Berry on (08) 8161 7244

Principal investigator: Dr Mike Gold on (08) 8161 7266

Or email us: valid.study@adelaide.edu.au

Study findings will be available from http://health.adelaide.edu.au/paediatrics/research/valid/ in March 2010

We thank you for your assistance.

Dr Mike Gold
Discipline of Paediatrics
Women's and Children's Hospital & the University of Adelaide

Vaccine Data Linkage Study IDnr | | | | | |

I, …… (*please print your name in full*), the parent or guardian of the new baby, understand that by signing this Study Form:

I give permission for my baby's vaccination records to be linked to any visits of my baby to hospital for the purpose of looking at vaccine safety

- I have had the study fully explained to my satisfaction in the Information Sheet and I have been given the opportunity to ask questions. My permission for data linkage is given freely.
- I am aware that I should keep a copy of the Information Sheet and this Study Form when completed.

Signed: ……..... **Date:** ..... / ..... /.....

Your relationship to baby: ……

Your date of birth: ..... / ..... /.....

Baby's name (in full): ……

Baby's date of birth: ..... / ..... /.....

If the reply-paid envelope is missing please send to (*no stamp required):*
VALiD Study
Discipline of Paediatrics
Clarence Rieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

Women's & Children's Hospital

Government of South Australia

SA Health

Vaccine Data Linkage Study

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I give permission for my baby's vaccination records to be linked to any visits of my baby to hospital for the purpose of looking at vaccine safety

- I have had the study fully explained to my satisfaction in the Information Sheet and I have been given the opportunity to ask questions. My permission for data linkage is given freely.
- I am aware that I should keep a copy of the Information Sheet and this Study Form when completed.

Signed: ……..... **Date:** ..... / ..... /.....

Your relationship to baby: ……

Your date of birth: ..... / ..... /.....

Baby's name (in full): ……

Baby's date of birth: ..... / ..... /.....

KEEP THIS COPY

Women's & Children's Hospital

Government of South Australia

SA Health

Vaccine Data Linkage Study

Appendix 5 Study invitation material: opt-out arm

Consent trial OPT-OUT Documentation

- Cover letter
- Information Sheet
- Study Form (two copies: first to be printed on yellow paper, the second on white paper)

27 July 2009

<mothertitle> <motherfirstname> <mothersurname>
<motheraddressline1>
<mothersuburb> <motherstate> <motherpostcode>

Women's & Children's Hospital

Postal address:
VALiD Study
Discipline of Paediatrics
Clarence Rieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

Dear Parent(s),

Congratulations on the birth of your new baby. As a doctor at the Women's and Children's Hospital, I am pleased to invite you to take part in a study conducted by my team of researchers from the hospital and the University of Adelaide. In a couple of weeks, your baby will be due for their 2 month vaccinations. We would like to link your baby's vaccination records with any hospital visits that may occur in the month after they receive their vaccinations. This is so we can trial a new way of checking for rare reactions to vaccines by looking at large numbers of children: called data linkage.

Studies have shown that vaccines are safe and it is rare for serious reactions to occur. Data linkage joins together records from the national vaccination and hospital databases, to see if there is a connection between the reason a child has come to hospital and being recently vaccinated.

Even if you do not vaccinate your baby at 2 months, we are still interested to look at any visits of your baby to hospital in order to make comparisons with babies that are vaccinated.

A researcher will contact you when your baby is about 10 weeks of age to invite you to take part in a 15–20 minute telephone interview to find out your views about data linkage and vaccination.

To let us link your baby's records, you do not need to do anything. If you **DO NOT** want us to link your baby's records, please **sign both copies of the enclosed Study Form** and **return the yellow copy to us** in the reply paid envelope. Please keep the white copy for reference when we call.

It would be helpful if you could have your child's 'Personal Health Record' otherwise known as the 'Blue Book' nearby for when we call. Further information on the study is in the Information Sheet.

Participation in the study is voluntary and involves no visits to the Women's and Children's Hospital. Any information you provide will be maintained in confidence. You are free to withdraw from the study at any time; this will in no way affect any future treatment that you, or your baby, may have at the hospital. We would be happy to answer any questions you might have. Please call Jesia Berry on (08) 8161 7244.

Sincerely,

Dr Mike Gold
Discipline of Paediatrics
Women's and Children's Hospital & the University of Adelaide

Government of South Australia
SA Health

CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE (CYWHS)

INFORMATION SHEET

Vaccine Data Linkage Study

Scientific title: Vaccine Assessment using Linked Data (VALiD)

Researchers: Dr Michael Gold, Associate/Professor Annette Braunack-Mayer, Professor Philip Ryan, Ms Katherine Duszynski, Ms Jesia Berry, and Ms Vicki Xafis.

Why have you been sent this information?

You are invited to join a study on vaccinations being conducted by researchers at the Women's and Children's Hospital and the University of Adelaide. You have been selected because you recently had a baby at the Women's and Children's Hospital, and in a couple of weeks, your baby will be due for their 2 month vaccinations.

What is this study about?

There are two parts to the study. Firstly, we would like to link your baby's vaccination records with any hospital visits that may occur in the month after they receive their 2 month vaccinations. This is so we can trial a new way of checking for rare reactions to vaccines called data linkage. Even if you do not vaccinate your baby at 2 months, we are still interested to look at any visits of your baby to hospital in order to make comparisons with babies that are vaccinated. The second part of the study involves us contacting you when your baby is about 10 weeks of age to invite you to take part in a 15–20 telephone interview to find out your views about data linkage and vaccination.

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Data linkage can **check for rare reactions to vaccines by looking at large numbers of children.** It is currently being used overseas, but it is new to Australia. If your baby is vaccinated, the vaccinations given to your baby and the date they are given are recorded on a national electronic database maintained by the Commonwealth Government — the Australian Childhood Immunisation Register (ACIR). If your baby goes to hospital, the reason for going to hospital is also recorded on a separate database.

Data linkage joins together records from the national vaccination and hospital databases, to see if there is a connection between the reason the baby has come to hospital and being recently vaccinated.

Eventually the aim will be to link all vaccination and hospital records for children in Australia. If we do this, we will be able to find out more quickly whether reactions to vaccines are occurring, and this will help health authorities to take appropriate action. It may also be possible for data linkage to be used in the future to check for milder effects arising from vaccination that would lead to a visit to a GP.

What health information will be collected for data linkage?

For each baby, their name, date of birth, gender, address, reason for hospital visit (if the baby goes to hospital) and vaccine details (if vaccination has occurred) will be collected. No other personal or health information will be collected.

How is your family's privacy protected?

Before your baby's vaccination records and hospital records are joined together, your baby's name and your home address will be replaced with a unique number, so that the researchers who look at the linked records will not be able to identify your baby. The steps taken to protect your privacy will include having special computer 'passwords' that only the researchers know, having computers in locked rooms, and the following of all State and Commonwealth privacy guidelines and laws.

Your personal details and answers to the telephone interview will be locked away and will only be looked at by the researchers. Your name and address will not appear in any way in relation to the results of this study. Your information, and your baby's, will remain confidential except in the case of a legal requirement to pass on personal information to authorised third parties. This requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare; however, we have an obligation to inform you of this possibility.

How can I find out more information on how my baby's information will be kept private?

For further details on how data linkage is done and how information is kept private, please visit the website http://health.adelaide.edu.au/paediatrics/research/valid/ or email any specific questions to valid.study@adelaide.edu.au

What do I need to do now?

If you give permission for your baby's vaccination records and any visits of your baby to hospital to be included in data linkage, you do not need to complete the enclosed Study Form.

If you DO NOT give permission, please complete both copies of the Study Form and return the yellow copy to us. This will mean your baby's information will be **REMOVED** from the process of linking records together. To do this:

- Fill in your name and sign both copies of the Study Form
- Complete the other details on the **yellow copy** of the Study Form
- **Return the yellow copy** to us in the reply-paid envelope provided, and
- Keep the white copy for future reference when we call

Your baby's information will be removed ONLY if you return the Study Form

If the reply paid envelope is lost, please return the Study Form in an envelope to (*no stamp required*):
VALiD Study
Discipline of Paediatrics
Clarence Rieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

What happens now?

Regardless of whether you decide that your baby's information will be included in the data linkage or not, we will contact you when your baby is about 10 weeks of age.

The reason to do this is to invite you to take part in a 15–20 telephone interview to find out your views on data linkage and vaccination. Consent for the telephone interview will be obtained from you at the time and you will be free to decline the interview. It would be helpful if you could have your child's 'Personal Health Record' otherwise known as the 'Blue Book' nearby for when we call.

Additional information

The study has received ethics approval from the Women's and Children's Human Research Ethics Committee. If, at any time, you wish to discuss the ethical approval process, or have a concern or complaint, please contact the Secretary of the Committee (Ms Brenda Penny) on (08) 8161 6521.

If you have any questions about the study: about your baby's safety, or your rights, or wish to withdraw your consent to data linkage, please call:

PhD Candidate: Jesia Berry on (08) 8161 7244

Principal investigator: Dr Mike Gold on (08) 8161 7266

Or email us: valid.study@adelaide.edu.au

Study findings will be available from http://health.adelaide.edu.au/paediatrics/research/valid/ in March 2010

We thank you for your assistance.

Dr Mike Gold
Discipline of Paediatrics
Women's and Children's Hospital & the University of Adelaide

Vaccine Data Linkage Study IDnr | | | | | |

If you give permission for data linkage, you DO NOT need to complete and return this form. Thank you.

If you DO NOT give permission for data linkage, please complete and return this form. Thank you.

I, …… (*please print your name in full*), the parent or guardian of the new baby, understand that by signing this Study Form:

I DO NOT give permission for my baby's vaccination records to be linked to any visits of my baby to hospital for the purpose of looking at vaccine safety

- I have had the study fully explained to my satisfaction in the Information Sheet and I have been given the opportunity to ask questions.
- I am aware that I should keep a copy of the Information Sheet and this Study Form when completed.

Signed: ……..... **Date:** ..... / ..... /.....

Your relationship to baby: ……

Your date of birth: ..... / ..... /.....

Baby's name (in full): ……

Baby's date of birth: ..... / ..... /.....

If the reply-paid envelope is missing please send to (*no stamp required):*

VALiD Study
Discipline of Paediatrics
Clarence Rieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

Women's & Children's Hospital

Government of South Australia

SA Health

Vaccine Data Linkage Study

If you give permission for data linkage, you DO NOT need to complete and return this form. Thank you.

If you DO NOT give permission for data linkage, please complete and return this form. Thank you.

I, …… (*please print your name in full*), the parent or guardian of the new baby, understand that by signing this Study Form:

I DO NOT give permission for my baby's vaccination records to be linked to any visits of my baby to hospital for the purpose of looking at vaccine safety

- I have had the study fully explained to my satisfaction in the Information Sheet and I have been given the opportunity to ask questions.
- I am aware that I should keep a copy of the Information Sheet and this Study Form when completed.

Signed: ……..... **Date:** ..... / ..... /.....

Your relationship to baby: ……

Your date of birth: ..... / ..... /.....

Baby's name (in full): ……

Baby's date of birth: ..... / ..... /.....

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Women's & Children's Hospital

Government of South Australia

SA Health

Vaccine Data Linkage Study

Appendix 6 Telephone survey

Active consent in opt-in arm (AOI)

The parent to be interviewed is known (mother, father or guardian) because they returned the Study Form to give consent to data linkage.

Hello. This is (interviewer's name). I am a researcher from the Women's and Children's Hospital.
I am calling about the Vaccine Data Linkage Study.
Is (parent on Study form) there please?

Yes, speaking *or* Yes, I'll go get her/him 1

No, not at home.....2

Unknown person *or* he/she has moved 3

(The number I was calling is…….. WRONG NUMBER, I'm sorry; I dialled the wrong number. SHE/HE HAS MOVED, May I please leave my number with you to pass on to her/him if they get in contact with you?) Y / N

→ Is there another parent or guardian of the new baby that I can talk to?

Yes, speaking *or* I'll go get her/him ..... 1 Name .....

Relationship to baby.....

Yes, but not at home 2

No other parent or guardian 3

→ When may I call back to speak to a parent or guardian of the new baby?

..... → END CALL

We received a reply from you / name on Study Form to say that you are / he is / she is happy for us to link your baby's health information. Thanks for sending that back. We would like to know what you think about data linkage and vaccination. Taking part in the interview is voluntary; if you refuse, this will in no way affect any future care that you receive at the hospital. Would you be willing to answer some questions now?

START INTERVIEW ← Yes 1

Yes, but no time now 2

When may I call you back? Not interested/Not sure 3

..... (If I could just ask you one thing — you returned the Study Form, which means we will be able to join your baby's vaccine and hospital records together. Can you give me a reason why you returned the form?)

.....

.....(Okay, thanks for your time. Bye.)

Passive decline in opt-in arm (POI)

The parent to be interviewed is unknown (mother, father or guardian) because they did not return the Study Form to give consent to data linkage.

Hello. This is (interviewer's name). I am a researcher from the Women's and Children's Hospital.
I am calling about the Vaccine Data Linkage Study.
May I please speak to a parent or guardian of the new baby?

Yes, speaking *or* Yes, I'll go get her/him..... 1
No, not at home 2
Unknown person *or* he/she has moved 3
(The number I was calling is…….. WRONG NUMBER, I'm sorry; I dialled the wrong number. SHE/HE HAS MOVED, May I please leave my number with you to pass on to her/him if they get in contact with you?) Y / N

When may I call back to speak to a parent or guardian of the new baby?
..... → END CALL

We sent you a letter about the Vaccine Data Linkage Study about a month ago. We are calling everyone we sent a letter to. Did you receive it? (CIRCLE ALL THAT APPLY)

Yes..... 1
No/ not sure 2

It would have had a picture of a purple bee stamped on the front of the envelope?
Yes, remembers..... 1
Still no/ not sure ..... 2 →

We would like to know what you think about data linkage and vaccination. Taking part in the interview is voluntary; if you refuse, this will in no way affect any future care that you receive at the hospital. Would you be willing to answer some questions now?

We would like to know what parents think about vaccination and a new way to check the ongoing safety of vaccines, called data linkage. Taking part in the interview is voluntary; if you refuse, this will in no way affect any future care that you receive at the hospital. Since you didn't receive the letter, you may not be able to answer all the questions, but would you be willing to answer as many as you can?

START INTERVIEW ← Yes 1
No time now..... 2 → When may I call you back? .....
Not interested/Not sure 3
(If I could just ask you one thing: you didn't return the Study Form, which means that we won't be able to join your baby's vaccine and hospital records together. Can you give me the reason why you didn't return the form?)
.....
..... (Okay, thanks for your time. Bye.)

Passive consent in opt-out arm (POO)

The parent to be interviewed is unknown (mother, father or guardian) because they did not return the Study Form to object to data linkage.

Hello. This is (interviewer's name). I am a researcher from the Women's and Children's Hospital.
I am calling about the Vaccine Data Linkage Study.
May I please speak to a parent or guardian of the new baby?

Yes, speaking *or* Yes, I'll go get her/him 1
No, not at home.....2
Unknown person *or* he/she has moved 3
(The number I was calling is…….. WRONG NUMBER, I'm sorry; I dialled the wrong number. SHE/HE HAS MOVED, May I please leave my number with you to pass on to her/him if they get in contact with you?) Y / N
When may I call back to speak to a parent or guardian of the new baby?
..... → END CALL

We sent you a letter about the Vaccine Data Linkage Study about a month ago. We are calling everyone we sent a letter to. Did you receive it? (CIRCLE ALL THAT APPLY)

Yes 1
No/ not sure.....2

It would have had a picture of a purple bee stamped on the front of the envelope?

Yes, remembers 1
Still no/ not sure.....2 →

We would like to know what you think about data linkage and vaccination. Taking part in the interview is voluntary; if you refuse, this will in no way affect any future care that you receive at the hospital. Would you be willing to answer some questions now?

We would like to know what parents think about vaccination and a new way to check the ongoing safety of vaccines, called data linkage. Taking part in the interview is voluntary; if you refuse, this will in no way affect any future care that you receive at the hospital. Since you didn't receive the letter, you may not be able to answer all the questions, but would you be willing to answer as many as you can?

START INTERVIEW

Yes 1
No time now ..... 2 → When may I call you back? .....
Not interested/Not sure 3
(If I could just ask you one thing: you didn't return the Study Form, which means that we will be able to join your baby's vaccine and hospital records together. Can you give me the reason why you didn't return the form?)
.....
.....(Okay, thanks for your time. Bye.)

Active decline in opt-out arm (AOO)

The parent to be interviewed is known (mother, father or guardian) because they returned the Study Form to object to data linkage.

Hello. This is (interviewer's name). I am a researcher from the Women's and Children's Hospital.
I am calling about the Vaccine Data Linkage Study.
Is (parent on Study form) there please?

Yes, speaking *or* Yes, I'll go get her/him..... 1

No, not at home 2

Unknown person *or* he/she has moved 3

(The number I was calling is…….. WRONG NUMBER, I'm sorry; I dialled the wrong number. SHE/HE HAS MOVED, May I please leave my number with you to pass on to her/him if they get in contact with you?) Y / N

→ Is there another parent or guardian of the new baby that I can talk to?

Yes, speaking *or* I'll go get her/him.....1 Name .....

Relationship to baby .....

Yes, but not at home.....2

No other parent or guardian.....3

When may I call back to speak to a parent or guardian of the new baby?

..... → END CALL

We have received a reply from you / name on Study Form to say that you do / he does / she does not want us to link your baby's health information. Thanks for sending that back, we respect your decision and your baby's health information will not be linked. We would like to know what you think about data linkage and vaccination. Taking part in the interview is voluntary; if you refuse, this will in no way affect any future care that you receive at the hospital. Would you be willing to answer some questions now?

START INTERVIEW ← Yes..... 1

Yes, but no time now..... 2

When may I call you back?

Not interested/Not sure..... 3

..... (If I could just ask you one thing —you returned the Study Form, which means that we won't be able to join your baby's vaccine and hospital records together. Can you give me the reason why you returned the form?)

.....

..... (Okay, thanks for your time. Bye.)

Verification of baby's home address via parent/guardian

Do you still live at _____ [read off suburb in database]? :

"Suburb & Postcode" If not, correct here…….

Attitudes to vaccine safety

Firstly, I will ask you some questions about your opinions on vaccination. I will be asking you to rate your opinion according to a list of options that I will give you.

Q.1 To begin with, what do you think about this statement? 'It is important to vaccinate children to prevent diseases such as polio, whooping cough and chicken-pox.' Would you say you strongly agree, agree, disagree, or strongly disagree?

Strongly agree.....1
Agree 2
Disagree 3
Strongly disagree 4
(Don't know) 98
(Refused) 99

Q.2 How concerned are you that a vaccination for your baby might not work, and your baby might end up getting the disease? Would you say you are very concerned, somewhat concerned, not too concerned or not at all concerned?

Very concerned.....1
Somewhat concerned 2
Not too concerned.....3
Not at all concerned 4
(Don't know) 98
(Refused) 99

Q.3 In general, how safe do you think the vaccines are, that are given to children in Australia? Would you say vaccines are very safe, safe, unsafe, or very unsafe?

Very safe.....1
Safe 2
Unsafe.....3
Very unsafe.....4
(Don't know) 98
(Refusal) 99

Q.4 What do you think about this statement? 'It is important to check the safety of vaccines given to children in Australia'. Would you say you strongly agree, agree, disagree, or strongly disagree?

Strongly agree.....1
Agree 2
Disagree 3
Strongly disagree 4
(Don't know) 98
(Refused) 99

Understanding of data linkage

Q.5 I am now interested to know how you found out about data linkage. Did you find out about data linkage from:

[CIRCLE ANSWER]

The letter and information sheet that we sent?	Yes_1	No_2	DK_98	REF_99
The website suggested in the information sheet that we sent?	Yes_1	No_2	DK_98	REF_99
Another website on the internet?	Yes_1	No_2	DK_98	REF_99
Newspaper, books, magazines, TV or radio (i.e. any media)?	Yes_1	No_2	DK_98	REF_99
Other?	Yes_1	No_2	DK_98	REF_99

(Other, PLEASE SPECIFY) .....

.....

.....

Q.6 In this data linkage study, we would like to link together two sources of information about your baby's health. I will give you some options to choose from, and get you to pick the <u>two</u> that you think it is that we would like to link together. <u>So pick two</u>. The options are: [READ OUT OPTIONS, AND CIRCLE ONLY TWO. IF MORE THAN TWO OPTIONS MENTIONED, ASK THE PARENT TO IDENTIFY THE TWO THAT THEY THINK ARE THE MOST LIKELY OPTIONS.]

Vaccination records	1
Medication records	2
Birth records	3
Visits of your baby to hospital	4
Visits of your baby to a GP	5
Visits of your baby to a Child and Youth Health clinic	6
(Don't know)	98
(Refused)	99

Would you like me to read out the options again? [RECORD THE NUMBER OF TIMES READ OUT] ....

Reason for consent decision

>For 'Active Consent' (**returned opt-in Study Form**)<

7a. You returned the Study Form, which means that we will be able to join your baby's vaccine and hospital records together. Can you give me a reason why you returned the form?

>For 'Passive Decline' (**did not return opt-in Study Form**)<

7b. You didn't return the Study Form, which means that we won't be able to join your baby's vaccine and hospital records together. Can you give me the reason why you didn't return the form?

>For 'Passive Consent' (**did not return opt-out Study Form**)<

7c. You didn't return the Study Form, which means that we will be able to join your baby's vaccine and hospital records together. Can you give me the reason why you didn't return the form?

>For 'Active Decline' (**returned opt-out Study Form**)<

7d. You returned the Study Form, which means that we won't be able to join your baby's vaccine and hospital records together. Can you give me the reason why you returned the form?

[PROBE IF NECESSARY, e.g. 'Can you think of any reason at all?']

(PLEASE SPECIFY).....

.....

.....

.....

.....

(Don't know) 98

(Refused) 99

Preference for consent

[IF THE PARENT HAS SAID THAT THEY DO NOT INTEND TO VACCINATE THEIR BABY, ASK THEM TO ANSWER THE FOLLOWING QUESTION HYPOTHETICALLY, AS IF THEY WERE GOING TO VACCINATE].

Q.8 We asked to join together your baby's vaccination records with any visits of your baby to hospital. Before your baby's records are linked, your baby's name and home address will be replaced by a unique number, which means that the researchers who look at the linked records will not be able to identify your baby.

Which of the following four statements best matches how you feel about your baby's health information being used for checking the safety of vaccines?

Your baby's health information should not be used at all	1	(Go to Q17)
The researchers should get your consent first.....	2	(Go to 'frequency of permission' Q9)
You would like to know this study is being done and you have the option to say 'no' to your baby being in it.....	3	(Go to 'opt-out' Q11)
I do not need to know about the study, just use the information	4	(Go to Q12)
(Parent insists it depends, PLEASE SPECIFY)	5	(Go to Q12)
.....		
.....		
.....		
(Don't know)	98	(Go to Q17)
(Refused)	99	(Go to Q17)

>frequency of permission<

Q.9 Would you like to be asked for your consent every time before your baby's health information is used, or just once, or would you prefer to give your general consent and be re-contacted from time-to-time?

Ask every time.....	1	(Go to Q12)
Ask once	2	(Go to Q12)
Get general consent and re-contacted.....	3	(Go to 'frequency of contact' Q10)
(Don't know)	98	(Go to Q12)
(Refused)	99	(Go to Q12)

>frequency of contact<

Q.10 Would you want to be re-contacted every year, about once every five years, or some other time period?

Every year	1	(Go to Q12)
Once every five years	2	(Go to Q12)
Some other time period (PLEASE SPECIFY)	3	(Go to Q12)
.....		
.....		
(Don't know)	98	(Go to Q12)
(Refused)	99	(Go to Q12)

>opt-out<

Q.11 When you are being informed that the data linkage study is being done, how important is it to have the option to say 'no' to your baby's health information being used: would you say it is very important, somewhat important, not too important, or not at all important?

Very important	1	(Go to Q12)
Somewhat important	2	(Go to Q12)
Not too important	3	(Go to Q12)
Not at all important	4	(Go to Q12)
(Don't know)	98	(Go to Q12)
(Refused)	99	(Go to Q12)

Preference for consent in relation to a contextual framework

Q.12 The Australian government has a set amount of money put aside for health and medical research. Spending money on one activity means there is less to spend on other things. I will read you two statements which describe different ways that time and money could be spent. With which statement do you most agree? If you cannot choose, just say so.

Asking parents for consent to link their baby's health information is more important than being able to perform quick, extensive and up-to-date checks on the safety of vaccines	1	(Go to Q13)
OR Being able to perform quick, extensive and up-to-date checks on the safety of vaccines is more important than asking parents for consent to link their baby's health information	2	(Go to Q13)
(Cannot choose)	3	(Go to Q13)
(Don't know)	98	(Go to Q13)
(Refused)	99	(Go to Q13)

Q.13 Now that I have told you about how money can be spent in health and medical research, I am going to ask you a repeat question. In this data linkage study, which of the following four statements best matches how you feel about your baby's health information being used for checking the safety of vaccines?

Your baby's health information should not be used at all	1	(Go to Q17)
The researchers should get your consent first	2	(Go to 'frequency of permission' Q14)
You would like to know this study is being done and you have the option to say 'no' to your baby being in it	3	(Go to 'opt-out' Q16)
I do not need to know about the study, just use the information	4	(Go to Q17)
(Parent insists it depends, PLEASE SPECIFY)	5	(Go to Q17)
.....		
(Don't know)	98	(Go to Q17)
(Refused)	99	(Go to Q17)

>frequency of permission<

Q.14 Would you like to be asked for your consent every time before your baby's health information is used, or just once, or would you prefer to give your general consent and be re-contacted from time-to-time?

Ask every time	1	(Go to Q17)
Ask once	2	(Go to Q17)
Get general consent and re-contacted	3	(Go to 'frequency of contact' Q15)
(Don't know)	98	(Go to Q17)
(Refused)	99	(Go to Q17)

>frequency of contact<

Q.15 Would you want to be re-contacted every year, about once every five years, or some other time period?

Every year	1	(Go to Q17)
Once every five years	2	(Go to Q17)
Some other time period (PLEASE SPECIFY)	3	(Go to Q17)
.....		
.....		
(Don't know)	98	(Go to Q17)
(Refused)	99	(Go to Q17)

>opt-out<

Q.16 When you are being informed that the data linkage study is being done, how important is it to have the option to say 'no' to your baby's health information being used: would you say it is very important, somewhat important, not too important, or not at all important?

Very important	1	(Go to Q17)
Somewhat important	2	(Go to Q17)
Not too important	3	(Go to Q17)
Not at all important	4	(Go to Q17)
(Don't know)	98	(Go to Q17)
(Refused)	99	(Go to Q17)

Parental concerns about data linkage, vaccine safety and vaccine effectiveness

Q.17 The usual measures for security in data linkage are replacing a person's name and home address with a unique number and storing any personal information in a secure place. How confident are you that this will protect a person's identity? Would you say you are very confident, somewhat confident, not too confident or not at all confident?

Very confident	1	(Go to Q18)
Somewhat confident	2	(Go to Q18)
Not too confident	2	(Go to Q18) [FLAG FOR Q19]
Not at all confident	4	(Go to Q18) [FLAG FOR Q19]
(Don't know)	98	(Go to Q18)
(Refused)	99	(Go to Q18)

Q.18 How concerned are you that a vaccination for your baby might not be safe and might cause a serious reaction? Would you say you are very concerned, somewhat concerned, not too concerned or not at all concerned?

Very concerned	1	(Go to Q19) [FLAG FOR Q19]
Somewhat concerned	2	(Go to Q19) [FLAG FOR Q19]
Not too concerned	3	(Go to Q20)
Not at all concerned	4	(Go to Q20)
(Don't know)	98	(Go to Q20)
(Refused)	99	(Go to Q20)

Q.19 [IF PARENT ANSWERS 'NOT TOO CONFIDENT', OR 'NOT AT ALL CONFIDENT' TO Q17 AND 'VERY CONCERNED', OR 'SOMEWHAT CONCERNED' TO Q18 (i.e. FLAGGED TWICE), THEN ASK. **'You have expressed some concerns about privacy protection in data linkage studies and also about vaccine safety. Which of your concerns is greater — concern about privacy protection or concern about vaccine safety?']**

More concerned about privacy protection	1	(Go to Q20)
More concerned about vaccine safety	2	(Go to Q20)
Equally concerned about privacy protection & vaccine safety	3	(Go to Q20)
(Parent insists it depends, PLEASE SPECIFY)	4	(Go to Q20)
.....		
.....		
(Don't know)	98	(Go to Q20)
(Refused)	99	(Go to Q20)

Vaccination information

Q.20 The following questions ask about vaccinations of your baby. Has your baby ever received a vaccination?

Yes	1	(Go to Q22)
No	2	(Go to Q21)
(Don't know)	98	(Go to Q22)
(Refused)	99	(Go to Q25)

Q.21 Do you intend to get your baby vaccinated at all?

Yes	1	(Go to Q25)
No	2	(Go to Q25)
(Don't know)	98	(Go to Q25)
(Refused)	99	(Go to Q25)

Q.22 Do you have the Blue Book (child's Personal Health Record book) to refer to for the dates*?* [READ IF NECESSARY, 'I will be happy to wait while you go get it'.]

Yes	1	(Go to Q23) (For those who can't find it, SKIP TO Q24)
No	2	(Go to Q24)
(Don't know)	2	(Go to Q24)
(Refused)	2	(Go to Q24)

Q.23a–23e It's on page 77 if you have the old book, or page 72 in the new book [PAUSE].
Q.24a–24e That's fine. Let's see if you can remember.

Has your baby received a: [READ OUT EACH VACCINE, IF YES, THEN FOR EACH VACCINE ASK, **When was the vaccine was given? [**IF THE DATE IS NOT RECORDED OR KNOWN, WRITE 99/99/99]

(CIRCLE ANSWER)

- Hepatitis B vaccine usually given by 7 days of age.
  It is sometimes called HB-Vax II.....Yes_1 No_2 DK_98 REF_99
  IF YES, Date_ _ / _ _ / _ _
- Combination vaccine usually given at 2 months of age.
  It is sometimes called Infanrix hexa or hexavalent vaccine
  [IF STILL UNSURE, 'It consists of DTPa[1]/IPV[2]/Hib[3]/Hep B']
  .....Yes_1 No_2 DK_98 REF_99
  IF YES, Date_ _ / _ _ / _ _
- Pneumococcal conjugate vaccine[4] usually given at
  2 months of age. It is sometimes called Prevenar .....Yes_1 No_2 DK_98 REF_99
  IF YES, Date_ _ / _ _ / _ _
- Oral rotavirus vaccine usually given at 2 months of age.
  It is sometimes called RotaTeq .....Yes_1 No_2 DK_98 REF_99
  IF YES, Date_ _ / _ _ / _ _
- Has your baby received any other vaccinations that are listed
  in the vaccine booklet that I have not asked about? .....Yes_1 No_2 DK_98 REF_99
  IF YES, PLEASE SPECIFY.....Date_ _ / _ _ / _ _
  IF YES, PLEASE SPECIFY.....Date_ _ / _ _ / _ _

[1] D-T-P-a is the vaccine against diphtheria, tetanus and whooping cough (or pertussis) — it is also known as D-T-P or D-T-a-P vaccine.
[2] I-P-V is the inactivated poliomyelitis vaccine. It is a vaccine against polio.
[3] H-i-b is the haemophilus influenzae type B vaccine. It is a vaccine against bacteria that cause meningitis.
[4] The pneumococcal conjugate vaccine is also known as 7-valent P-C-V. It is a vaccine against bacteria that cause ear infections, blood infections, meningitis and pneumonia.

Hospital visits (for all conditions)

Q.25 Apart from birth, has your baby been admitted to a hospital ward for any reason?

Yes	1	(Go to Q26)
No	2	(Go to Q27)
(Don't know)	98	(Go to Q27)
(Refused)	99	(Go to Q27)

Q.26a–26c [ASK THE FOLLOWING DETAILS ABOUT EACH ADMISSION TO HOSPITAL, STARTING WITH THE MOST RECENT AND WORKING BACKWARDS]

Name of hospital .....

Date of admission _ _ / _ _ / _ _ ..... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Reason(s) for admission (diagnosis) .....

[IF 'YES' TO Q20, THAT IS, BABY WAS VACCINATED, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

Name of hospital .....

Date of admission _ _ / _ _ / _ _ ..... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Reason(s) for admission (diagnosis) .....

[IF 'YES' TO Q20, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

Name of hospital .....

Date of admission _ _ / _ _ / _ _ ..... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Reason(s) for admission (diagnosis) .....

[IF 'YES' TO Q20, 'Do you think your baby's condition was caused by vaccination?'

Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

Emergency dept visits (for all conditions)

Q.27 What about an Emergency Department?

Yes	1	(Go to Q28)
No	2	(Go to Q29)
(Don't know)	98	(Go to Q29)
(Refused)	99	(Go to Q29)

Q.28a–28c [ASK THE FOLLOWING DETAILS ABOUT EACH VISIT TO AN EMERGENCY DEPT, STARTING WITH THE MOST RECENT AND WORKING BACKWARDS]

Name of hospital .....

Date of visit _ _ / _ _ / _ _ ..... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Reason(s) for visit .....

[IF 'YES' TO Q20, THAT IS, BABY WAS VACCINATED, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

Name of hospital .....

Date of visit _ _ / _ _ / _ _ ..... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Reason(s) for visit .....

[IF 'YES' TO Q20, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

Name of hospital .....

Date of visit _ _ / _ _ / _ _ ..... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Reason(s) for visit .....

[IF 'YES' TO Q20, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

Suspected minor adverse reactions to vaccines

Q.29 Has your baby been unwell, but it was not serious enough for them to go to hospital?

Yes..1 (Go to Q.30)
No..2 (Go to Q.31)
(Don't know)..98 (Go to Q.31)
(Refused)..99 (Go to Q.31)

Q.30a–30c [ASK THE FOLLOWING DETAILS ABOUT EACH CONDITION, STARTING WITH THE MOST RECENT AND WORKING BACKWARDS]

What were the symptoms? ....

Date it occurred _ _ / _ _ / _ _ .... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Did you go to a GP? YES_1 / NO_2 / DK_98 / REF_99 (CIRCLE ANSWER)

[IF 'YES' TO Q20, THAT IS, BABY WAS VACCINATED, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

What were the symptoms? ....

Date it occurred _ _ / _ _ / _ _ .... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Did you go to a GP? YES_1 / NO_2 / DK_98 / REF_99 (CIRCLE ANSWER)

[IF 'YES' TO Q20, THAT IS, BABY WAS VACCINATED, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

What were the symptoms? ....

Date it occurred _ _ / _ _ / _ _ .... [IF NOT KNOWN, THEN APPROX AGE IN WEEKS]

Did you go to a GP? YES_1 / NO_2 / DK_98 / REF_99 (CIRCLE ANSWER)

[IF 'YES' TO Q20, THAT IS, BABY WAS VACCINATED, 'Do you think your baby's condition was caused by vaccination?' Yes_1 / No_2 / DK_98 / REF_99 (CIRCLE ANSWER)]

DEMOGRAPHICS

Finally, I am now going to ask you some questions about you and your household and your answers will be kept confidential. If I ask a question that you would prefer not to answer, just let me know and we will skip it.

Q.31 Is this your first baby? Yes.....1
No.....2
(Don't know).....98
(Refused).....99

Q.32 Including yourself and your baby, how many people live in your household?

. .....people
(Refused).....99 (GO TO Q.34)

Q.33A–D

A. **I'd like to ask a few details about each person in the house. Let's start with the oldest.** (ASK FOR EACH PERSON FROM OLDEST TO YOUNGEST): **How old (<u>was that person /were you</u>) on (<u>his/her/your</u>) last birthday?**) (RECORD AGE BELOW AND ASK B–C)	B. ASK FOR EACH PERSON: **What is their relationship to the baby?** (IF PARENT OR SIBLING, CHECK IF IT IS A BIOLOGICAL OR STEP-RELATION) (IF IT IS THE BABY, WRITE 'BABY') (PROBE: Have we missed anyone? – yourself or the baby, or someone who lives here but is away right now)	C. CODE GENDER FOR EACH PERSON	
		M	F
		1	2
		1	2
		1	2
		1	2
		1	2
		1	2
		1	2
		1	2
		1	2
		1	2
		1	2

Q.34 What is your marital status? Are you…

Married or in a *de facto* relationship.....1
Widowed.....2
Separated or divorced.....3
Never married.....4
Other.....5
(Refused).....99

Q.35 In what country were you born?

Australia.....1
Other, PLEASE SPECIFY.....
(Refused).....99

Q.36 What is the main language spoken in your home? [MARK ONE RESPONSE ONLY, IF MORE THAN ONE LANGUAGE, ASK WHICH ONE IS SPOKEN MOST OFTEN.]

English 1
Chinese/Mandarin/Cantonese 2
Greek 3
Italian 4
German 5
Arabic (including Lebanese) 6
Vietnamese 7
Japanese 8
Korean 9
Indian (e.g. Hindi, Urdu) 10
Indonesion/Bahasa 11
Aboriginal language (e.g. Kuarna) 12
Other, PLEASE SPECIFY .....
(Refused) 99

Q.37 What is the highest year of schooling that you completed? [2006 Census]

Never attended school 1
Year 8 or below 2
Year 9 or equivalent 3
Year 10 or equivalent 4
Year 11 or equivalent 5
Year 12 or equivalent 6
(Refused) 99

Q.38 Have you completed any further education? [2006 Census]

No 1
Diploma/Certificate at a TAFE college or similar (includes trades) 2
University degree (Diploma, Bachelor, Honours) 3
Postgraduate degree (Grad Diploma/Grad Certificate, Masters, PhD) 4
(Refused) 99

Q.39 I would now like to ask you about your total family income last year in 2008. I will read out four broad income categories; tell me which one your family slots into. It is income from all sources, before tax, includes government family benefit payments. I can read out the categories as income per week or income per year. Which one do you prefer? [READ CHOSEN OPTION]

	Per week	Per year	[2006 Census]
A…..	Less than $400	Less than $20,800	
B…..	$400–$799	$20,800–$41,599	
C…..	$800–$1599	$41,600–$83,199	
D…..	$1600 or more	$83,200 or more	
E…..Prefer not to answer			

Q.40 And the last question, are you willing to be interviewed later this year for additional research on data linkage being conducted under the supervision of Dr Mike Gold?

Yes 1
No 2

That's all I need to ask you. Thank you for your help. Just in case you missed it my name is (name) and I am calling on behalf of Dr Mike Gold from the Women's and Children's Hospital.

Appendix 7 Preliminary results distributed to parents

13 April 2010

<mothertitle> <motherfirstname> <mothersurname>
<motheraddressline1>
<mothersuburb> <motherstate> <motherpostcode>

Women's & Children's Hospital

Postal address:
VALiD Study
Discipline of Paediatrics
Clarence Rieger Building
Women's and Children's Hospital
Reply Paid 60836
NORTH ADELAIDE SA 5006

Dear Parent(s),
This letter is to thank you for participating in the **Vaccine Data Linkage Study** conducted by researchers at the Women's and Children's Hospital and the University of Adelaide. You may remember that late last year we asked for your permission to link your baby's vaccination records with any hospital visits that occurred in the month after they received their vaccinations. Our purpose was to investigate a new way of checking for rare reactions to vaccines by looking at large numbers of children. This new method is called data linkage.

One of our researchers contacted you when your baby was about 10 weeks of age and invited you to take part in a telephone interview to find out your views on the safety of vaccines, what you thought about data linkage, and whether you thought consent is necessary for data linkage. You were also asked about your experiences in relation to vaccinating your baby, and if your baby had been admitted to hospital, visited an emergency department, or had any minor illnesses since birth. We would like to thank you sincerely for your time and goodwill in answering these questions; the answers you gave are very valuable to us.

You may be interested to know about the preliminary findings from this research. We have enclosed a summary. Your views on data linkage and vaccination will be used to guide the way in which data linkage is developed and used in Australia for checking the ongoing safety of vaccines. If you have any further queries about the findings, please call Katherine Duszynski on (08) 8161 7244 or email valid.study@adelaide.edu.au.

Sincerely,

Dr Mike Gold
Discipline of Paediatrics
Women's and Children's Hospital & the University of Adelaide

Government of South Australia
SA Health

CHILDREN, YOUTH & WOMEN'S HEALTH SERVICE (CYWHS)

PRELIMINARY FINDINGS

Vaccine Data Linkage Study

Scientific title: Vaccine Assessment using Linked Data (VALiD)

Researchers: Dr Michael Gold, Professor Annette Braunack-Mayer, Professor Philip Ryan, Ms Katherine Duszynski, Ms Jesia Berry, and Ms Vicki Xafis.

What was the study about?

The purpose of the study was to find out parental views on the safety of vaccines, and the acceptability of using data linkage to check for rare reactions to vaccines.

The study was conducted as a randomised controlled trial; the people taking part were randomly assigned (like tossing a coin) to one of two groups. The aim was to compare two ways of asking for consent to data linkage:

1. **opt-in consent**, where parents returned a reply form to be included in the study, and
2. **opt-out consent**, where parents were automatically included unless they returned a reply form indicating an unwillingness to participate.

We wanted to see how many parents would opt-in or opt-out of the study, if parents thought consent was necessary for data linkage, and, if so, which consent option was preferred. Parents were not informed that the study was a randomised controlled trial, in case it influenced their likelihood of returning the reply form.

There were two parts to the study:

1. We asked your permission to link your baby's vaccination records with any hospital visits that occurred after the 2 month vaccinations. This allowed us to use data linkage to check for rare reactions to vaccines.
2. Later, a researcher contacted you for a telephone interview to find out your views about data linkage and vaccination.

The preliminary findings below do not include results from the data linkage itself, as the technical aspects of the data linkage process are still undergoing further development. Only the results from the interview are presented.

How many parents gave consent to data linkage?

- 1,129 parents participated in the study: half were able to opt-in to the data linkage study and half were able to opt-out.
- Participation was low in the opt-in group with only 120 of the 564 parents (21%) consenting to data linkage compared with 96% in the opt-out group.
- Only 25 or 4% of 565 parents in the opt-out group elected to opt-out.
- 925 parents (82%) fully completed the interview. Parental opinions about vaccine safety, data linkage and consent preferences were similar in the opt-in and opt-out group, so the results from both groups are combined and presented below.

What did parents think about vaccination and its safety?

- 869 or 94% of parents indicated their baby had received at least one vaccine by 10 weeks of age.
- Most parents viewed vaccination favourably; 76% *strongly agreed* and 21% *agreed* that it was important to vaccinate children to prevent diseases such as polio, whooping cough and chicken-pox.
- However, the majority of parents tended to say vaccines were *safe* (55%) rather than *very safe* (35%). The remainder said they *didn't know* (7%) or thought vaccines were *unsafe* or *very unsafe* (3%).
- Many parents were either *very concerne*d (25%) or *somewhat concerned* (37%) that their baby would experience a serious reaction.
- Over a third of parents were *very concerned* (18%) or *somewhat concerned* (23%) that a vaccination would not be effective in preventing their baby getting the disease.

How many parents reported that their baby had a reaction to a vaccine?

Hospital Admissions

- 37 or 4% of parents reported that their baby had been admitted to hospital in the 10 weeks after birth.
- Most common reasons for admission were reflux, vomiting, failure to thrive, cold and flu-like symptoms, and jaundice.
- Only one parent thought that their baby's condition was caused by vaccination.

Emergency Department visits

- Visits of their baby to an emergency department were reported by 104 or 11% of parents.
- Most common reasons for visits were for reflux, vomiting, diarrhoea, constipation, cold and flu-like symptoms, failure to thrive, and falls.
- Again, only one of these parents thought that their baby's condition was caused by vaccination.

Minor Illnesses

- Minor illnesses that did not require a visit to hospital were reported by 255 or 28% of parents — the most common illnesses were cold and flu-like symptoms, reflux, vomiting, diarrhoea and constipation.
- 84 or 9% of parents thought that their baby's minor illness was caused by vaccination. The most common illnesses thought to be vaccine-related were fever, diarrhoea, crying, irritability, cold and flu-like symptoms, rashes, swelling and lumps at the injection site.

What did parents think of data linkage?

- Only 23 or 2% of parents thought that their baby's health information should not be used at all for data linkage.
- Two-thirds of parents indicated they wanted to be asked for consent for data linkage; 42% preferred opt-out consent; and 24% preferred opt-in consent.
- About 30% indicated consent was not necessary.
- Almost every parent *strongly agreed* (79%) or *agreed* (20%) that it was important to check the safety of vaccines given to Australian children.
- The majority of parents were *very confident* (29%) or *somewhat confident* (55%) that the security measures in data linkage were adequate to protect a person's identity. The remainder were *not too confident* (11%), *not at all confident* (1%), or *didn't know* (4%).

Parents were told that the Australian Government has a set amount of money put aside for health and medical research and spending money on one activity meant there was less to spend on other things. They were then asked to indicate which one of two statements they most agreed with.

Sixty-two per cent stated that it was more important to be able to perform quick, extensive and up-to-date checks on the safety of vaccines than it was to ask parents for consent to link their baby's information; 21% stated the opposite; 12% could not choose or didn't know. The question was not applicable to 5% of the parents.

What are the implications of this study?

Many parents were worried that their baby would experience a serious reaction to a vaccine, but only two acute serious illnesses were thought to be vaccine-related. Minor illnesses that may have been caused by vaccination were more common; about 1 in 10 parents reported these.

This study evaluated how many parents chose to participate or not participate in data linkage, and how many thought consent was necessary for data linkage. The following conclusions were made:

- The majority of parents would like to be asked for consent for data linkage, but more favoured opt-out consent than opt-in consent.
- Due to low participation, opt-in consent is not a feasible way of asking for consent for data linkage.
- Opt-out consent is a more representative and less burdensome alternative to opt-in consent that still provides parents with a choice.

We thank you kindly for your assistance and participation in this study.

Appendix 8 Health Monitor survey 2011 — March

HM Survey
[2011 – March]

INTRODUCTION

Good ..... My name is ..... I'm calling on behalf of The University of Adelaide. We are conducting a survey on a range of health issues. We recently sent you a letter about the survey on behalf of the University. Did you receive the letter?

(Single response)

1. Yes
2. No
3. Don't know

Interviewer note: If respondent did not receive letter, offer to read the following: '**The survey will be conducted by The University of Adelaide, on behalf of organisations interested in public health issues. This particular survey will address a number of topics relevant to the health of the South Australians. The feedback that you provide will help us to improve the health of South Australians and inform planning of services in our community**.'

Intro1 Records prior to survey are randomly allocated into three aged groups:

1. 16 to 24 years Go to Intro2A
2. 25 to 34 years Go to Intro2B
3. 35 to 44 years Go to Intro2C

Intro2A To ensure that we get a good representation of the community, could you please tell me if there is anyone in your household aged <u>between 18 to 24 years</u>.

(Single Response)

1. Yes Go to Intro4A
2. No / Not stated Go to Intro3

Intro2B To ensure that we get a good representation of the community can you please tell me if there is anyone in your household who is aged <u>between 25 to 34 years</u>.

(Single Response)

1. Yes Go to Intro4B
2. No / Not stated Go to Intro3

Intro2C To ensure that we get a good representation of the community can you please tell me if there is anyone in your household who is aged <u>between 35 to 44 years</u>.

(Single Response)

1. Yes Go to Intro4C
2. No / Not stated Go to Intro3

Intro3 Since there is no-one in this age group, can I please speak to the person in the household who was the last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Intro4A Can I please speak to the person aged between 18 and 24 years in the household who was last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Intro4B Can I please speak to the person aged between 25 and 34 years in the household who was last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Intro4C Can I please speak to the person aged between 35 and 44 years in the household who was last to have a birthday.

(Interviewer note: some of the questions are only asked of people in certain age groups.)

Sequence guide: go to A1

Your phone number has been selected randomly from all telephone listings in the State.
I can assure you that all information given will remain confidential. The answers from all people interviewed will be gathered together and presented in a report.
No individual answers will be passed on.
The questionnaire will take approximately 15 minutes to complete, but may take longer depending on the number of questions that are relevant to you.
Whilst your input to the survey is very important to us, participation is voluntary and you can choose not to answer any particular question or any section. You are free to withdraw from the survey at any time.
Please be aware that this phone call may be listened to by my Supervisor for quality control and training purposes.

A. DEMOGRAPHICS SCREEN

As some of the next questions relate to certain groups of people only, could you please tell me…

A.1 How old you are?

(Single Response. *Interviewer note enter 998 Don't know, 999 refused*)

1. Enter age
2. Not stated
3. Don't know

Sequence Guide: If A1 <998 Go to A3

A.2 Which age group are you in? Would it be...

(Read options, single response)

1. 18 to 24 years
2. 25 to 34 years
3. 35 to 44 years
4. 45 to 54 years
5. 55 to 64 years
6. 65 years and over
7. Refused (End interview)

A.3 Voice (ask if unsure)

(Single response)

1. Male
2. Female

A.4 Including yourself, how many people aged 18 years and over live in this household?

(Single response. *Enter number of people 18 years and over.*)

1. Enter number
2. Not stated [999]

A.5 How many children under 18 years live in your household?

(Single Response. *Enter number of people under 18 years. Enter 0 if none.*)

1. Enter number
2. Not stated [999]

A.6 What is your postcode?

(Single response. *Enter 5999 if postcode is not known.*)

1. Enter number
2. Not stated [5999]

Sequence Guide: If A.6 ≠ 5999 Go to NS

A.7 What town or suburb do you live in?

(Single Response. *Enter town/suburb*)

1. Enter town/suburb

A. VACCINE SAFETY & EFFECTIVENESS

[Discipline of Paediatrics, CYWHS]

The next few questions are about the vaccination of children in Australia.

B.1 In general, how safe would you say the vaccines given to children are?
(Single response)
1. Very safe
2. Safe
3. Unsafe
4. Very unsafe
5. Don't know/ Can't say
6. Refusal

B.2 How concerned are you that a vaccine given to children might not work and they might still get the disease?
(Single response)
1. Very concerned
2. Somewhat concerned
3. Not too concerned
4. Not at all concerned
5. Don't know/ Can't say
6. Refusal

B.3 How concerned are you that a vaccine given to children might not be safe and might cause a <u>serious reaction</u>? Would you say you are:
(Single response)
1. Very concerned
2. Somewhat concerned
3. Not too concerned
4. Not at all concerned
5. Don't know/ Can't say
6. Refusal

D. CHILDHOOD VACCINATIONS

Sequence Guide: If A.5= 0 or 999, go to NS

D.0 The next few questions ask specifically about vaccinations relating to children in the household. Are you a parent or legal guardian of the children?
(Single response.)
1. Yes
2. No
3. Don't know
4. Refusal

Sequence Guide: If D.0>1 Go to NS

D.1 What is the age of the (next (for 2nd and subsequent children) **) youngest child in the house for whom you are the parent or legal guardian?**
(Single response. Interviewer note: if child is under 13 months, specify months)
1. Specify years _____
2. Specify months_____
3. No other children
4. Don't know
5. Refusal

Sequence Guide: If D.1=3 Go to NS

D.2 Are they male or female?
(Single response)
1. Male
2. Female
3. Refusal

D.3 Is the child up to date with their immunisations, according to the recommended childhood immunisation schedule?
(Single response)
1. Yes
2. No
3. Don't know
4. Refusal

Sequence Guide: If D.3=1 Go to D.1

D.4 Has the child ever received an immunisation?
(Single response)
1. Yes
2. No
3. Don't know
4. Refusal

Go to D.1

E. DATA LINKAGE & VACCINE SAFETY MONITORING

The next few questions are about checking the safety of vaccines using data linkage.

Data linkage matches pieces of information about the child which come from different sources. If a child goes to hospital, the information about their illness can be linked to their vaccination records to see if a vaccination may have caused their illness. Before the linkage occurs, the child's identifying information is removed and replaced with a unique number. This prevents the researchers who look at the linked records from identifying any child.

(*As required***) Imagine you have a child...**

E.1 Which of the following four statements best matches how you feel about your child's health information being used for checking the safety of vaccines?
(Read options. Single response)
1. **Your child's health information should not be used at all**
2. **The researchers should get your consent first**
3. **You would like to know the linkage is being done and you have the option to say 'no'**
4. **I do not need to know about the linkage, just use the information**
5. If respondent insists it depends, Specify _____
6. Don't know
7. Refusal

Sequence guide: If E1 = 1 or >5 Go to E6
If E1 = 3 Go to E4
If E1 = 4,5 Go to E5

E.2 Would you like to be asked for your consent:
(Read options. Single response)
1. **Every time**
2. **Just once**
3. **Get your general consent and be re-contacted from time-to-time**
4. Don't know
5. Refusal

Sequence guide: If E2 = 3 Go to E3
Else Go to E5

E.3 Would you want to be re-contacted:
(Read options. Single response)
1. **Every year**
2. **Once every five years**
3. **Some other time period** (Specify)
4. Don't know
5. Refusal

Sequence guide: Go to E5

E.4 How important is it to have the option to say 'no'? Would you say:
(Read options Single response)
1. **Very important**
2. **Somewhat important**
3. **Not too important**
4. **Not at all important**
5. Don't know
6. Refusal

E.5 When money is spent on one health activity, the Australian Government has less to spend on other things. These two statements describe different ways that time and money could be spent. With which statement do you most agree? If you cannot choose just say so.
(Read options. Single response)
1. **<u>Asking parents for consent to link their child's health information</u> is more important than being able to perform quick, extensive and up-to-date checks on the safety of vaccines…OR**
2. **<u>Being able to perform quick, extensive and up-to-date checks on the safety of vaccines</u> is more important than asking parents for consent to link their child's health information.**
3. **Cannot choose**
4. Don't know
5. Refusal

E.6 The usual measures for security in data linkage are to replace a person's name and home address with a unique number and store any personal information in a secure place. How confident are you that this will protect a person's identity? Would you say:
(Read options. Single response)
1. **Very confident**
2. **Somewhat confident**
3. **Not too confident**
4. **Not at all confident**

5. Don't know
6. Refusal

Z. DEMOGRAPHICS

Now to finish with some general questions.

Z.1 Which of the following best describes your current marital status?
(Read options. Single response. *Interviewer note: 'De facto' equals 'Living with partner'*)
1. Married
2. Living with a partner
3. Widowed
4. Divorced
5. Separated
6. Never married
7. Not stated / inadequately described

Z.2 What is your work status?
(Read options if necessary. Single response. *Interviewer note: Self-employed is either full or part time*)
1. Full time employed
2. Part time / casual employment
3. Unemployed
4. Home duties
5. Retired
6. Student
7. Unable to work because of disability / Workcover / invalid
8. Other (specify)

(Sequence guide: If Z.2 = 1 or 2, go to Z.4)

Z.3 Do you receive any of the following pension benefits?
(Read options. Multiple response)
1. Disability Support Pension
2. Unemployment Benefits
3. Sickness Benefits
4. Aged /widow's pension
5. Service or defence/ War widow's/ Repatriation Pension
6. Supporting parents benefit
7. AUSTUDY/student allowance
8. Other (specify)
9. None
10. Refused

Z.4 In which country were you born?
(Single response)
1. Australia
2. Austria
3. Bosnia-Herzegovina
4. Canada
5. China
6. Croatia
7. France
8. Germany
9. Greece
10. Holland/Netherlands
11. Hong Kong
12. Iran
13. Italy
14. Japan
15. Malaysia
16. New Zealand
17. Philippines
18. Poland
19. Slovenia
20. Spain
21. U.K. and Ireland
22. USA
23. Vietnam
24. Former Yugoslav Republic of Macedonia
25. Former Yugoslav Republics of Serbia & Montenegro
26. Other country (specify)
27. Refused

(Sequence guide: If Z.4 = 1, go to Z.6)

Z.5 What year did you arrive in Australia?
(Single response)
1. Enter year
2. Don't know

(Sequence guide: go to Z.7)

Z.6 Are you of Aboriginal or Torres Strait Islander origin?
(Single response)
1. Yes
2. No
3. Refused

Z.7 What is the main language you speak at home?
(Single response)
1. English
2. Cambodian
3. Cantonese
4. Chinese
5. Croatian
6. Dutch
7. Filipino
8. German
9. Greek
10. Italian
11. Polish
12. Serbian
13. Spanish
14. Vietnamese
15. Other (specify)

Z.8 Which best describes the highest educational qualification you have obtained?
(Read options. Single response)
1. Still at school
2. Left school at 16 years or less
3. Left school after age 16
4. Left school after age 16 but still studying
5. Trade / Apprenticeship
6. Certificate / Diploma
7. Bachelor degree or higher
8. Refused

Z.9 The next question is about housing. Is your dwelling ….
(Read options. Single response)
1. Owned or being purchased by the occupants
2. Rented from the Housing Trust
3. Rented privately
4. Retirement village
5. Other (specify)
6. Refused

Z.10 I would now like to ask you about your household's income. We are interested in how income relates to lifestyle and access to health services. Before tax is taken out, which of the following ranges best describes your household's income, from all sources, over the last 12 months?
(Read options. Single response)
1. Up to $12,000
2. $12,001 - $20,000
3. $20,001 - $30,000
4. $30,001 - $40,000
5. $40,001 - $50,000
6. $50,001 - $60,000
7. $60,001 - $80,000
8. $80,001 - $100,000
9. $100,001 - $150,000
10. $150,001 - $200,000
11. More than $200,000
12. Not stated/refused
13. Don't know

That concludes the survey. On behalf of The University of Adelaide, thank you very much for taking part in this survey.

Please record what language this interview was conducted in. (Single response)
1. English
2. Italian
3. Greek
4. Vietnamese
5. Other (specify)

Date of interview
Day of week interview undertaken
Time of day interview undertaken