Exploring the inclusion of women, children and the elderly in clinical trials

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This thesis is dedicated to my Grandmother “Naani” whom I miss every day.

Saba Nabi
Abbreviations

ACSM: Advisory Committee on the Safety of Medicines
ADEC: Australian Drug Evaluation Committee
ADR: Adverse Drug Reaction
ANZCTR: Australia and New Zealand Clinical Trial Registry
ARC: Australia Research Council
ARTG: Australian Register of Therapeutic Goods
AUST: Australian Register
CERN: Collaborative Ependymoma Research Network
CHMP: Committee for Medicinal Products for Human Use
CIOMS: Council for International Organisations of Medical Sciences
CMI: Consumer Medicine Information
COPD: Chronic Obstructive Pulmonary Disease
CRO: Contract Research Organisation
CTAG: Clinical Trials Action Group
CTN: Clinical Trial Notification
CTX: Clinical Trial Exemption
EMA: European Medicines Agency
EU: European Union
FCBP: Females of Childbearing Potential
FDA: Food and Drug Administration, United States
GCP: Good Clinical Practice
GP: General Practitioner
HERC: Human Research Ethics Committee
ICH: International Conference of Harmonisation
ICMJE: International Committee of Medical Journal Editors
IND: Investigational New Drug
IRB: Institutional Review Board
ITT: Intention to Treat
IVD: Intravenous Devices
J&J: Johnson and Johnson
KPMG: Klynveld Peat Main Goerdeler
LHAC: Local Health Advisory Committee
MCWW: Multicultural Council of Wagga Wagga
MLHD: Murrumbidgee Local Health District
MoU: Memorandum of Understanding
NDA: New Drug Application
NEAF: National Ethics Application Form
NHRMC: Australian National Health and Medical Research Council
NICE: National Institute for Clinical Excellence
NIH: National Institute of Health
NSAIDs: Non-steroidal Anti-inflammatory Drugs
NZ: New Zealand
OSAS: Obstructive Sleep Apnoea Syndrome
OTC: Over the Counter
PBAC: Pharmaceutical Benefits Advisory Committee
PBS: Pharmaceutical Benefit Scheme
P&C: Parents and Citizens
PHARMAC: Pharmaceutical Management Agency
PIL: Patient Information Leaflet

PPI: Proton Pump Inhibitor

PREDICT: Participation of the elderly in clinical trials

PTNA: Paediatric Trials Network Australia

QUM: Quality Use of Medicines

R&D: Research and Development

RCT: Randomised Control Trial

SAS: Statistical Analysis System

SOP: Standard Operating Procedure

TGA: Therapeutic Goods Administration

UK: United Kingdom

UMC: Uppsala Monitoring Centre

WHO: World Health Organization
Certificate of Authorship

I, Saba Nabi, student number 11478809, hereby declare that this submission is my own work and to the best of my knowledge and belief, understand that it contains no material previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any other degree or diploma at Charles Sturt University or any other educational institution, except where due acknowledgement is made in the thesis. Any contribution made to the research by colleagues with whom I have worked at Charles Sturt University or elsewhere during my candidature is fully acknowledged.

I agree that this thesis be accessible for the purpose of study and research in accordance with normal conditions established by the Executive Director, Library Services, Charles Sturt University or nominee, for the care, loan and reproduction of thesis, subject to confidentiality provisions as approved by the University.

SABA NABI

Date 5th August 2016
Abstract

Introduction

Before a new medicine is licensed, or an established medicine is used for a new indication and can be marketed for the treatment of a human disease, it must undergo extensive safety, efficacy and formulation testing. Toxicity is first tested in animals, then in humans. Subsequently safety and efficacy is investigated in a series of clinical trials under strictly controlled conditions, first to determine whether the medication is tolerated by humans and then to assess if it actually can treat or stabilise the indicated condition. Finally, the results of these trials are reviewed by national medicine regulatory bodies to consider registration and licencing for use. In Australia, this body is the Therapeutic Goods Administration (TGA).

Aim

The aim of this study was to investigate whether the participation in clinical trials for drug discovery in Australia and New Zealand provides a true representation of the intended populations in which the medication is likely to be used.

Methods

This project was preliminary in nature, and designed as a descriptive research study to evaluate the complex issue concerning inclusion of all population groups in clinical trials and mitigation of the associated risk, rather than exclusion to avoid the consequences of the risk. Evaluation (audit) of research can be used to analyse a system, program or the performance of an organisation. Here, it was used to analyse the data from the Australia and New Zealand Clinical Trial registry (ANZCTR) to better understand the level of participation of the target populations and compare that to the literature. The study hypothesised that there is an intentional under-representation of the elderly, women
and children caused by excluding them during recruitments for clinical trials. It also tested the assumption that the information in the ANZCTR database, public access, would be sufficient to confirm or deny the study hypothesis. The study was conducted through three phases: a literature review, analysis of the ANZCTR public data between 2009 and 2013 and a public-opinion survey. The survey aimed to establish whether the finding from the literature and the ANZCTR data analysis provides a true reflection of the study population feedback.

**Results**

The literature indicated that there is a significant under-representation of women, the elderly and children who are more likely to be intentionally excluded from participation. The ANZCTR records presented challenges, as only four out of 3000 studies had been updated after the end date to include the number of participants who had actually been enrolled. Additionally, reasons for withdrawal from participation were not recorded. There were no significant under-representations of women, the elderly or children found in those four trials.

Finally, out of the 103 participants in the survey, 27.8% of women, 45.5% of the elderly and 17.6% of parents strongly agreed to participate in a clinical trial without having the disease; and 30.6% of women, 33.3% of the elderly and 20.6% of parents agreed to participate even if they were happy with their current treatment. Furthermore, 66.7% of women, 42.4% of the elderly and 35.3% of parents strongly agreed that they would participate if they were not happy with their current treatment. Similarly, 77.8% of women, 51.5% of the elderly and 67.6% of parents strongly agreed to participate if the treatment was their last hope for a cure. Additionally, 58.3% of women, 39.4% of the elderly and 41.2% of parents strongly agreed to participate in a clinical trial if they had the disease the new medicine was treating, and they were offered lifelong health insurance.
which covered any side-effect or damage caused by the tested medicine, whether or not there was another treatment currently working. In comparison, 55.5% of women, 33.3% of the elderly and 47.1% of parents strongly agreed to participate to do the same, but only if there was no other treatment working for them. Finally, 44.5% of women, 18.2% of elders and 64.7% of parents strongly agreed to participate in a clinical trial if they had the disease the new medicine was treating for a payment, regardless of if there was or there was no other treatment working; while 47.2% of women, 45.5% of the elderly and 52.9% of parents strongly agreed to do the same, but only if there were no other treatments working.

Discussion

There was an assumption that the confidential ANZCTR system captured complete data on current clinical trials; however, the data available through the public portal was clearly suboptimal both for the researchers and the public. This study was questioning apparent under-representation of the elderly, women, and children in clinical trials and the reasons for the level of representation. One possible explanation was thought to be a lack of intention by researchers and the industry to include those groups. However, the study concluded that there was insufficient evidence to confirm this explanation and suggested that the problem might be multifactorial. Some under-representation might be due to the exclusion criteria in some studies as required due to specialisation or high risk; however, it appeared that there was a significant element related to participants’ personal choices.

Conclusion

A better insurance cover system is required to assure participants that any damage to their health which might occur during the clinical trials would not cause them financial burden, and that the researchers would take all possible risk mitigation measures before
conducting such trials. Broader communication through the provision of accessible historical data would improve confidence in those invited to participate, that their rights would be protected and they would benefit from their participation—both at an individual and a societal level. Improving the awareness of benefits and risks experienced by the previous participants would provide the public with a better understanding of clinical trials.

**Keywords**

Chapter I – Executive summary

Before a new medicine is marketed for the treatment of a human disease, it has to undergo extensive laboratory and clinical research. Scientists investigate potential new treatments for diseases for many reasons, such as to deal with global or national diseases that have been included in the top health priority areas, to treat rare diseases with no current treatment, and to prevent infectious diseases, etc. New drugs usually aim to benefit the majority, cause no (or least) harm and be cost effective. In this study, it was found that new drugs were tested in clinical trials, firstly in animals in the laboratory setting to test safety and toxicity and then on humans to test their efficacy. The safety and efficacy of the medicine were further investigated in a series of clinical trials, firstly on selected groups of healthy individuals under strictly controlled conditions to determine whether the drug was tolerated in humans, and then to assess its ability to treat the condition and the dose. Finally, the results of these trials were reviewed by the government body responsible for drug approval; in Australia, the Therapeutic Goods Administration (TGA) is the regulatory body for medicinal and medical devices and products.

Chapter 2 of this thesis reviews the literature concerning the area of drug discovery, in a global context. Additionally, it compares different countries’ approaches to licensing drugs, using New Zealand and the United Kingdom as case studies owing to them having similar health systems to that in Australia.

Chapter 3 covers in more detail the development of the study concept through further review of the literature on clinical trials.

Chapter 4 presents the study methodology and design. This project was preliminary in nature, and designed as a descriptive research study to evaluate a complex issue;
‘inclusion of all population groups in clinical trials and mitigating the risk, rather than exclusion to avoid the consequences of the risk’. Evaluation (audit) of research can be used to analyse a system, program or the performance of an organisation. Here, it was used to analyse the data from the ANZCTR to better understand the level of participation of the target populations and to compared this to the literature. The study hypothesised that there was an intentional under-representation of the elderly, women and children caused by excluding them during recruitments for clinical trials. It also tested the assumption that the information in the ANZCTR, publically-accessible database’ would be sufficient to confirm or deny the study hypothesis. The study was conducted through three phases: a literature review, analysis of the ANZCTR public data between 2009 and 2013 and a public-opinion survey. The survey aimed to establish whether the finding from the literature and the ANZCTR data analysis provided a true reflection of the study population feedback.

Chapter 5 consists of three parts: part one provides the results from the literature review, part two provides the results from the ANZCTR public portal data analysis and part three presents the data gathered from the public survey.

Chapter 6 discusses the findings and the limitations of the study and is followed by a conclusion and recommendations in Chapter 7. It is argued that a better insurance cover system is required to assure participants that any damage to their health which might occur during the clinical trials will not cause them financial burden, and that the researchers need to take all possible risk mitigation measures before conducting such trials. Broader communication provision of accessible historical data would improve confidence in those invited to participate, that their rights would be protected. Their participation would provide benefits, both at an individual and a societal level. Improving
the awareness of benefits and risks experienced by previous participants would provide
the public with a better understanding of clinical trials.
Chapter II – Literature review

The structure of the Australian pharmaceutical industry

Historically, the testing of the efficacy of new drugs was a mandatory requirement before such drugs could be licensed. However, testing for safety and toxicity were not standardised until recently. The connection between thalidomide and severe birth defects, in the early 1960s, was one of the main catalysts for nations to establish a research code of ethics and to tightly regulate the licensing process for new drugs (Kelman et al., 2007). It also became clear that some of the already marketed medications needed urgent review and evaluation to correct their indications and contraindications, and assign a teratogenicity category as a corrective approach for appropriate usage (Guah, 2011).

The earliest framework to reshape safety risk management of new medications was developed in part by a stakeholder collaboration through the International Conference on Harmonisation (ICH) and the Council for International Organisations of Medical Sciences (CIOMS), as well as by the formal regulatory guidelines of the Committee for Medicinal Products for Human Use of the European Medicines Agency (CHMP/EMA) and the Food and Drug Administration (FDA) (Tsintis & La Mache, 2004).

The safety testing of medicines placed obligations on all parties — the pharmaceutical innovators, the healthcare professionals and the regulators — to participate in developing guidelines for effective drug safety management and enhanced pharmacovigilance in the life-cycle of drug development (Hartford et al., 2006). A ‘safety specification’ is now in place and constitutes part of the pre-marketing phase during drug registration (Lowman et al., 2011). A ‘pharmacovigilance plan’ is normally developed by sponsors and discussed in detail with regulators prior to approval of medication (Milá Cáceres, 2010).
Pharmaceutical industries foster research in areas such as new drug molecules, new medical devices, new drug delivery methods, generic drugs and devices, over-the-counter (OTC) medicines and devices, complementary medicines, vaccines and many others. Those products are used as consumer self-selected products or prescribed by health practitioners. In Australia, they are classified as: prescription medicines, OTC medicines, complementary medicines, sunscreens, medical devices and intravenous devices (IVDs), blood, tissues and biologicals or other therapeutic goods (Lofgren & de Boer, 2004). According to the Australian National Health and Medical Research Council (NHMRC) and World Health Organization (WHO) (as cited by the NHMRC), a clinical trial is ‘any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes’. For the purposes of this study, reference to pharmaceutical industries will be limited to drug discoveries, new drug registrations and new indications, doses or formulations. Additionally, reference to clinical trials will be limited to those conducted for the purpose of registering newly discovered drugs, new drug indications, new drug doses or new drug formulations. The aims and scope of pharmaceutical industries are global and these industries promise consumers a safe, effective and affordable medicine, which is designed to treat their condition with the least possible side-effects (Lofgren & de Boer, 2004). Australia’s 12.85-billion-dollar pharmaceutical market is the fifth largest in the Asia-Pacific region (Askie, 2011). It has the region’s second highest annual spending on the medicinal industry, after Japan (Spencer, 2005).

The rising cost of medicines has triggered global concern, which has led to countries implementing long- and short-term strategic plans to reduce cost and ensure equitable public access to medicine (Raftery, 2008). All individuals, regardless of age, gender or ethnicity, who take medicines, are subject to potential risks. All drugs have potential
safety concerns, but the level of risk in all cases should not outweigh the benefit (Hartford et al., 2006).

Clinical studies conducted during the development of new medicines are generally designed to prove safety and efficacy under strict conditions (Gill et al., 2010). They are performed on a relatively small sample of healthy subjects during the first phase (Duijnhoven et al., 2013; Gill et al., 2010; Suraj Sudhakar, 2013). In Phase 1, the drug is trialled on a small number of healthy patients to ascertain the therapeutic dose (Ardito, 2012), with the total number of patients exposed to a new drug before its approval being around 20–80. After successful testing on healthy patients, the drug is trialled on sick patients to test its efficacy, which involves testing it in 50–300 participants (Ardito, 2012). If successful, the drug is tested on a much larger number of sick patients in Phase 3 (which ranges from several hundred up to 3000) and an even greater number if the trial enters Phase 4 (up to several thousand) (Figure 1) (Ardito, 2012). This should be the representative of the target population for the medication in question.

The number of patients exposed to a medicine before approval during any clinical trial directly accords with the level of information known about the drug efficacy and adverse effects in populations similar to the one tested (Doran & Henry, 2008). This makes post-marketing testing a very valuable stage of the new drug development journey (Fischer, 2012). It also means that healthcare providers are less equipped on how to manage any side-effects that are not detected in the initial clinical trial samples (Guah, 2011).
Drug development stages

Drug discovery is becoming increasingly complex and challenging (Leufkens et al., 2011). Pharmaceutical industries are required to achieve more specialised or individual-patient targeting drugs at the lowest possible cost. This challenge is also hindered by the cuts in the research funding and the new patenting rules that limit the number of years for which a patent may be held and the limitation on the number of times the patent can be renewed (Doran & Henry, 2008). Innovation patents may be renewed for up to eight years, standard patents may be renewed for up to 20 years and pharmaceutical patents may be renewed for up to 25 years (Doran & Henry, 2008).

The clinical trial can take place at a single or at multiple locations (Ardito, 2012). Bio-statistical analysis determines whether the drug is effective or not (Ardito, 2012). The trial is followed up by patients providing reports concerning adverse drug reactions (post-marketing) (Ardito, 2012).
Figure 2 describes the life-cycle of a new drug from the preclinical to the short-term post-marketing stages in the first 12 months of its license, followed by a long-term post-marketing stage mapping its use even after patency expires (Black et al., 1994). The cycle may take up to 20 years (Black et al., 1994).

Regulatory agencies like the FDA in the USA and TGA in Australia require every drug to undergo testing for efficacy and safety for future human use (Ardito, 2012). Each sponsor of a clinical trial develops a plan known as a protocol that is approved by the regulatory body before the start of the trial (Ardito, 2012). Each detail of the clinical trial, such as the age and gender of participants, exclusion–inclusion criteria, start and end dates, drug strengths, length of the study, dosages and chemical and toxicity testing, is specified in the protocol (Ardito, 2012; Damoiseaux, 2001). The drug is then trialled according to the protocol (Ardito, 2012; Damoiseaux, 2001).
Limited available resources require companies to conduct their research on new agents and be able to cover the cost of research during the patent years (Fiscus, 2009). In recent years the number of new drugs reaching the market has decreased by 20% while research and development (R&D) expenditure has increased by 60% (Fiscus, 2009). Consequently, the cost of bringing a new medicine to the world market has increased drastically (Fiscus, 2009). Additionally, as a specialised equipment cost increases, more researchers are contracted to bigger and better equipped laboratories, which contribute to the additional spending and increase the final product cost (Lowman et al., 2011).

**Funding sources and criteria in the United Kingdom, Australia and New Zealand**

The United Kingdom (UK), Australia and New Zealand (NZ) are three countries that share many similarities in terms of economic development and expenditure on healthcare services, especially on pharmaceuticals (Raftery, 2008). According to the Australian Institute of Health and Welfare (2015), the Australian government spent an average of $2,725 per person during the 2013–2014 financial year. Additionally out of the $54.7 billion spent on primary healthcare (2013–14 financial year), $10.1 billion was spent on subsidising pharmaceuticals (McEwan, 2007).

The appraisal bodies for each of these three nations are the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia and the Pharmaceutical Management Agency (PHARMAC) in NZ (Berger & Grainger, 2010; Gleeson et al., 2013). New drug registration appraisal criteria are varied among the three countries in the area of cost and access; however, there are great similarities in the criteria of safety and efficacy (Berger & Grainger, 2010; Gleeson et al., 2013).
Factors driving pharmaceutical funding decisions

While the provision of health services is different, there are vast similarities between the UK, Australia and NZ in the approval of new medication licensing and registration; each country has occasionally licensed controversial drugs with poor cost-effectiveness due to the local need (Boumil et al., 2010). The MHRA has licensed more controversial medications when compared with Australia and NZ, both of which differ from the UK in their use of ‘reference pricing’ and their concern for the effect of funding allocation on their budgets (Boumil et al., 2010). NZ is slightly more conservative than Australia. Decisions to list drugs are usually made on the basis of economic criteria and the nature of the diseases that the drugs will treat. These decisions play an important role in investing in a drug (Selvarajan et al., 2013).

Australia applies the ‘rule of rescue’ in its drug registration criteria (Gleeson et al., 2013). The ‘rule of rescue’ is a term invented to describe a country’s immediate duty to schedule or list drugs that are essential to treating conditions experienced by a number of citizens and that may otherwise be fatal if not treated (McKie & Richardson, 2003). However, expenditure on medications depends on the funding allocated in the healthcare budget (Martens & Hawamdeh, 2012), which is referred to as the ‘budget impact’ (Raftery, 2008). Table 1 shows criteria used by regulatory agencies for funding new drugs (Gleeson et al., 2013; Raftery, 2008).
Table 1. Criteria used by regulatory agencies for funding new drugs (NICE: National Institute for Clinical Excellence).

<table>
<thead>
<tr>
<th>England (NICE)</th>
<th>Australia (PBAC)</th>
<th>New Zealand (PHARMAC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical effectiveness and cost-effectiveness (cost/QALY)</td>
<td>Clinical effectiveness and cost-effectiveness (cost/QALY)</td>
<td>Clinical effectiveness and cost-effectiveness (cost/QALY)</td>
</tr>
<tr>
<td>Uncertainty</td>
<td>Price of alternative brands or drugs in same therapeutic class</td>
<td>Health needs, including those of Māori and Pacific Islander peoples</td>
</tr>
<tr>
<td>Nature of health conditions</td>
<td>Budget impact</td>
<td>Budget impact</td>
</tr>
<tr>
<td>Innovation of technology</td>
<td>‘Rule of rescue’ (where appropriate)</td>
<td>Cost-effectiveness of drugs versus other interventions</td>
</tr>
<tr>
<td>Wider costs and benefits</td>
<td>Clinical benefits and risks</td>
<td>Direct costs to users</td>
</tr>
<tr>
<td>Precedents</td>
<td></td>
<td>Availability of alternative treatments</td>
</tr>
</tbody>
</table>

Even with small numbers of patients and high costs, drugs for life-threatening diseases such as breast cancer or leukemia (Boumil et al., 2010; Milá Cáceres, 2010) or drugs to alleviate symptoms and delay disease progression in conditions, such as multiple sclerosis and rheumatoid arthritis, have been approved for licensing as it is unethical to decline their licensing due to lack of funding (Scott, 2006). Patient lobbying and public perception plays a pivotal role in allocating the funding for these medicines (Raftery, 2008).

**Evaluation of a new medicine: the TGA’s drug registration life-cycle**

The TGA is a division of the Commonwealth Department of Health and Ageing (Nkeng et al., 2012), which was established to safeguard and enhance the health of the community through the effective regulation of therapeutic medicines (Lofgren & de Boer, 2004). The administration aims to ensure that the community has access to all possible therapeutic advances within a reasonable timeframe (Lofgren & de Boer, 2004).

No medical product is completely free of risk (Loy et al., 2011). Those classified as being of higher risk are classed as prescription medicines (Loy et al., 2011). For prescription medications to be scheduled and marketed in Australia, they have to be...
registered through the Australian Register of Therapeutic Goods (ARTG) and issued with an AUSTR number that must be managed and used in accordance with the Therapeutic Goods Act 1989 (Australia et al., 2001).

Before a prescription medicine is marketed in Australia, the TGA assesses the risks and benefits from the available sources and if, after analysis, the result is considered favorable then the medicine is registered to be used in Australia (Lofgren & de Boer, 2004). Additionally, the TGA assesses medical devices and medicines for export from Australia (Lofgren & de Boer, 2004).

The TGA also regulates the manufacture of therapeutic goods and medical devices to ensure they adhere to manufacturing standards (Henderson et al., 2013). The administration has a team of inspectors that audit manufacturing facilities globally, ensuring that products supplied are of a high standard and quality (Henderson et al., 2013). All therapeutic goods carry some potential risks that may be minor or serious and thus all risk factors are assessed, such as side-effects, potential harm caused by a drug if taken for longer durations, seriousness of the medical conditions of the target patients and the toxicity associated with the drug intended to be used (McEwan, 2007).

In 2009, a policy was put into place to ensure that all prescription medicines have a risk-management plan, which portrays how the potential risks are identified, evaluated, managed and reviewed over time (Kaminsky et al., 2012). The risk-benefit plan assures consumers that the products are safe for their intended use (Kaminsky et al., 2012). There is also a reporting system for adverse events that is constantly monitored by the TGA and, if needed, followed up with appropriate regulatory action (Kaminsky et al., 2012).

The process of evaluating a new prescription drug adopted by TGA is as follows (Umscheid et al., 2011):

- “chemical tests are conducted to describe the composition of the medicine
The new drug file is submitted by the manufacturer or sponsor to the PBAC for evaluation. The PBAC then make number of decisions regarding new medicine registration for distribution in the Australian market and assign a certain drug schedule to it, which determines the type of prescriber and whether the drug will be listed in the pharmaceutical benefit scheme (i.e. the level of government cost subsidy) (King & Green, 2012).

**Post-marketing safety monitoring**

The TGA monitors the safety of medicines (Kummar et al., 2008). It maintains a database for the reporting of adverse effects post-marking, and monitors off-label use where a drug is used outside the conditions to which it was tested in the clinical trials (Kummar et al., 2008). Post-market safety monitoring includes (Kummar et al., 2008):

- identifying and scrutinising safety signals
- communication of information to health professionals, consumers and the public
- the taking of appropriate and justified action, such as suspending or cancelling the registration of a particular medicine, or keeping a check on the population dependent on a particular medication.

The TGA monitors the safety of medicines marketed in Australia by different strategies including risk management plans and adverse reactions reports (Milá Cáceres, 2010).
Risk management plans

Since 2009, all medicine applications must include a risk-management plan designed to define and manage associated risks that may occur over the medicine’s entire life-cycle (Hernando et al., 2006). The TGA may also request additional risk management measures, post-marketing research, more frequent reporting or certain types of data collection if the application is related to a high risk medication or when the population who will use this medication is considered vulnerable (Griffiths, 2011).

A risk-management plan gives an overview of a plan of activities that might be considered to minimise the risks associated with the medicine in the long term (Guah, 2011). Such activities might include providing educational materials and activities for health professionals and consumers, investigating particular risks, filling gaps in knowledge by incorporating further studies or active monitoring for certain adverse effects (Pratt & Loff, 2012).

Adverse reaction reports

Adverse reactions suspected from a medicine or medical device are reported to the TGA (Merle et al., 2005). Pharmaceutical companies, health professionals or consumers can report adverse reactions (Adams, 2010). Reports by consumers and health professionals are voluntary, but it is mandatory for pharmaceutical companies to report any adverse effects they become aware of (Adams, 2010).

The adverse reaction reports are recorded in the database and regularly viewed by the expert committee at the TGA, which comprises both scientific and medical staff (Kelman et al., 2007). The TGA reports are also sent to the WHO database of individual case safety reports (VigiBase), and the TGA uses the data from VigiBase to monitor or
investigate any potential safety concerns associated with medicines registered in Australia (Rahimi & Timpka, 2011).

VigiBase is the most comprehensive and the largest data source in the world and it is developed and maintained by the Uppsala Monitoring Centre (UMC), situated in Uppsala, Sweden on behalf of the WHO (Lindquist, 2008). VigiBase contains useful information about the safety profiles of medicinal products, and can be used by pharmaceutical companies, academia and national regulatory authorities to obtain safety data with global coverage (Lindquist, 2008). The TGA does not provide clinical advice to consumers, but can direct them to the correct drug information services or medical information provided by the manufacturer of the medication in question or to their health provider (Kelman et al., 2007). The TGA encourages consumers and the public to consult a health professional if they think they are experiencing any adverse reactions to a medication (Pritchard & Kenner, 2012). The Quality Use of Medicines (QUM) is one of the main objectives of Australia’s National Medicines Policy, a policy that aims to make the best possible use of medicines to improve health outcomes for all Australians (Smith & McGettigan, 2000). QUM means wise management of medication options, choosing the most suitable medicine for a particular medical condition and using medicines in a safe and effective manner (Smith & McGettigan, 2000).

Some of the actions taken by the TGA in response to safety concerns are as follows (Smith & McGettigan, 2000):

- alerting the public through articles in the TGA publication, Medicines Safety Update and the Australian prescribers, which plays a crucial role in informing health professionals and consumers
- adding warnings, precautions and adverse reaction information to product labels, also called Consumer Medicine Information (CMI); CMI leaflets are
produced by pharmaceutical companies to give detailed information about medicines to consumers

- suspending or cancelling the registration of products or limiting the use of products in the target population
- requiring sponsors to undertake post-marketing studies to investigate safety concerns and to ascertain if more information is needed before a judgement is made regarding further action.

**Evidence-based updates by the TGA**

The TGA constantly reviews published papers on new medications which remain under patent arrangement, which support or reject any aspects of adverse effects, safety and efficacy which were included in the medicine registration file, to ensure vigilance regarding particular medicines and any risks associated with them is maintained (Schaeffer et al., 1996). These medications are known as ‘medicines of interest’ (Schaeffer et al., 1996). Manufacturers then have the responsibility to conduct additional research to confirm or deny any benefit or risks identified from post-marketing reporting by health professionals or consumers (Viergever & Ghersi, 2011).

The increased vigilance by TGA is due to reports of numerous cases of published literature having concerns of inappropriate conduct by investigators and the sponsors of clinical research. Within the past 10 years, studies have been published where required ethics approval had not been obtained, participants were not invited to consent to participate and the investigators had erroneously extrapolated or even fabricated data (Viergever & Ghersi, 2011). Trials with positive results are generally published more frequently than studies that conclude that a new drug poses greater risks or is little more effective than standard therapy or a placebo (Viergever & Ghersi, 2011). Furthermore,
some articles may distort trial findings by omitting important data or by modifying the specified outcome measures (Zarin & Tse, 2008). Lack of access to detailed information about comprehensive clinical trials can undermine the integrity of medical knowledge (Zarin & Tse, 2008). Nonetheless, actual trial registration sometimes falls short of regulatory requirements (Leufkens et al., 2011; Viergever & Ghersi, 2011).

A systematic review conducted in France triggered the mandatory requirement for investigators to register their trials prior to patient recruitment as a precondition of publishing the trial’s findings in member journals (Mathieu et al., 2009). The review included randomised controlled trials (RCT) in three medical areas (cardiology, rheumatology, and gastroenterology), which were indexed in 2008 in ten general medical and specialist journals with the highest impact factors. The French research team obtained the trial registration information by using the standardised data-extraction form (Mathieu et al., 2009). The team reviewed 323 trials and, out of these, 147 (45%) were adequately registered, 89 published reports (27.6%) lacked trial registration, 45 trials (13.9%) were registered after the study was completed, 39 (12%) were registered with no or an unclear description of the primary outcome, and 3 (0.9%) were registered after the completion of the study and provided an unclear description of the primary outcome (Mathieu et al., 2009). Out of the 147 articles with trials that were adequately registered, 31% (46 out of 147) showed some evidence of discrepancies between the outcomes registered and the outcomes published (Mathieu et al., 2009). Current regulatory agencies require registration of sufficient information to ensure accuracy, completeness or reasonable interpretation of the findings (Rodwin & Abramson, 2012). The TGA follows the 1989 Therapeutics Goods Act of Australia and has a number of mechanisms in place to provide information on the regulation of therapeutic goods to consumers, health professionals and stakeholders (Fischer, 2012).
Pharmaceutical industries have an ethical obligation to provide the timely public dissemination of trial data (Fischer, 2012). Under-reporting of data constitutes research misconduct and has very serious consequences, putting patients at risk and wasting healthcare resources (Valkenhoef et al., 2012). The non-publication of studies, whether positive or negative, is perceived by those who have volunteered as a form of deception (Bevan et al., 1993).

The Australian Register of Therapeutic Goods (ARTG) includes details of all the therapeutic goods authorised by the TGA for use in Australia, including public summaries, product information and official certificates, and can be accessed through the TGA website (Palter, 1996).

The role of the Advisory Committee on the Safety of Medicines

The TGA seeks advice from the Advisory Committee on the Safety of Medicines (ACSGOM) to inform decisions about the safety of the medicines (Simons et al., 1992). This committee was formed in January 2010 and comprises experts in pharmaco-epidemiology, pharmacy, clinical medicine and issues related to consumers (Simons et al., 1992). It conducts regular consultations on options to modify existing regulations and procedures in response to the community and their needs, and also in response to medical and technological advancements (Sansom, 2010). ACSGOM advises and makes recommendations to the TGA on the following points (Simons et al., 1992):

- the safety of medicines
- the risk assessment and management of medicines
- the detection, assessment, validation and prevention of adverse effects of medicines.
Role of the Australia New Zealand Clinical Trial Registry

The Australia New Zealand Clinical Trial Registry (ANZCTR) was established in 2005 by the Australian National Health and Medical Research Council (NHMRC), with funding from the NHMRC and New Zealand Health Research Council (Viergever & Ghersi, 2011). The NHMRC raises the standard of individual and public health throughout Australia. It fosters medical research, training and the consideration of ethical issues relating to health. It also funds the ANZCTR (Viergever & Ghersi, 2011).

The ANZCTR is an essential infrastructure facility that takes into consideration the reports and recommendations of the Clinical Trials Action Group (CTAG) (Viergever & Ghersi, 2011). It is a primary registry in the WHO Registry Network and it accepts trials for registration from all countries and for all therapeutic areas, including trials for pharmaceuticals, surgical procedures, preventive measures, lifestyle changes, devices, treatment and rehabilitation strategies and complementary therapies (Stafinski et al., 2011).

The ANZCTR is overseen by an advisory committee with wide representation from a variety of stakeholders including government officials, clinicians, members of the research community, journal editors, pharmaceutical industry regulators and members of the wider community consumers (Viergever & Ghersi, 2011).

There are around 40 clinical trial networks in Australia (Byrnes et al., 2012). These groups are led by senior clinician researchers working in the health system, and they are dedicated to undertaking well-designed clinical trials to provide the type of high quality evidence that would aid in saving or improving lives (Segelov et al., 1992). As the latest report highlights, their work provides cutting-edge care for Australians and shapes new frontiers in clinical medicine on a global scale (Shah et al., 2004).
The purpose of the ANZCTR

The ANZCTR’s primary responsibility is to make all clinical trial data public excluding those relating to patents (Sambharya & Rasheed, 2012). Through the ANZCTR, individuals can discover which clinical trials are taking place in the areas of health — for example, trials relating to new drugs, treatments, therapies, surgical procedures and medical devices (Rodwin & Abramson, 2012).

People who are interested in participating in a clinical trial can access what is perceived to be a reputable and comprehensive online register showing which trials are occurring in particular locations around Australia. Health professionals can also access the site to investigate relevant trials for their patients (Palter, 1996).

The ANZCTR provides valuable insights for researchers, helping them to identify gaps in their own research and preventing the duplication of clinical trials (Nkeng et al., 2012). It provides patients and health professionals with access to information about trials that they may consider worthy of participating in (Rodwin & Abramson, 2012). Patients may participate as volunteers for clinical trials and contribute to knowledge about future treatments that will be made available once the trials are complete (Peterson, 2011).

The benefits of a clinical trials registry

A clinical trial registry increases the efficacy of trials through (Peterson, 2011):

- reducing unnecessary duplication of research efforts
- achieving a higher recruitment rate of clinical trial participants, which increases the chance of a successful outcome for the clinical trial
- timely disclosure of the results of clinical trials
- providing access to better information about various treatment and healthcare.
Information about the trials registered on the ANZCTR is available to the public and is searchable through the website ‘www.anzctr.org.au’ by clicking on the ‘searching for a trial’ button (Wright, 2004). It is also possible to conduct an advanced search, which allows healthcare professionals or the public to access a particular trial that they are interested in (Wright, 2004). However, not all clinical trials being conducted in Australia and NZ are registered on the ANZCTR as clinical trial registration is not currently mandatory (Griffiths, 2011).

All trial information that is published through the registry and on the website, is provided by the registrant/sponsor of each trial. ANZCTR clearly states that it is not responsible for any data inaccuracies as the information is not validated before publication on the website. Hence, it is the responsibility of the consumer to discuss the potential suitability of any new trials or medications with their healthcare professional (Viergever & Ghersi, 2011).

Studies that meet the International Committee of Medical Journal Editors (ICMJE)/WHO 2008 definition of a clinical trial should be registered through the registry and trials should be registered before the actual clinical work takes place (Gill et al., 2010). The clinical trial registry records the main objectives, design features, sample size and recruitment statuses, treatments under investigation, outcomes being assessed, principal investigators and contact details as specific trial information (Flood & Lemmens, 2013). Access to trial information is free for all and is publicly available (Selvarajan et al., 2013b). There is also no charge for registering a trial (Selvarajan et al., 2013b).
The role of clinical trials in the provision of effective health services

Clinical research is an essential component of the healthcare system of any country (Bourgeois, 2008; Brown & Ryan, 2003). It is a driver of quality improvement in the provision of services in more effective, evidence-based ways (Bourgeois, 2008; Brown & Ryan, 2003). It takes on average 12 to 15 years and an investment of between US$800 million to US$1.7 billion to successfully bring to market a new medicinal product; these amounts only account for discovery and up to Phase 4 clinical trials (Boumil et al., 2010; Bourgeois, 2008).

A clinical trial can be a prospective biomedical or behavioural research study that involves human volunteers and is designed to use therapeutic methods, devices or agents that are not yet registered as approved therapies, devices or medicines, to solve or address certain hypotheses and to provide better patient outcomes, in new and different ways than those currently known or employed (Duijnhoven et al., 2013). Clinical trials can also evaluate existing drugs, medical devices, and different types of surgery, as well as different forms of supportive care or any intervention that might impact on health (Duijnhoven et al., 2013). They are a vital link in the chain between new discoveries related to human biology and the actual delivery of effective and efficient health services (Umscheid et al., 2011).

Preclinical studies involve in vitro (i.e. in situ or laboratory) studies and trials on animal (in vivo) populations that determine drug safety in doses equivalent to the estimated exposure levels for human volunteers — considering pharmacodynamics (mechanisms of action and effect of drug) and pharmacokinetics (i.e. drug absorption, distribution, metabolism, excretion, and potential drug–drug interactions) — or greater to determine drug toxicity, teratogenicity and lethality (Pritchard & Kenner, 2012). The submission of preclinical data is helpful in acquiring Investigational New Drug (IND)
approval, which further aids in conducting a clinical trial (Field & Boat, 2010). In general, a clinical trial consists of three different phases with different purposes (Kummar et al., 2008; Umscheid et al., 2011).

Some funding opportunities may also carry the risk of conflict of interest arising from investigators who contribute to clinical trials or rarely receive funding, either directly or indirectly, from sponsors with an interest in the outcome and reporting of these trials (Krimsky & Rothenberg, 1998). The available data collected during post-marketing surveillance demonstrates that industry is the major funder of clinical research in Australia (Bourgeois, 2008). On average, 65% of funds come from biotechnology, pharmaceutical and medical device companies, 10% comes from NHMRC grants, 7% from state governments, 4% from other government sources and 14% from other sources (e.g. charitable organisations, societies, foundations and collaborative groups; Bourgeois, 2008). Moreover, few studies highlight the necessity of industry-sponsored research, which is more common in developed countries (Abbas, 2007).

There should be clear guidelines governing industry-sponsored research in developing countries, similar to those established in developed countries (Alhaqhani & Fidge, 2011).

**Clinical trial phases**

Currently, clinical trials can be divided into five phases (i.e. Phases 0, I, II, III, and IV) depending on the specific conditions and requirements of the researchers. The phases are defined below and listed in Table 2 (Kummar et al., 2008).
Table 2. Different phases of the clinical trial.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Goal</th>
<th>Dosage</th>
<th>Number of participants</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Expedite the clinical evaluation of new molecular entities</td>
<td>Very small sub-therapeutic</td>
<td>10–15</td>
<td>Kummar et al., 2008</td>
</tr>
<tr>
<td>I</td>
<td>Evaluate the drug dose ranging in healthy volunteers</td>
<td>Often sub-therapeutic but with ascending dose</td>
<td>20–80</td>
<td>Ivy et al., 2010</td>
</tr>
<tr>
<td>II</td>
<td>Determine the right dosage along with the effectiveness in treating that particular disease</td>
<td>Therapeutic dose</td>
<td>Several hundreds</td>
<td>Umscheid et al., 2011</td>
</tr>
<tr>
<td>III</td>
<td>Determine optimal doses, dose frequencies, administration routes, and endpoints</td>
<td>Therapeutic dose</td>
<td>From several hundred to several thousands</td>
<td>Umscheid et al., 2011</td>
</tr>
<tr>
<td>IV</td>
<td>Identify less common adverse reactions to drugs and cost and/or drug effectiveness for diseases and populations</td>
<td>Therapeutic dose</td>
<td>Patient seeking treatment</td>
<td>Glasser et al., 2007</td>
</tr>
</tbody>
</table>

Clinical trial statistics

In addition to the fact that clinical trials aim to test therapies that save lives, prevent disabilities and contribute to countries’ economies, it needs a lot of investment and complies to regulatory guidelines (Zarin et al., 2007). The website ClinicalTrials.gov is the largest global trial registry and was established in the US in 2000 (Zarin et al., 2007).

The clinical trial European register (www.clinicaltrialsregister.eu) is also the largest medicinal registry serving the European community, followed by the USA registry (www.ClinicalTrials.gov), and there are smaller local registries in several countries around the world (Faure & Hrynaszkiewicz, 2011). Data suggest that Asian countries, especially India, Malaysia, Thailand, Singapore and China, have become prominent outsourcing locations for clinical research, especially for Phase III clinical trials, while countries such as the US, Canada and the UK undertake mostly Phase I clinical trials (Rahman & Majumder, 2013).

The popularity of Asia for the conducting of clinical trials is attributed to the increasing prevalence of metabolic diseases, such as diabetes mellitus, hypertension and
dyslipidaemia, resulting from changes in dietary patterns and sedentary lifestyles (Diamond, 2011). In 2009, the total number of clinical trials registered in developed countries, represented by the US, the EU and Japan, was 47%, 18% and 11% respectively, while China and India emerged as the largest contributors from Asian countries, contributing 8% and 2.7%, respectively (Selvarajan et al., 2013b) (Figure 3).

![Figure 3](http://www.picronline.org/viewimage.asp?img=PerspectClinRes_2013_4_3_160_115373_f1.jpg)

**Figure 3.** Total clinical trials registered in different countries from 2007 to 2011. Source: Selvarajan et al., 2013b accessed from: http://www.picronline.org/viewimage.asp?img=PerspectClinRes_2013_4_3_160_115373_f1.jpg on 30 July 17.

Diseases with maximum ongoing trials around the world include cancer, diabetes, coronary artery disease, asthma, chronic obstructive pulmonary disease (COPD), epilepsy, hypertension, schizophrenia, heart failure, stroke, HIV, malaria, depression, tuberculosis and osteoporosis, as indicated in Table 3 (Selvarajan et al., 2013a). The table represents the total number of trials registered by different countries during the trial period from 20 July 2007 to 29 August 2011 (Selvarajan et al., 2013b). There were 67,448 trials found across seven study nations (Selvarajan et al., 2013a).
As can be observed from the Clinical Trials Registry, when a comparison was made with infectious disease-related mortality and disability (as defined by the WHO’s Global Burden of Disease Study), five subcategories were chosen for more detailed characterisation: HIV–AIDS, Hepatitis C, lower respiratory tract infections, malaria, and tuberculosis (Selvarajan et al., 2013a).

‘Treatment’ was the primary purpose in the majority of both infectious and non-infectious disease trials (53% and 77%, respectively; Selvarajan et al., 2013a). Moreover, cancer, diabetes and respiratory diseases were the most widely researched areas overall and had great prospects for frequent clinical trials (Selvarajan et al., 2013a).

Table 3. Global distribution of clinical trials by disease state.

<table>
<thead>
<tr>
<th>Trial</th>
<th>US (%)</th>
<th>EU (%)</th>
<th>AUS (%)</th>
<th>China (%)</th>
<th>Canada (%)</th>
<th>Japan (%)</th>
<th>India (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total trials</td>
<td>31698  (100)</td>
<td>9843  (100)</td>
<td>4425 (100)</td>
<td>5111 (100)</td>
<td>5145 (100)</td>
<td>7282 (100)</td>
<td>1826 (100)</td>
</tr>
<tr>
<td>Cancer</td>
<td>8589  (27.10)</td>
<td>1678  (17.05)</td>
<td>518  (11.71)</td>
<td>1039 (20.33)</td>
<td>794  (15.43)</td>
<td>2233 (30.66)</td>
<td>232  (12.71)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1583  (4.99)</td>
<td>544  (5.53)</td>
<td>220  (4.97)</td>
<td>288 (5.63)</td>
<td>258 (5.01)</td>
<td>435 (5.97)</td>
<td>194  (10.62)</td>
</tr>
<tr>
<td>CAD*</td>
<td>527  (1.66)</td>
<td>94  (0.95)</td>
<td>44  (0.99)</td>
<td>100 (1.96)</td>
<td>61 (1.19)</td>
<td>90 (1.24)</td>
<td>59  (3.23)</td>
</tr>
<tr>
<td>Asthma</td>
<td>392  (1.24)</td>
<td>226  (2.30)</td>
<td>57  (1.29)</td>
<td>47 (0.92)</td>
<td>93 (1.81)</td>
<td>118 (1.62)</td>
<td>42  (2.30)</td>
</tr>
<tr>
<td>COPD</td>
<td>264  (0.83)</td>
<td>175  (1.78)</td>
<td>57  (1.29)</td>
<td>51 (1.00)</td>
<td>57 (1.11)</td>
<td>64 (0.88)</td>
<td>39  (2.14)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>167  (0.53)</td>
<td>78  (0.79)</td>
<td>23  (0.52)</td>
<td>16 (0.31)</td>
<td>27 (0.52)</td>
<td>21 (0.29)</td>
<td>33  (1.81)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>641  (2.02)</td>
<td>339  (3.44)</td>
<td>33  (0.75)</td>
<td>84 (1.64)</td>
<td>61 (1.19)</td>
<td>259 (3.56)</td>
<td>30  (1.64)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>303  (0.96)</td>
<td>98  (1.00)</td>
<td>22  (0.50)</td>
<td>77 (1.51)</td>
<td>27 (0.52)</td>
<td>50 (0.69)</td>
<td>27  (1.48)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>347  (1.09)</td>
<td>94  (0.95)</td>
<td>52  (1.18)</td>
<td>55 (1.08)</td>
<td>73 (1.42)</td>
<td>65 (0.89)</td>
<td>20  (1.10)</td>
</tr>
<tr>
<td>Stroke</td>
<td>285  (0.90)</td>
<td>107  (1.09)</td>
<td>63  (1.42)</td>
<td>124 (2.43)</td>
<td>65 (1.26)</td>
<td>62 (0.85)</td>
<td>14  (0.77)</td>
</tr>
<tr>
<td>HIV</td>
<td>789  (2.49)</td>
<td>176  (1.79)</td>
<td>48  (1.08)</td>
<td>42 (0.82)</td>
<td>57 (1.11)</td>
<td>14 (0.19)</td>
<td>14  (0.77)</td>
</tr>
<tr>
<td>Malaria</td>
<td>25  (0.08)</td>
<td>3  (0.03)</td>
<td>6  (0.14)</td>
<td>4 (0.08)</td>
<td>0 (0)</td>
<td>1 (0.01)</td>
<td>14  (0.77)</td>
</tr>
<tr>
<td>Depression</td>
<td>766  (2.42)</td>
<td>86  (0.87)</td>
<td>131 (2.96)</td>
<td>43 (0.84)</td>
<td>61 (1.19)</td>
<td>35 (0.48)</td>
<td>12  (0.66)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>32  (0.10)</td>
<td>17  (0.17)</td>
<td>3  (0.07)</td>
<td>22 (0.43)</td>
<td>3 (0.06)</td>
<td>3 (0.04)</td>
<td>12  (0.66)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>133  (0.42)</td>
<td>64  (0.65)</td>
<td>35  (0.79)</td>
<td>22 (0.43)</td>
<td>41 (0.80)</td>
<td>39 (0.54)</td>
<td>9  (0.49)</td>
</tr>
<tr>
<td>Others</td>
<td>16853  (53.17)</td>
<td>6064  (61.61)</td>
<td>3113 (70.35)</td>
<td>3097 (60.59)</td>
<td>3467 (67.39)</td>
<td>3793 (52.09)</td>
<td>1075  (58.87)</td>
</tr>
</tbody>
</table>

* Coronary artery disease

Australia as a destination for clinical trials

Klynveld Peat Marwick Main Goerdeler (KPMG) is a global network of professional firms that provide audits and tax and advisory services. KPMG is involved in health, ageing, human services and social policy, and works with federal and state government agencies and with not-for-profit and private-sector providers (KPMG, 2016).

In 2012, a KPMG Competitive Alternatives Report showed that Australia was the second least competitive country in the market for clinical trial investment (Dunlevy 2012b). Japan is the only country in which it is more expensive to invest in clinical trials (Dunlevy, 2012c; Selvarajan et al., 2013a) (Figure 4). This report reflects the volume of work that needs to be undertaken to make Australia more competitive in attracting clinical trials from overseas (Dunlevy, 2012c). Australia has some of the best medical scientists and research infrastructure in the world and the industry must work with the government to find ways to capitalise on these advantages (Dunlevy, 2012c).

![Cost of running clinical trials](http://www.kpmg.com/RU/en/IssuesAndInsights/ArticlesPublications/Documents/Competitive-Alternatives-2012.pdf; permission to use the figure granted on 11 January 2016 by Petra Sandanam, Communications Consultant, KPMG).

**Figure 4.** Cost of running clinical trials.

There are many factors that make Australia a favourable destination to conduct clinical trials. They are documented as follows:

**High quality researchers and facilities**

Australia has a good reputation for the quality of its scientific and medical research (Harris & Harris, 1998). Internationally, it is recognised for its highly trained health professionals and experienced research teams (Harris & Harris, 1998). Australia adheres to standard procedures and quality control measures; hence, Australian clinical data and results are accepted by all regulatory agencies such as the FDA and the EMA (Ghosh et al., 2006).

**Efficient ethics and regulatory frameworks**

Australia has fast and pragmatic regulatory pathways for conducting clinical trials (Hughes & James, 2012). The ethical review process for multicenter research assists in reducing the duplication of research reviews (King et al., 2012). Under the Clinical Trial Notification (CTN) and Clinical Trial Exemption (CTX) schemes, special attention is paid to regulatory protocols (King et al., 2012).

**Diverse participant recruitment pools**

Australia is a multicultural country with a diverse population that is capable of meeting the needs of clinical trials (King et al., 2012). The CTAG raises awareness about trials and supports patient recruitment (King et al., 2012). It also provides information to sponsors and stakeholders considering Australia as a destination for clinical trials (Loy et al., 2011).
Investment incentives

The Australian Government’s R&D tax incentive encourages more industry investment in R&D (Loy et al., 2011). The refundable R&D tax offset on aggregated annual turnover is appealing to many stakeholders (Lofgren & Boer, 2004).

Healthcare environment

Australian clinical practices are similar to those in other developed countries (Loy et al., 2011). They use English as the primary language of communication and support good communication between national and international groups (Lofgren & Boer, 2004). These factors have established Australia as a world leader in the conduct of large, investigator-led, pragmatic clinical trials in several areas of medicine including cancer and neurological and cardiovascular diseases (Ardito, 2012).

Factors discouraging the conducting of clinical trials in Australia

There are also some factors that are disincentives for conducting clinical trials in Australia. Keeping clinical trials in Australia, why action is needed now, Nov 2011 is a report describing the various problems that the Australian clinical trial industry is facing. Some of these problems are detailed below (Duijnhoven et al., 2013).

Lack of awareness of appropriate clinical trials

Healthcare professionals are not always aware of and do not always have access to active or current clinical trial data (Whitstock et al., 2011). In some instances, healthcare professionals prefer to continue to use therapies they are comfortable with, assuming that existing trials may not be appropriate for their patients (McMahon et al., 2011).

Unwillingness to ‘lose control’ of a person’s care

Most doctors want the best for their patients, but sometimes if a patient is referred to a different destination to participate in a clinical trial, doctors fear they may lose control
of that patient’s care (Whitstock et al., 2011). Many doctors believe that standard therapies are the best; some healthcare professionals may not adequately understand the significance of conducting a clinical trial, believing trials are not as good as standard and readily available treatments (McMahon et al., 2011).

Administration burdens of referring to and/or participating in a clinical trial has cost implications too (McMahon et al., 2011).

Some healthcare professionals perceive that participation in research is time consuming and will burden their already very busy schedules for patient care (Morgan & Boothe, 2010). The possibility of incurring additional costs and expenses that might be inadequately reimbursed, or not compensated for at all, is a deterrent for many (O'Connor & Liddle, 2013). The most significant barriers to patient enrolment include the volume of paperwork and filing and the extra time needed to train staff and other healthcare professionals in the process of enrolment and the completion of data collection forms (O'Connor & Liddle, 2013).

**Lack of participant awareness, access and adequate information and knowledge**

Many potential clinical trial participants are not fully aware of options to participate in clinical trials (Scott, 2013). Mobility barriers and time constraints also discourage some participants.

**Participant insurance**

Clinical trial participants may fear that their involvement in research could increase insurance costs or prohibit them from being able to maintain or secure private health insurance in future (Scott, 2013). Some clinical trials advertise health cover for all future possible adverse events caused by the trialed medications; however, the fine print of contracts may stipulate certain maximum payout amounts or a specific number of years for which the insurance is payable post-trial (Spencer, 2005).
**Ethnic and cultural considerations**

Many participants, especially those from developing countries such as India and China, fear being treated as ‘experimental animals’ (Krishna & Kumar, 2014). Participants distrust trial management based on negative experiences from past centuries or knowledge of historical incidents (Cassileth et al., 1980; Krishna & Kumar, 2014). There is still distrust of the system among minorities because of the notorious Tuskegee syphilis experiments on black men in the rural US from 1932 to 1972 (Cassileth et al., 1980).

People from certain racial or ethnic groups or from non-English-speaking backgrounds may feel that the levels of care provided within trials will not adhere to their cultural and social needs (Cassileth et al., 1980). Language and literacy barriers make it difficult for people to understand documentation, including patient consent forms, which are complex in nature (Cassileth et al., 1980). Translation, a mandatory requirement for all documents assessed by people from minority backgrounds with minimal knowledge of English, can be difficult in cases where the person translating the document does not have prior specialised training (Hussain-Gambles, 2003; Hussain-Gambles et al., 2004).

**Clinical trials and drug registration**

The following are examples of some of the reasons for conducting clinical trials in Australia (Kelman et al., 2007):

- to test new drugs, delivery systems or devices
- to test goods that have not yet been approved by the TGA
- to vary goods registered by the TGA from their registered indications, age groups, durations or frequencies of formulation.
All clinical trials in Australia must be approved by a Human Research Ethics Committee (HREC) before commencement (Kelman et al., 2007).

Figure 5 demonstrates the registration process of drugs through the TGA (Ghosh et al., 2006; McEwan, 2007). Initially an applicant, either a sponsor or a primary investigator, completes the application form to initiate the clinical trial (Ghosh et al., 2006; McEwan, 2007). The form contains the protocols for and a detailed description of the clinical trial to be conducted (Ghosh et al., 2006; McEwan, 2007). Once the form is completed, it is processed and then reviewed by a review board, who can seek additional information from applicants within a given time frame (Ghosh et al., 2006; McEwan, 2007). Once the board is satisfied with the application and applicant responses, then applicants are granted permission to conduct a clinical trial. However, if the form is incomplete or the applicant is unable to provide satisfactory responses, then the committee refuses to process the application (Ghosh et al., 2006; McEwan, 2007).
According to a “Call to Action Responses Report”, Australia can be more competitive by achieving the following points (Colagiuri & Johnson, 2014):

- collaboration between stakeholders, sponsors and investigating bodies
• development of a united vision, which requires national leadership and coordinated action
• harmonisation of multicentre ethical review processes and streamlining of multicentre trial reviews
• improvement of participant recruitment and satisfaction levels.

A Call to Action Responses Report is a roadmap for a series of strategic and practical actions, to be implemented across all sectors and by all Australians between now and 2020. The implementation of these actions presents a major challenge for the nation, but the rewards will be immense in terms of lives saved, and improved health and wellbeing. The Call to Action Responses Report also provides an online national forum for organisations, local governments, businesses and industry, community groups, families and individuals to share commitments and plans to making Australia healthy (Colagiuri & Johnson, 2014).

**Ethical issues and patient perception in clinical trials**

Clinical trials are large and strictly regulated enterprises that must comply with ethical requirements (Nardini, 2014). They need to maintain high standards of quality and adhere to research protocols throughout the trial (Nardini, 2014).

The Nuremberg Code (1949) is a legal and ethical code that was employed by US judges at the trial of Nazi doctors in Nuremberg after World War II (Grodin, 1992). Many consider it to be the most authoritative legal reference on the subject of human experimentation (Grodin, 1992). The code is based on universal principles of natural law and human rights, and it establishes the basic principle that participation in research requires the free, informed consent of participating subjects (Grodin, 1992; Shuster, 1997).
The Declaration of Helsinki is arguably the most widely known and influential document in medical research worldwide (Williams, 2008). It is an official policy of the World Medical Association (WMA), which was adopted for the first time in 1964 and has since undergone a number of revisions (Williams, 2008).

Finally, the Belmont Report is a short document on moral principles that was published in 1978 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research in the aftermath of scandals arising from research misconduct that were uncovered in the 1970s (National Commission for the Protection of Human Subjects, 1978). The Belmont Report is known for establishing a framework of basic moral principles—concerning respect for persons, beneficence, and justice, which should guide the conduct of research (Viergever & Ghersi, 2011).

It was found that public perceptions of clinical trials are coloured by connotations of high-risk medical experimentation and of human subjects being used instead of laboratory animals (Segelov et al., 1992). Normally these distinctions are reinforced by differing standards of consent for treatment as part of a clinical trial, especially when compared with standards of treatment outside of the setting of a clinical trial (Segelov et al., 1992). However, many participants enrolled in trials to treat serious conditions view the trial as the last hope of cure, as is often the case in cancer research, which can make it confusing for the lay person (Palter, 1996).

In order to safeguard the interests of clinical trial participants, there is an ethical obligation that trials be of sufficient quality to have a favourable impact on society in the future (Lilford, 1992). Evaluation of the ethical foundations of the design and implementation of clinical trials needs to assess not only the degree of uncertainty surrounding trials, but also the anticipated benefits from trials, the assumed risks by the participants and any alternative treatment options available for the patient (Palter, 1996).
Patient attitudes towards clinical trials

Generally, patients have positive attitudes to clinical research (Madsen et al., 1999; Madsen et al., 2002). Qualitative studies and research that collects data from post-marketing public records are on the increase and more prevalent than studies that involve active administration of new yet-to-be-registered medications (Verheggen, Nieman, Reerink, et al., 1998). This makes it difficult to compare hypothetical studies directly with real-life scenarios (Madsen et al., 1999; Solomon et al., 2003).

An increasing number of studies have been published using qualitative research methodologies (Featherstone & Donovan, 2002). Unlike most questionnaire-based studies, such studies have the capacity to explore the unexpected, explain the multiplicities of existing phenomena and engage with detailed narratives of lived experiences (Pope & Mays, 1995). However, very few patients consider participating personally in a randomised clinical trial (Fallowfield et al., 1998).

According to the Australian National Statement in Human Research, any person interested in participating in a clinical study should be aware of the purpose, plan and statement of methodology of the study (Ardito, 2012; Featherstone & Donovan, 2002).

Commonly asked questions concerning clinical trials

Many questions are specific to clinical trials, but some also apply to observational studies (Ardito, 2012).

- What is being studied?
- Why do researchers believe that the intervention being tested might be effective? What if it is not effective? Has it been tested before?
• What are the possible interventions that clinical trial participants receive during the trial?
• How will it be determined which interventions a participant should receive?
• Who will know which interventions a participant received? Are interventions the responsibility of a member of the research team, the primary investigator or the sponsor?
• What will be the possible side-effects, benefits or risks in participating in the clinical trial?
• What tests and procedures are involved?
• How often will the participant have to visit the hospital or clinic?
• Will hospitalisation be required?
• How long will the study last?
• How will the participants be paid for participating in a clinical trial and who will pay them?
• Will other expenses be reimbursed?
• What type of long-term follow-up care is part of the trial?
• If the participants benefit from the intervention, will they be allowed to continue receiving it after the trial ends?
• Will the results of the study be provided to the participants?
• Will the participants get compensation and what options are available if the participant is injured during the study?

Reasons for participating in clinical trials

There have been arguments made to the effect that altruism is the only reason that patients would participate in clinical trials (Emanuel & Patterson, 1998). According to
Cassileth et al. (1982), common reasons for participating in clinical trials are benefiting others and advancing medical knowledge. Other authors have also found that contributing to scientific knowledge is rated highly by patients (Ross et al., 1994; Slevin et al., 1995). Additionally, many patients choose to participate in clinical trials in the hope of receiving better care or treatment (Schaeffer et al., 1996). It has been well established through a systematic review of published literature examining patient motivation to participate in clinical trials that self-interest is a more common reason for participating than altruism (Edwards et al., 1998).

A number of distinct demographic characteristics have also been reported to be associated with willingness to participate in RCTs (Joseph, 1994). It has been found that male patients who are less educated and relatively older or from lower socio-economic backgrounds appear more willing to participate in clinical trials than others (Watts, 2012). Additionally, reduced disease progression and severity are proportional to the willingness to take part in clinical trials as a way of possible cure (Mastroianni & Kahn, 2001). The cost of treatment or financial benefits may also be reasons for people of low socio-economic status to participate in cost-free treatment or clinical trials (Bevan et al., 1993; Verheggen, Nieman, & Jonkers, 1998). Also, it has been noticed that patients who trust their doctor appear more likely to participate in clinical trials if asked to do so. These patient groups depend on their doctors to assist them with decisions regarding participation in clinical trials and, in some cases, may also prefer to receive less information about their illnesses (Degner et al., 1997; Llewellyn-Thomas et al., 1995).

Another motivational tool for participating in clinical trials is free access to healthcare (Quirk, 2013). Monetary benefits are another motivational tool to attract participants in clinical trials (Quirk, 2013). People from low socio-economic backgrounds with financial liabilities are more likely to participate in clinical trials (Ardito, 2012).
These issues each indicate valid points concerning the possibility for subtle coercion of such patients to join randomised trials (Quirk, 2013).

**Reasons for not participating in randomised clinical trials**

Many people still decide not to volunteer for clinical trials despite favourable attitudes to research in general (Featherstone & Donovan, 1998). Random allocation of treatment is a major reason for refusal to participate in clinical trials (Featherstone & Donovan, 1998). Many patients who are not well informed have a poor understanding of the rationale for randomisation as a method of treatment allocation and express reservations or feelings that it is unfair; hence, they do not participate (Featherstone & Donovan, 1998; Snowdon et al., 1997). Patients who desire active involvement in clinical decision-making may also be reluctant to participate in RCTs (Featherstone & Donovan, 1998).

Several studies have indicated that patients commonly decline to participate for two reasons: either they have a preference for a doctor or they feel the need to make their own decision about the treatment they will receive (Llewellyn-Thomas et al., 1995). There are a variety of other factors reported in the literature that influence patient decisions not to participate in RCTs. Many patients object to the notion that they are being treated as guinea pigs (Joseph, 1994).

Two major barriers hamper the recruitment of volunteer subjects in clinical trials: distrust of the medical profession and lack of knowledge (Cunny & Miller, 1994). Additionally, patients sometimes express concerns about specific treatments offered in clinical trials (Cunny & Miller, 1994).

It is often difficult to recruit subjects for RCTs where potential participants are aware that there will be large differences in the treatments offered (placebo and active)
or that the active medications may be toxic or cause side-effects (Yeomans-Kinney et al., 1995).

**Views of clinical trial participants**

There have been surveys conducted on patients who have earlier participated in RCTs for cardiovascular treatments (Welton et al., 1999). These surveys show that the patients were generally satisfied with their overall experience (Welton et al., 1999), with many stating that they would recommend the trial to a friend or colleagues (Welton et al., 1999). Nevertheless, a minority of people did not report a positive experience from participating in the trial. The disadvantages they perceived were largely practical issues or nuisance-related problems (Baum, 1993).

Participants considering clinical trials have often exhausted all approved treatment and, by participating in the clinical trials, they anticipate that the particular research will be beneficial to them and potentially cure their diseases (Ardito, 2012). Other participants view their involvement as a social obligation, while those without medical insurance or with limited coverage often volunteer to receive free medical tests, exams and advice about treating their medical conditions (Ardito, 2012).

**Informed consent for clinical trials**

Informed consent is very important for clinical trials (Giesen, 1993; Tattersall & Simes, 1992). It requires full disclosure of information about the treatment to the subjects including the possible financial burden, time burden, potential benefits and possible unintentional harm, and possible adverse events or effects. In the case of new drugs and life-threatening diseases or when the quality of life might be at risk of an untreated condition, especially in blinded-controlled trials, additional information on alternative
treatments must be given, allowing patients to make autonomous decisions regarding their participation (Giesen, 1993; Tattersall & Simes, 1992).

Informed consent has a number of essential components attached to it (Miller et al., 1994; Rimer, Jones, Keintz, Catalano, & Engstrom, 1984). These include the provision of written information and documentation to explain the need for the study; its main purposes and objectives; any additional tests, procedures or risks involved in the study compared with standard treatments; and the voluntary nature of the research, which clearly states that participants may leave the study at any stage (Miller et al., 1994; Rimer et al., 1984). However, there is evidence that the goals and objectives of informed consent for clinical trials are not always achieved (Cassileth et al., 1980). There are several studies that clearly mention that the patients were not given enough or detailed enough information about active medications or placebos before participating in the clinical trials. In these cases, patients recall only a small proportion of the information that was provided to them at the start of the study (Dunn et al., 1993; Oliver et al., 1995).

**Factors that may influence participation in clinical trials**

Personal characteristics, attitudes of volunteers, enabling factors and socio-economic barriers are some examples of the factors that have been implicated in the willingness of patients to participate in clinical trials (Townsley et al., 2006). From a practical standpoint, understanding motivations behind participation or refusal to participate in clinical trials is vital to the success of any ongoing clinical trial in terms of cost-effectiveness, speedy recruitment of subjects, statistical power and maintaining the motivation of clinical researchers to actively participate in engaging participants during ongoing and future clinical trials (Tattersall & Simes, 1992). Patients depend to a high extent on the doctor’s decision to participate in a clinic trial or not to and are perceived
by many to conflict with their individual decision-making and clinical judgement skills, skills which they have inherited from their school (Tattersall & Simes, 1992). It is still a challenge to engage doctors to discuss the therapeutic benefits and treatment choices with patients, which also include the patient’s participation in clinical trials (Ellis, 2000).

Concerns regarding the doctor-patient relationship included trial eligibility requirements, relevancy, difficulties with informed consent and dislike of open discussions about the uncertainty of a particular clinical trial (Ellis, 2000). Some of the major reasons for not entering as patients into clinical trials were a lack of resources (including limited access to data management, and a lack of time) and a feeling that clinical trial participation was not worth the effort (Ellis, 2000). Nevertheless, many patients chose to participate in clinical trials in the hope of receiving better care or treatment (Ellis, 2000).’ A number of demographic characteristics have also been reported to be associated with willingness to participate in randomised clinical trials (Ellis, 2000). Additionally, patients who trust their doctor appear more likely to participate in clinical trials if asked and these patient groups may also prefer to receive less information about their illness and are more likely to leave decision-making regarding their treatment to their doctor (Ellis, 2000). Access to free health care has also been reported as a motivation factor to participate in clinical trials (Ellis, 2000).

These issues all raise concerns about the possibility of subtle coercion of such patients to join randomised trials. (Table 4).
Table 4. Common factors influencing participation in clinical trials.

<table>
<thead>
<tr>
<th>Doctor factors</th>
<th>Patient factors</th>
<th>Trial factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logistic difficulties</td>
<td>Personal difficulties</td>
<td>Demographics such as age and education</td>
</tr>
<tr>
<td>Unawareness of trials open for accrual</td>
<td>Effect on doctor–patient relationship</td>
<td>Presence of a no-treatment arm</td>
</tr>
<tr>
<td>Lack of time</td>
<td>Discomfort with randomisation</td>
<td>Preference for a particular treatment</td>
</tr>
<tr>
<td>Lack of resources e.g. data management</td>
<td>Difficulty with informed consent procedures</td>
<td>Concerns about treatment toxicity</td>
</tr>
<tr>
<td>Financial constraints</td>
<td>Preference for a particular treatment</td>
<td>Dislike of randomisation and experimentation</td>
</tr>
<tr>
<td>Type of practice (public versus private)</td>
<td>Overall too difficult (too much time and effort)</td>
<td>Loss of control</td>
</tr>
<tr>
<td>Difficulty with ethics requirements</td>
<td>Lack of acknowledgment</td>
<td>Practical issues such as inconvenience</td>
</tr>
<tr>
<td>Identification of eligible patients</td>
<td>Opinion of referring doctor</td>
<td>Access to free medical care</td>
</tr>
</tbody>
</table>


Additional follow-up care can add to the benefits of intrinsic motivational factors; however, this is more relevant in the US, as the Australian healthcare system provides comparatively more equitable, free access to health services (Baquet et al., 2006). Few data are available on factors influencing patients in Australian rural clinical trials (McMahon et al., 2011). Clinical trial participation could be improved if participants were better informed about trials as this is a valuable factor in enabling recruitment (McMahon et al., 2011).

A study conducted to investigate the effect of pre-operative education about coronary artery bypass graft surgery indicated that those patients who received education one week prior to surgery had greater knowledge, more positive moods, higher physiologic recovery scores and less anxiety than those patients who received details of the treatment post treatment (Cupples, 1991).
Research examining doctor–patient communication imparting knowledge of clinical trials to subjects is also inadequate and scarce (Valkenhoef et al., 2012). Inadequate knowledge about clinical trials by some of the doctors involved in referring patients to clinical trials and incomplete patient details on consent forms, all clearly indicate inadequate communication between healthcare professionals and volunteers who consent to be subjects in a clinical trial study (Valkenhoef et al., 2012). Specialised clinical trials and communication-skill training for doctors should be addressed in the future (Weaver, 2010). This will improve patients’ understanding and willingness to participate in RCTs (Weaver, 2010).

**Chapter summary**

There is a continual need to improve recruitment in clinical trial studies given the increasing importance and necessity of RCTs in order to support new treatment discovery and licensing (Baum, 1993, 1994). It has been documented in the literature that there is a need to raise awareness throughout the community concerning the need for and importance of RCTs (Baum, 1993, 1994). The dissemination of such information should be well planned and well executed and should be focused on enabling further research (Tattersall & Simes, 1992).

There has been a significant amount of progress made in the designing and development of new medicines over the last few years. The risks associated with new drug development are varied (Tattersall & Simes, 1992). All therapeutic drugs have risks associated with them. If the risks are not captured during clinical trials, it can be hazardous to the society. However, with the rising demands and potential ‘loopholes’ in the regulatory system, the marketers may want to get the immediate approval and market the new drug immediately, despite the increasing cost of clinical trials. The literature
discussed the fact that agencies assigned to collect clinical trials data for public and reporting purposes have not been able to keep accurate records of participation of women, children and elders, when the participation is appropriate for the trialled drug.

The following chapter introduces the concept of this study regarding the participation of the elderly, women and children in clinical trials and the barriers and challenges associated with their inclusion.

For the purpose of this study, children and young adults were combined in age group under the age of 21 years, since this was nominated by the ANZCTR as the cut-off age. In this study, members of this age group were referred to as children. Adults were those at or above the age of 21 years and women were those born as females, while the elderly were defined as those at or over the age of 65 years.
Chapter III - Research concept development

Level of participation of women, children and the elderly in clinical trials

The elderly population (>65 years) represents the fastest growing subgroup of the world population (Lutz et al., 2008). Historically, it was found that one in 20 people was aged 65 years or over. In 2008 this became one in six, and by 2050, it is estimated that the number will rise to one in four (Lutz et al., 2008). It is estimated that in Australia over 140,000 people die annually because of a terminal chronic condition, which does not discriminate between people from different age groups or genders (Rowett, 2014).

According to the Australian Bureau of Statistics (2014), the Australian population aged 65 years and over increased from 11.8% to 14.7% between 1994 and 2014, and the proportion of people aged 85 years and over almost doubled from 1.0% of the total population in 1994 to 1.9% in 2014 (Australian Bureau of Statistics, 2014).

A number of biological, physiological, functional and psychological changes occur throughout the process of ageing (Watts, 2012). The impact of these changes varies depending on genetic factors, frailty and reserved organ functions (Avorn, 1997). Ageing is also associated with increased social-related needs (Aalami et al., 2003; McLean & Le Couteur, 2004). While diseases affect all ages, being older, younger or pregnant might change the pharmacokinetics and pharmacodynamics parameters which contribute to the poor disease progression due to the altering of responses to or tolerance of pharmacological treatment; hence, representation of these groups in clinical trials is vital.

Additionally, elderly medication consumption is higher than the rest of the population (Avorn, 1997). Representation of the elderly validates the safety and efficacy of new medicines when used in an ageing population (Herrera et al., 2010).
**Medicine use and the elderly**

Medicines are essential for treating conditions that require pharmacological interventions. Such pharmacological intervention is usually based on established or understood risk-benefit measures to enable decision-making and monitoring of side-effects, toxicity and efficacy. However, in some cases Phase III trials exclude the elderly, the very young or pregnant women due to either drug specialisation (for men- or women-only-related conditions), the need for people suffering from a single disease only (many elderly people have comorbidity), moral issues (pregnant women), or the ethical dilemma of consenting (for children when other treatment is available). Consequently, the medication indications and administration information either state that the medication should be used with caution or that it is not recommended for use by these groups of the population as the safety and efficacy have not been tested (Avorn, 1997).

Due to constant changes in pharmacokinetic and pharmacodynamic parameters and functions, aged people’s response and tolerance to medications is naturally altered (Crome et al., 2014). Many of the older people would also start to show complications or comorbidities: the presence of one or more additional disorders or diseases co-occurring with a primary disease or disorder (Crome et al., 2014). As the immune system weakens and comorbidity or complications increases, organ functions start to compensate and their function might start to be compromised or even impaired, the risk of infection increases due to changes in the immune system, tolerability to side-effects is reduced due to changes in liver function and renal clearance and responses to medications are altered due to a reduction in the sensitivity of receptors, which all contribute to making the elderly a unique group of the population (Witham & McMurdo, 2007). Asthma and COPD account for around 80% of the total chronic respiratory diseases in the elderly in Australia, which corresponds to 29.2% of the total older population above the age of 75 years (Frith et al.,
This creates a significant burden for the Australian healthcare system and creates problems in both primary-care and hospital settings (Frith et al., 2008). In Australia, 5–10% of older patients who attend a GP for an initial consultation will experience an adverse drug reaction in the six months following that consultation (Frith et al., 2008).

**OTC medicines and elderly population**

There are many OTC medicines that have adverse effects on the ageing population (Simons et al., 1992), such as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) or proton pump inhibitors (PPI). OTC medicines are used on the basis of self-diagnosis of condition and medication self-selection. When OTC medicines are taken in combination with prescribed medicines without the knowledge of the prescriber or the pharmacist, and for longer than they should be taken, or in a dose that should not be used in the age group, they may cause adverse drug reactions or organ damage (Gill et al., 2010). In some cases, OTC medicines are sourced to treat the side-effects of other prescribed medicines, which when not communicated with the prescriber or the pharmacist could further complicate the elderly regime (Gill et al., 2010; Miller-Larsson & Selroos, 2006). This is complicated by the use of traditional medicines, health supplements and complementary medicines, which may increase the risk of developing adverse drug reactions in the general population and have a higher impact on the health of the elderly (Merle et al., 2005; Routledge et al., 2004).

**Polypharmacy and elderly**

An Australian study has revealed that polypharmacy in the elderly is very high (Cohen et al., 1998). Another study on elderly polypharmacy found that at least four drugs
(prescription and non-prescription) were regularly consumed by 70% of women and 61% of men in the population sample (Elliott, 2006; Schmucker & Vesell, 1999).

It has also been shown that most problems arising from multiple drug use in aged Australians come from drug–drug interactions or drug–food interactions (Elliott, 2006).

An increasing number of elderly patients are hospitalised because of cocktails of prescription and OTC medicines (Routledge et al., 2004).

A study by Routledge et al. (2004) found that patients who are over the age of 65 are prescribed new medicines as soon as they are approved without taking into consideration patient-related factors such as frailty, pharmacokinetics and pharmacodynamics. The FDA estimates that up to 10% of reports to the MedWatch system are reporting an adverse drug effect (Kessler et al., 1993; Whitstock, 2011). MedWatch is a free and reliable web portal that reports adverse events related to medicines; it was created by the FDA to raise public awareness about the safety of medicines (Kessler et al., 1993).

**Participation by the elderly in clinical trials**

The FDA has strongly recommended the adequate inclusion of elderly people in clinical trials for drugs requiring licensing that will be used to treat highly prevalent diseases (Alemayehu et al., 2012). Pharmaceutical companies are also required to include a compulsory geriatric-use subsection in documentation for their drugs licensing based on pre-marketing and post-marketing surveillance (World Medical Association, 2008). This may suggest that there is a need to ensure that the drug’s safety and effectiveness is confirmed prior to marketing and not post marketing.

Schmucker and Vessell (1999) reported that elderly people were under-represented in clinical trials as volunteers and that this was a fact commonly highlighted by geriatricians.
(Schmucker & Vesell, 1999). Nevertheless, their inclusion is also widely understood to be highly problematic (McMurdo et al., 2011). Some of the reasons for exclusion included the identification of elderly participants as having many health complications and conditions and enduring disproportionately high rates of cancer (Townsley et al., 2006), cardiovascular disease (Heiat et al., 2002), dementia (Arean et al., 2003), arthritis and Parkinson’s disease (Witham & McMurdo, 2007).

Studies have suggested that the number of cancer patients older than 65 accounts for two thirds of all cases of cancer, but only 25% of clinical cancer trial participants have attained this age (Herrera et al., 2010). Another study has pointed that only 32% of enrolled elderly participants take part in Phase II and Phase III clinical trials, despite the fact that this age group comprises 60% of national disease cases (Herrera et al., 2010). This may suggest that there is an element of intentional exclusion of the elderly from pre-marketing clinical trials to avoid carrying the entire risk as a manufacturer and to leave it for post-marketing where the risk is shared with the society.

RCTs are the most common trials that exclude vulnerable groups (Zelen, 1979). RCT is a method designed to compare new drugs to placebos, other drugs from the same class, and/or other drugs used to treat the condition (Zelen, 1979). In RCT studies, if the health of patients who are receiving experimental therapy declines, they are entitled to receive the standard treatment and exit the study (Zelen, 1979). Those patients who do not complete a trial because of side-effects, toxicity or declining health must be clearly reported on; however, the report may list them only as withdrawals without disclosure of the reason for withdrawal (Zelen, 1979). Additionally, anticipation of the possibility of complicating or devaluing the study as a result of withdrawals may make researchers less inclined to enrol elderly participants. Adjustments to the endpoint of any study are possible, but to do so adds an extra layer of complexity to studies that are already designed
in a very complex way (Whitstock et al., 2011; Zelen, 1979). This may suggest that there may be an element of intentional exclusion of the elderly from clinical trials to avoid withdrawals that may affect the drug licensing and cause a loss of profit.

Possible causes of the exclusion of elderly people from clinical trials

Exclusion from clinical trial studies is designed to protect the patient from unanticipated harm and also make studies easier to progress and be completed without unexpected complications (Simons et al., 1992). However, in terms of the consumer’s perspective, this may mean that some groups of the population who were excluded from the trials, but have the condition, may not be eligible to use this drug in the future as a result of being excluded in the drug licensing portfolio (Avorn, 1997). The reasons for excluding the elderly in clinical trials are challenging and complex (Arean et al., 2003; Bellia et al., 2007; Herrera et al., 2010). Challenges may include the presence of comorbidities; economic or financial constraints; a lack of current private health insurance; oversights pertaining to the disclosure of trial participation to private health insurance companies, which may compromise future healthcare cover (the participant is unaware of the insurance policy or the policy itself lacks transparency); communication issues (e.g. hearing difficulties that interfere with telephone interviews and impaired vision that affects written surveys); and physical immobility that affects transportation options and acts as a barrier to clinical involvement (Herrera et al., 2010).

Increasing the Participation of the Elderly in Clinical Trials (PREDICT) is a patient advocate group, funded by the European Union to study the participation of elderly people in clinical trials in Europe (Bartlam et al., 2012; Crome et al., 2014). It operates in many countries including the UK, Italy and Spain (Crome et al., 2014). Initially, the group started by validating the representation of the elderly in clinical trials and then assessed
whether the level representation is factual or perceived (Crome et al., 2014). It reviewed trials completed over the last decade concerning treatment for six conditions: heart failure, hypertension, coronary heart disease, depression, Alzheimer’s disease and colorectal cancer (Bartlam et al., 2012; Crome et al., 2014). The group found that under-representation still exists for a number of reasons and not solely because the elderly are excluded or not invited (Crome et al., 2014).

A recent example can be found in the WHO’s identification of the failure of elderly recruitment in clinical trials on heart failure medication, followed by the PREDICT consortium’s conclusion that the ‘exclusion of older patients at the level of eligibility criteria was evident’ (Bartlam et al., 2012; Crome et al., 2014). Older patients with comorbidity and cognitive impairment were excluded from the trials (Bartlam et al., 2012).

It is the responsibility of the sponsors to make all possible arrangements to ensure that the recruitment process and ethical arrangements accommodate elderly enrolment in clinical trials to achieve justice and inclusion (Bartlam et al., 2012). Timely identification of any adverse effects or risks of health decline will encourage the elderly to participate as they will become confident that their participation may at some stage allow them access to appropriate treatment and that they are not gambling with their health (Tunis et al., 2003).

**Exclusion of women from clinical trials**

Historically, clinical trials only recruited males (Baquet et al., 2006). Females were excluded not only to prevent an effect on a foetus, but also due to their differing pharmacokinetics and pharmacodynamics, which might complicate the interpretation of results (Baquet et al., 2006). In the past, primary investigators have been hesitant to
include female volunteers in the trials due, in part, to concerns about their participation leading to potential birth defects (Mastroianni et al., 1994).

Female subjects were excluded in clinical trials conducted for New Drug Applications (NDAs) submitted to the FDA for drug approval before marketing (Merkatz, 1998), which may have led to inequality in the understanding, diagnosis, and treatment of diseases in both sexes (Merkatz et al., 1993; Uhl et al., 2007). The thalidomide tragedy in the 1960s alerted the world to the risks of the inclusion of females of childbearing potential (FCBP) in clinical studies (Kim & Scialli, 2011). Another incident concerns the death of 34 Indian women from modest backgrounds over the course of a 15-year, US-funded clinical trial for cervical cancer treatment, triggering questions about the ethics of conducting trials in a safe and well-informed manner (Sankaranarayanan et al., 2009).

A review of Phase I clinical trials, conducted from 1985 to 1991 investigating the pharmacokinetics of new drugs, suggests that females, regardless of childbearing potential, were entirely excluded from >50% of pharmacokinetic protocols (Sherman et al., 1995). A review of protocols submitted to the FDA between 1988 and 1994 showed that 24 (16%) of 152 HIV studies did not enrol women participants, although none of these 24 protocols presented any specific exclusion criteria for women (Sherman et al., 1995). Conversely, clinical trials for certain indications, such as heart disease, continue to include a disproportionate number of female subjects (Merkatz, 1998); however, there is no up-to-date research found on this topic that can confirm or deny if it is still the case.

**Studies related to representation of women in clinical trials**

Over the past 20 years, a number of literature reviews have revealed that, despite continuous efforts, women are still under-represented in clinical trials and that few studies conduct gender-specific analyses (Yang et al., 2009). A comparative study, canvassing
all government-funded clinical research studies published in four major journals during the years 1993, 1995, 1997 and 1998, showed that approximately one fifth of published studies excluded female participants, and that the majority of studies enrolling both men and women did not examine results by gender (67–75%; Vidaver et al., 2000). Furthermore, another comparative study showed that 86% of the 120 trials that were examined did not conduct gender-specific analyses (Ramasubbu et al., 2001). These findings show that the enrolment of women in research has increased; however, less progress has been made in terms of increasing the level of analysis by gender.

The US National Institute of Health (NIH) established a Public Health Service Task Force on Women’s Health, which seeks to draw attention to women’s health issues (Women’s Health, 1985). It developed specific guidelines in 1986 regarding the inclusion of women as volunteers in NIH-funded extramural research, encouraging both the inclusion of women in clinical research and the evaluation of gender differences in health outcomes (Goldman & Hatch, 2000).

In the UK, historically women and minority groups were excluded from government-funded clinical trials according to the National Institutes of Health Revitalisation Act of 1993.

In 2000, new guidelines were jointly issued by the Office of Research on Women’s Health and the Office of Research on Minority Health (Merkatz, 1998; Vidaver et al., 2000). While implementing the new recommendations into the National Institutes of Health Revitalisation Act, the FDA re-examined their 1977 guidelines, which had initially excluded ‘women of childbearing potential’ from participating in early studies (i.e., Phase I and Phase II) of clinical trials (Merkatz, 1998).

Significant outcomes resulted from this restrictive policy, which also lacked information about how women would respond to medications tested exclusively on men as well as the effects of female physiology on the tested drug, for example, the menstrual
cycle, menopause and hormonal fluctuations during the female life span (Quirk, 2013). In Australia, few studies have reported the under representation of women in clinical trials (Goldman & Hatch, 2000).

An Australian study raised the issue of women’s inclusion and showed for the first time a strong Australian case (Rogers et al., 2008). The study suggested that clinical studies on women’s health continue to focus predominantly on their reproductive capacity and function, whereas research on men continues to investigate conditions that are not specific to one sex (Rogers et al., 2008). The authors highlighted the role of HRECs in Australia and showed that they do not currently play an active role in monitoring the inclusion of men and women in Australian clinical research for three key reasons (Ballantyne et al., 2008). First, HRECs in general do not consider this a crucial component of analysis, possibly because they lack knowledge about the sex-specific physiological impacts on pharmacokinetic and pharmacodynamic medications (Ballantyne et al., 2008). Second, HRECs do not consider gender exclusion as a weakness, but rather promote it as a safety measure (Ballantyne et al., 2008). Third, some HRECs do not believe that research should be discontinued on the grounds of sex inequity among the research participants because, in many cases, sex equity is outside the control of the researcher; as individuals enroll voluntarily, controlling gender balance would negate the voluntary aspect of enrolment (Ballantyne et al., 2008). It remains unclear whether HRECs are missing important gender- and sex-specific dimensions of studies or whether Australian researchers are simply unwilling to risk enrolling women of a childbearing age (Ballantyne et al., 2008).

An Australian report reviewing 400 clinical studies showed that out of the total sample, comprising 546,824 participants, 73% of participants were female; 36 studies were male-only, 78 were female-only, the reminder were mixed (Rogers et al., 2008). Of
the participants in 286 studies that were not sex-specific, 56% were female. The study clearly suggests that there is a need to analyse findings against the sex of participants (Rogers et al., 2008).

As a result of these studies, in 1963 the government established the Australian Drug Evaluation Committee (ADEC) to keep a check on the safety and adverse effects of new drugs introduced to Australia, especially medications that are used during pregnancy (Kennedy, 2014).

**Direct exclusion**

Physiology studies: women were excluded from studies on tissue samples because of the effects of female hormones on the physiological process being investigated in the trial (Pierce et al., 2002; Yang et al., 2009). Men were preferred by researchers because of the conception that oestrogen may affect the results (Rogers, 2008). Researchers argued that it is easier, quicker and cheaper to conduct a study on a homogeneous male population (Ballantyne et al., 2008; Pierce et al., 2002). In March 2005, contrary to expectation, it was proved via studies that aspirin had effects on women unlike those on men with regard to primary protection against stroke and fatal heart attack (Ridker et al., 2005). Pregnancy is a ‘natural state’ that has been treated as a medical condition resulting in the exclusion of women. The lack of information on the use of medicines during pregnancy remains an area of concern for both consumers and health professionals (Nelson & Forfar, 1971). However, it is understood that pregnant women themselves may be apprehensive towards the idea of enrolling in clinical trials and risking the future health of their foetuses (Nelson & Forfar, 1971).
Indirect exclusion

Obstructive sleep-apnoea: Obstructive sleep-apnoea syndrome (OSAS) affects up to 14% of middle-aged men and 2% of middle-aged women and is strongly associated with obesity. Common symptoms are excessive daytime sleepiness and loud snoring (Gibson, 2004). Although the population affected by OSAS is predominantly male, women are also affected by this condition. Nonetheless, studies commonly only include men and exclude the female cohort (Ballantyne et al., 2008; Strohl & Redline, 1996).

Alzheimer’s disease: Patients suffering from Alzheimer’s disease who are included in clinical trials require a full-time carer to provide an objective assessment of their progress (Bartlam et al., 2012). Most eligible participants are men who are living and being cared for at home by a female spouse (Bartlam et al., 2012). The results of most of the trials on Alzheimer’s disease are based on the male population, whereas the majority of the people affected by Alzheimer’s disease are female (Ballantyne et al., 2008).

Participation of children in clinical trials

There are approximately 2.5 billion children in the world, representing 40% of the population (Henderson, 2010; Johnson & Unguru, 2015). Adults and children respond differently to drugs (Pandolfini & Bonati, 2005). Life-threatening paediatric disorders are relatively rare (Burns, 2003). For example, in the US, the apparent incidence of sickle-cell disease (as diagnosed by newborn screening) is only 0.549; 0.22 for cystic fibrosis, and 0.05 for phenylketonuria (Johnson & Unguru, 2015). Only 1% of all cancers diagnosed annually in the US are paediatric patients (diagnosed before age 20; Johnson & Unguru, 2015). In paediatrics cancer research, the RCT only allows investigators to use two interventions, not interventions and placebos, which are believed to have comparative efficacy (also known as clinical equipoise) in which one has a known effect
in adults and the other has the same effect in adults, but is tested for a new indication in children to prevent injustice (Joffe & Miller, 2008).

The market for paediatric drugs worldwide reached $43 billion as of 2011, according to Kalorama Information Research (Henderson, 2010). Most drugs in development for children are in the areas of genetic diseases including cystic fibrosis, Gaucher disease, leukaemia and infectious diseases, including influenza or infestations such as head lice (Pandolfini & Bonati, 2005) (Figure 6). In addition to the medical conditions mentioned in Figure 6, biopharmaceutical companies are working to meet two new challenges related to children’s health—heart disease and obesity (Henderson, 2010). Many of the medications used in children are used off-label, as they are only tested in adults and licensed for use in adults but are recoded as ‘no safety data available in children’ (Henderson, 2010). New medicines and new knowledge about pediatric medicines means that the children will recover very quickly from their illness and can grow into the healthiest adults they can be (Henderson, 2010).

Figure 6. Conditions requiring pharmacological intervention in children.
Historical evidences related to representation of children

Over the centuries, the participation of children in clinical research has gained momentum (Barlow et al., 2013). During the eighteenth and nineteenth centuries, children, often viewed as the property of adults, were recruited as research subjects to observe the effects of infectious diseases, such as syphilis, gonorrhoea, tuberculosis, and yellow fever on humans (Kellett, 2005). Later, researchers recruited children into trials that tested vaccines (Ryan et al., 1998). Procedures protecting children from such exploitation were not established until after the World War II, Nazi war crimes, were investigated (Burns, 2003; Meaux & Bell, 2001). Unfortunately, since that time, protecting children in research has often been translated into excluding children from clinical trials (Burns, 2003; Meaux & Bell, 2001). In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research produced the Belmont Report, which set out three basic principles to guide the conduct of human-subject research: respect for persons, beneficence, and justice (National Commission for the Protection of Human Subjects, 1978). The principle of justice as articulated in the Belmont Report is primarily concerned with the protection of vulnerable sections of society from exploitation (National Commission for the Protection of Human Subjects, 1978). Children fall in this category because they possess limited developmental capabilities to consent and rely on adults for protection (Mastroianni & Kahn, 2001).

It has been globally accepted that children cannot be provided with safe and effective drugs compared with those available for adults without involving children in clinical trials (Pinxten et al., 2009). EU paediatric regulations currently require that clinical trials on minors should be planned and conducted for all new products (Pinxten et al., 2009). During 2003, it was estimated that only up to 30% of drugs approved by the FDA were labelled for paediatric use (Meadows, 2003).
The danger in applying the findings from research conducted exclusively in the adult population to the paediatric population is well recognised (Shah et al., 2004). The physiology of the human body differs in children to that in adults, and reaches maturity during the first few years of a child’s life. Accordingly, a child’s response to disease state and medications differs to that of an adult’s (Burns, 2003).

Only one third of drugs used to treat children have been studied in the paediatric population and have relevant information on the product labels, while for the other two thirds of drugs, information regarding the safety and efficacy for paediatric patients is either absent or insufficient (Shah et al., 2004). Medicine is manipulated to obtain a ‘paediatric’ dose (e.g. tablets are used to formulate oral liquid preparations) or avoided altogether where pharmacokinetics are known to be specific to adults (e.g. avoiding intramuscular injections in children; Pinxten et al., 2009). This is common practice in off-label or unlicensed medication use, i.e. outside the specifications included in the product information including the medication indications, dosage information or patient age group guidelines (Pritchard & Kenner, 2012).

Off-label and unlicensed drug usage in children

Off-label and unlicensed drug use may benefit children, but there is also a possibility that it will produce no therapeutic effects or that it may produce adverse drug reactions. However, not all prescribers are willing to take such risks and many prefer not to prescribe off-label at all (especially in a primary health care setting), or refer to the hospital pharmacist for advice, when in reality there is no data or only theoretical data available (Pandolfini & Bonati, 2005).

Off-label and unlicensed drug use is global and it affects children of all age groups (Pandolfini & Bonati, 2005). Although a number of studies have addressed the issue, very
little information is available concerning the barriers preventing parents from allowing their children to be enrolled in a clinical trial (Palčevski et al., 2012).

**Regulations regarding the participation of children in clinical trials**

There are a number of regulations that provide guidance on the inclusion of children in clinical trials (Stafford, 2008). The guidelines provide a framework for pharmacovigilance and risk-management approaches, which include risk communication with parents and risk mitigation by sponsors (Dresser & Frader, 2009; Zisowsky et al., 2010). It is important for national and international regulatory authorities and agencies to monitor medicines for safety and efficacy and take appropriate measures to identify research priorities (Zisowsky et al., 2010). Regulatory authorities should use existing clinical evidence in decision-making and support research that is necessary in order to fill the gaps in paediatric pharmacotherapy (Pandolfini & Bonati, 2005). Regular meetings emphasising the importance of global engagement in addressing the issue of paediatric drug use should be held (Palčevski et al., 2012).

In the past, data from medical research conducted on adults was extrapolated and used in relation to children, which was inappropriate for many reasons (Caldwell et al., 2004). First, children cannot be portrayed as small adults as diseases progress differently in adults and children (Pandolfini & Bonati, 2005). Second, the physiological makeup of children and their pharmacodynamic responses to drugs vary with age and are different to those of adults (Pandolfini & Bonati, 2005). Therefore, medicines need to be tested in all age groups from premature infants to adolescents as medicines behave differently in different age groups (Pocock, 2013). Finally, the routes of administration adopted by adults, such as tablets, are not easily adapted to small children and infants who may find medicines hard to swallow (Pocock, 2013).
Paediatric regulation’s main priority is to stimulate research on these medicines (Li et al., 2007). One incentive given to companies who incorporate children in clinical trials is that they will benefit from 10 years of data protection as a reward for the development of new indications for children or formulations appropriate for children of all ages (Ernest et al., 2007). This legislation, however, has failed to produce good results, with only one medication (buccal midazolam) approved so far. Another example is amoxicillin, which changed its label and updated the licensed recommendations for paediatric dose (Ernest et al., 2007).

**Risk associated with involving children in clinical trials**

Risk is defined as the potential for harm (real or theoretical) as a consequence of an action; it can be physical, psychological or social and may be immediate or delayed (Kraemer et al., 2014). The biggest concern in involving children in research is ethical consideration (Emanuel et al., 2000). Risk assessment and management seek to evaluate a protocol and conduct clinical trials in conjunction with the severity of the conditions or diseases that need to be studied, the ages of children who are taking part in a trial and the risks and benefits of alternative treatments (Emanuel et al., 2000). If Institutional Review Boards (IRBs) assess the trial, it means the trial has a greater than minimal risk; additional safeguards must be initiated (Meaux & Bell, 2001). The US Department of Health and Human Resources, the Public Health Service and the NIH outline four categories of research involving children based upon the risks assessed by the IRB (Meaux, 2001).

Table 5 (Meaux & Bell, 2001) elaborates on the series of studies conducted by Abramovitch, Freedman, Thoden, and Nikolich in 1991 to examine the ability of children to agree to participate in psychological research (Meaux & Bell, 2001). They were between the ages of 7 and 12 and were asked about their knowledge of the content of the
clinical study in which they had participated and their understanding of confidentiality and their rights to stop participating (Meaux & Bell, 2001). They were then asked about hypothetical studies that incorporated ethical problems and their responses were framed in a tabular format (Meaux & Bell, 2001).

It has been made mandatory by the regulatory agencies that children involved as research subjects give informed, voluntary, uncoerced assent (Meaux & Bell, 2001). These children may not fully understand the exact description of the research, but will grasp the essence using audio-visual aids (Meaux & Bell, 2001). Like the informed consent form, the assent form should explain the purpose of the research and what the child will experience at each stage of the research process (Meaux & Bell, 2001). The child should also be provided with very clear guidelines for withdrawing from the study at any time (Meaux & Bell, 2001). While psychological trials are unique cases which may not involve pharmacological interventions, the concept is sound and may be used as a guide for other clinical trials where medications are used.
Table 5. Levels of IRB clinical research risk involving children.

<table>
<thead>
<tr>
<th>Category</th>
<th>Child assent</th>
<th>Parental permission</th>
<th>Research example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not greater than minimal risk</td>
<td>Yes, when possible</td>
<td>One parent sufficient</td>
<td>Collecting tracheal aspirates as part of routine care for infants on ventilators to check for inflammatory cytokines</td>
</tr>
<tr>
<td>Greater than minimal risk, but the prospect of direct benefit to individual subjects</td>
<td>Yes, when possible</td>
<td>One parent sufficient</td>
<td>Evaluation of ibuprofen as an agent to resolve patent ductus arteriosus in preterm infants</td>
</tr>
<tr>
<td>Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalisable knowledge about the subject’s disorder or condition</td>
<td>Yes, when possible</td>
<td>Both parents required, can only be waived if a parent is deceased, incompetent, unknown, or if one parent has sole custody</td>
<td>Protocol on meal-related changes in gut hormones in obese versus non-obese children that involves admission into the research facility, peripheral intravenous placement and multiple blood samplings</td>
</tr>
<tr>
<td>Does not meet the criteria of the aforementioned categories, but the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children</td>
<td>Yes, when possible</td>
<td>Both parents, unless above criteria are met</td>
<td>Protocol measuring glycogen, glutamate, turnover rate, and glutamate-glutamine cycling in wakefulness and sleeps in adolescent children. The investigator also proposes to study a subset of children in a similar manner following sleep deprivation. This study on sleep and sleep-related disorders involves three visits to the hospital. Measurements include magnetic resonance spectroscopy following intravenous infusion.</td>
</tr>
</tbody>
</table>


The EU ethical guidelines that support paediatric regulation define three levels of risk, as seen in Table 6, and practical examples have been included for each group (Meaux & Bell, 2001).

Table 6. Categories of risk and their measurement procedures.

<table>
<thead>
<tr>
<th>Categories of risk</th>
<th>Procedures</th>
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<tbody>
<tr>
<td>Minimal risk</td>
<td>History and examination</td>
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<tr>
<td></td>
<td>Blood pressure</td>
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<td></td>
<td>Ultrasound</td>
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<td></td>
<td>Single venepuncture</td>
</tr>
<tr>
<td>Minor risk</td>
<td>Multiple venepuncture</td>
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<tr>
<td></td>
<td>Nasogastric tube</td>
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<tr>
<td></td>
<td>CT scan</td>
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<td></td>
<td>Lumbar puncture venous line</td>
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<tr>
<td>Major risk</td>
<td>Endoscopy</td>
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<tr>
<td></td>
<td>Sedation</td>
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<tr>
<td></td>
<td>Anaesthesia</td>
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<tr>
<td></td>
<td>Surgery</td>
</tr>
</tbody>
</table>

Minimal risk is defined as the probability of harm or discomfort that is not greater than that ordinarily encountered in daily life or during routine tests (Slevin et al., 1995). The description of risk has a significant impact on family understanding and acceptance of research proposals (Slevin et al., 1995). Research has studied children aged 7–14 years and parent’s views on the risks associated with clinical trials (Slevin et al., 1995). In this case, 81 children’s parent pairs were interviewed (Wendler & Jenkins, 2008). For a theoretical study that had no benefit but a one-in-a-million chance of death, only 40% of children and 19% of parents were willing to participate, but when the risk was described as ‘the same risk as riding in a car’ (a single car trip across town during a rush hour poses approximately a 1 in 100,000 chance of death for a child), 89% of children and 93% of parents agreed, which clearly demonstrates the importance of the way ‘risk’ is perceived by parents and children (Slevin et al., 1995).

Benefit for a child can be defined as continuous progress in treatment, diagnosis or prevention of the affected medical condition (Adams, 2010). This may be apparent in the increased efficacy, the safety of a drug, or an alternative to existing treatments that may include changes to the route of administration, dosing frequency or the duration of a drug (Adams, 2010). It may also involve the reduction of medication errors or the production of a more age-appropriate formulation (Adams, 2010).

The current EU guidelines allow the following levels of risk benefit in trials on children (Macrae, 2007):

- Risk needs to be minimal, benefiting the individual or the group.
- A minor increase in minimal risk benefiting the individual or group may be undertaken where the benefit-to-risk balance is at least as favourable as alternative approaches.
• A greater increase of minimal risk benefiting the individual, which is especially favourable in relation to available alternative approaches to the individual’s condition, may be undertaken.

There are other complexities that contribute to the enrolment of children in clinical trials, such as limited safety databases in smaller studies, concerns of parents, acceptability of placebo groups, difficulty in collecting post-marketing data, potential for long-term or delayed safety issues that may develop at a later stage of growth and development risks and issues related to the specific phases of childhood (Hartford et al., 2006).

Off-label prescription for paediatrics are utilised in the treatment of orphan diseases where additional trials to test the medications in different population are not an option or are not financially viable for pharmaceutical companies (Franco, 2013; Lavandeira, 2002). The orphan drug program was initiated in 1998 in collaboration with the FDA, with the TGA waiving the marketing-evaluation fees and allowing shorter review times (Aronson, 2006). Deferipone for the treatment of iron-load in thalassemia major is an example of a drug that comes under the orphan drug category in Australia (Simoens, 2011) retrieved from https://www.tga.gov.au/orphan-drugs. Ursodeoxycholic acid is another orphan drug registered in Australia, which is indicated for the treatment of primary biliary cirrhosis (Simoens, 2011).

The Pediatrics Trials Network Australia

The Paediatric Trials Network Australia (PTNA, 2014) draws together paediatric researchers from all over Australia. It is committed to improving child health through the facilitation of paediatric clinical trials. PTNA is a not-for-profit, virtual and inclusive
network that is open for membership by any paediatric research organisation or individual that is dedicated to increasing the quality and quantity of paediatric research in Australia.

PTNA hopes to advocate for the health benefits of Australian children by complementing the activity of other networks, thus benefiting all paediatric researchers. The PTNA focuses on conducting multicenter paediatric studies that are developed by researchers or industry partners across all therapeutic areas in order to improve the health of children. The PTNA aims to:

- provide a platform for advocacy for collaborative clinical research for paediatrics in Australia
- improve the Australian operating environment for paediatric clinical trials sponsored by industry
- increase the quality and quantity of investigator-driven paediatric trials
- strengthen the evidence base for the treatment of all children and adolescents.

Chapter summary

This chapter discussed the barriers and challenges that prevent the elderly, women and children from participating in clinical trials. There is an agreement in the literature that potential participants may elect not to participate due to a lack of awareness regarding the benefit of participating, concerns over side-effects and subsequent costs if permanent health damage occurs, concerns over logistics due to the need to travel to and from the study sites, and the belief that the researchers and healthcare professionals may lack compassion or cannot be trusted as they are more interested in the research and its commercial value rather than a patient’s well-being.

There are a small number of studies, which support the argument that poor participation of the elderly, women and children is created by the researchers. More
systematic and evidence-based research is needed. The next chapter explains the design and methodology for this study.
Chapter IV – Design and methodology

Ascertaining the safety and efficacy of a drug generally requires the drug to be taken by a number of patients that are representative of the population who will use it (Kelman et al., 2007). The sponsors, researchers and the health professionals involved in conducting a clinical trial must follow the national statement of ethics in human research (Harris & Harris, 1998).

RCTs provide the best evidence for evaluating treatment (Lofgren & de Boer, 2004). The major challenge faced by pharmaceutical companies wishing to conduct RCTs is patient recruitment, which is not always restricted because of selection criteria, but may also be limited by community members who are unwilling to take part, fearing risks or possible lifelong disabilities (Gerathy, 2010). Prolonged recruitment periods in clinical trials cause significant delays in reaching trial conclusions, increasing the cost of projects and sometimes causing the cessation of the trials (Gerathy, 2010; Weaver, 2010).

The way in which participants are approached by researchers may influence their participation experience. It was reported that when participants are nominated by their healthcare professionals — for example, when all treatment options are exhausted and research is the last available option — the patients perceive this as being a continuation of care and support through their existing therapeutic relationship (O’Connor & Liddle, 2013).

Aim

The aim of this study was to investigate whether the participation in clinical trials for drug discovery in Australia and New Zealand was truly representative of the intended populations in which the medication was likely to be used.
Objectives

The study was designed to achieve the aim by addressing five objectives. These were to:

1. undertake a review of the literature to inform the study concept and methodology and the current gaps in the literature that this study could contribute towards

2. review a block of ANZCTR historical clinical trial ‘public access data’ to establish trends in those trial methods of sample selection and possibly the relationship between selection criteria and the level of participation of the elderly, women and children groups.

3. gather the opinions of a small sample of each of the same three groups (the elderly, women and parents) on participation in clinical trials and perceptions of risks and benefits arising from their involvement to better understand the public’s perception of volunteering in clinical trials and the drivers that might influence their choices.

4. undertake a comparison between the findings of objectives 2 and 3 to understand if there is an issue of under-representation by intentional ‘exclusion from participation’ or unintentional ‘personal choices not to participate’, and to provide guidance on the need for future studies that investigate the issue of ‘clinical trial participation’ in more depth.

5. recommend future steps to ensure public awareness and informed equitable participation in clinical trials and the way forward for future research (based on the findings from objectives 1 to 4).
Study question

Is the level of representation of the elderly, women and children equitable to that of men under the age of 65, or it is affected by either the selection criteria of clinical trials or the potential participants’ personal choices or both?

Ethics

The study did not require ethics clearance to conduct Phases 1 and 2, which comprised the literature review and ANZCTR data analysis; however, clearance was required for Phase 3. Phase 3 involved surveying recording opinions of the elderly, women and parents of children with chronic diseases on participation in clinical trials. Low-risk ethics clearance was provided by the Charles Sturt University (CSU) Human Ethics Research Committee on 20 June 2016; protocol number: 400/2016/18. The ethics approval letter is attached in the Appendix 1.

Materials

The following materials were developed:

1. a formal email to the ANZCTR detailing a request to release data required for Phase 2 (Appendix 2)
2. a letter to community groups and organisations detailing a request to attend and administer the public-opinion survey for Phase 3 (Appendix 3)
3. a marketing poster for community groups and organisations to use to invite their members (Appendix 4)
4. a public-opinion survey (Appendix 5).
**Study design**

This study was designed as a descriptive research project, to evaluate the complex issue concerning inclusion of all population groups in clinical trials and mitigation of the associated risk, rather than exclusion to avoid the consequences of the risk. Evaluation research audits can be used to analyse a system, program or the performance of an organisation. The study aim was expected to be achieved through the analysis of the data captured by the ANZCTR, in order to have a better understanding of the level of participation of the whole population, based on gender and age, and to compare the findings to those from the current literature. The study was preliminary in nature, and intended to confirm or deny the viewpoint of the researcher (the evaluator) that an under-representation of the elderly, women and children existed.

This project was a first attempt to address the question, and it was believed at the outset, and supported by the description received, that the information in the ANZCTR database would be sufficient to address this question. It was only after the data had been obtained and analysed that it became apparent that the information in the database was seriously flawed through gaps and omissions. With the benefit of hindsight, it was then clear that trying to base this study on the ANZCTR data alone was inadequate. However, this was not apparent during the planning stage when only the number of registered studies, and the data that was supposed to be submitted to the database on each trial was known, and the extent of missing data was unknown.

The study was conducted over three phases: a review of the literature, followed by ANZCTR public access data analysis and then finally a preliminary public survey.
Phase 1 – Literature review

A literature review was conducted to identify gaps in knowledge in the current literature and to inform the development of the concept of this study. A number of electronic databases (PubMed, EMBASE, the Cochrane Library, and the FDA repository) were searched for peer-reviewed articles, reports and clinical trial updates (from and for 2008 to 2015). There was no restriction on the types of disease, treatments and success (or lack thereof) in registering medicines. The following search terms were used: ‘pharmaceuticals’, ‘drugs’, ‘clinical trials’, ‘medicines’, ‘formulations’, ‘randomised clinical trials’, ‘Australian clinical trials’, ‘elderly in clinical trials’, ‘children in clinical trials’, ‘women in clinical trials’, ‘sex’, ‘age’, ‘paediatrics’. After the removal of duplicate articles, the remaining articles were individually examined to check if they met the selection criteria.

Literature review papers selection criteria

- RCTs which do no involve gender-specific medication; and papers published in English
- All or at least one of the women, children and elderly groups should be included

This phase formed the background section of the study and identified the limits of the existing research, enabling the development of the study concept.

Phase 2 – ANZCTR historical public portal data analysis

This phase was conducted to analyse the current ANZCTR data on clinical trials, specifically in regards to participation by the elderly, women and children during the period of 2009 to 2013. A clinical trial was included in the review when it was classified
as an RCT, double-blinded and placebo-controlled, and for medications which were not specialised for men or women only. Only the drug-based trials were eligible and any other treatment types, including non-drug interventions, were excluded.

The researcher contacted the ANZCTR by email. The ANZCTR then supplied the ‘publically accessible’ data in a Microsoft Excel™ spreadsheet containing every trial registered through the ANZCTR that was:

- interventional
- related to treatment using drugs, surgery, devices and ‘other’ (miscellaneous)
- registered on the ANZCTR from 1 January 2008 until 27 June 2013.

The ANZCTR did not include trials related to diagnosis/diagnostic test trials. The Excel spreadsheet contained all information provided in the record for each trial meeting the above-mentioned criteria, with columns containing information on each trial’s key inclusion criteria, key exclusion criteria, age range and gender highlighted in yellow in a separate worksheet named ‘Trials’.

The data were manually cleaned by converting character to numerical values to enable categorisation for analysis. Quality assurance was conducted by the researcher and supervisors.

A series of electronic searches for variables in the ANZCTR historical data were conducted to prevent information from being overlooked during analysis — for example, the variation in entries of Australian states, such as ‘New South Wales’, ‘new south wales’, ‘N.S.W’, ‘nsw’ or ‘NSW’; all were changed to ‘NSW’.

For age groupings, the minimum-age-type field was analysed since that provided units (days, weeks, months, etc.). If the minimum-age type was less than ‘year’ then the data were moved into the youngest category, otherwise, the minimum age determined the category for the study.
All age ranges were included for the women in the clinical trials. Above or equal to 65 years of age was the cut-off for trials on elderly males or females and parents of children (20 years was the upper age limit) that were used for clinical trials (Figure 7).

**Inclusion criteria**

- RCTs including children, women and elderly subjects
- Drug-based trials
- Women of all ages
- Elderly people aged 65 years or over
- Children 21 years and under
- Published during the period from 2008 to 2013
- Australian participants.

**Exclusion criteria**

- Studies including only adult male subjects
- Abstracts from conference or meeting publications
- Treatments including homeopathic or herbal trials.

Initially 133,000 potential relevant publications were identified. This number was then refined after excluding 21,890 duplicate publications, thus leaving 111,110 publications.

An additional filter was then applied based on the title and the abstract, leading to the exclusion of a further 110,553 publications. Using the PICO (population, intervention, comparator/control and outcome) principle, the remaining 557 full text publications were screened. Out of those, only 132 publications were selected and referred for the current
study. These 132 selected publications met the inclusion criteria by being the most relevant and suitable for this research.

Figure 7. Flow diagram of the literature search and selection from the database.

The researcher made the first attempt of the analysis using Microsoft Excel™. However, after the analysis was reviewed by a statistician, it was advised that the data was complex and required specialist analysis, much beyond the scope and capability of Excel and SPSS. An expert from Contract Research Organisation (CRO) DataPharm™ Australia Pty Ltd was contacted to conduct the analysis using SAS™ (Statistical Analysis System, SAS Institute, Inc. Cary, North Carolina, USA, version 9.4). (Littell et al., 2006).

DataPharm™ is Australia’s CRO and provides clinical trial services, such as clinical trial site selection, regulatory and site set-up, clinical trial monitoring services, data management, statistics, medical and scientific writing, medical monitoring and pharmacovigilance, quality control processes and GCP auditing (DataPharm™ Australia,
2014). All data obtained from the ANZCTR was categorical, and thus data cross tabulation was used in the analysis. All interpretation was performed by the researcher.

**Phase 3 – Public survey**

**Survey development**

Based on the references listed in Table 7, the survey questions were developed. The questions were based on the following criteria; reasons for not to participate indicated by subjects as feedback post participation in trials, information relayed to the public to encourage their participation, and organisations’ perceptions of reasons of poor participation in clinical trials. Three sets of eight-question questionnaires for each cohort (elderly, women and children) were designed based on the information presented in the resources listed in Table 7. The first part of the survey was designed to collect demographics and ensure selection criteria were met, while the second part consisted of eight close-ended questions with a Likert scale of four. The final part was an open-end question to allow participants to add any comments that had not been covered by the closed-end questions.
Table 7. Development of the survey questions.

<table>
<thead>
<tr>
<th>Source</th>
<th>Link</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Should your child be in a clinical trial? U.S. Food and Drug Administration, 10903 New Hampshire Avenue Silver Spring, MD 20993 1-888-INFO-FDA (1-888-463-6332) Page last updated: 23 January 2017</td>
<td><a href="http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048699.htm">http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048699.htm</a>,</td>
<td>Children</td>
</tr>
<tr>
<td>Is recruitment more difficult with a placebo arm in randomised controlled trials? A quasirandomised, interview based study. Welton et al. (1999)</td>
<td><a href="http://www.bmj.com/content/318/7191/1114">http://www.bmj.com/content/318/7191/1114</a>,</td>
<td>Women</td>
</tr>
<tr>
<td></td>
<td><a href="https://www.nia.nih.gov/health/publication/clinical-trials-and-older-people">https://www.nia.nih.gov/health/publication/clinical-trials-and-older-people</a>,</td>
<td></td>
</tr>
<tr>
<td></td>
<td><a href="http://rtjournalonline.com/10.08.1342.pdf">http://rtjournalonline.com/10.08.1342.pdf</a></td>
<td></td>
</tr>
<tr>
<td>The importance of children in clinical trials. An interview with Daniel K. Benjamin, Jr., MD, PhD, professor of pediatrics at the Duke Clinical Research Institute and Director of the BPCA Paediatric Trials Network (PTN). Winter 2012 Issue: Volume 6 Number 4 Page 6-7</td>
<td><a href="https://medlineplus.gov/magazine/issues/winter12/articles/winter12pg6-7.html">https://medlineplus.gov/magazine/issues/winter12/articles/winter12pg6-7.html</a></td>
<td>Children</td>
</tr>
<tr>
<td>Representation of the elderly, women, and minorities in heart failure clinical trials Asefeh Heiat, MD, MPH; Cary P. Gross, MD; Harlan M. Krumholz, MD Arch Intern Med. 2002;162(15): No pagination specified. doi:10.1001/archinte.162.15.1682 Figure 4 - Comparison between RCT patients and HF patients in the community</td>
<td><a href="http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1148796">http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1148796</a></td>
<td>All</td>
</tr>
<tr>
<td>Clinical Trials and Older People National Institute on Aging, 31 Center Drive, MSC 2292, Bethesda, MD 20892 Page last updated: 25 January 2017</td>
<td><a href="https://www.nia.nih.gov/health/publication/clinical-trials-and-older-people">https://www.nia.nih.gov/health/publication/clinical-trials-and-older-people</a></td>
<td>The elderly</td>
</tr>
</tbody>
</table>

The survey was an initial attempt, and would need to be validated by other samples from another location in Australia, to ensure that the questions were sound and could be used by others and not just the developer. Additionally, a readability evaluation was undertaken prior to using the survey (Figure 8). The Flesch–Kincaid grade score was 9.5 and the flesh reading ease score was 58.2%. (A low Flesch–Kincaid grade corresponds to a high readability ease score).
The intention of conducting this survey was to assess the feasibility of the use of a survey to gather public opinion regarding participation in clinical trials to inform future studies, rather than to establish reasons for poor participation by the general population. A secondary aim of the survey was to understand the public perception of possible motives to be involved and participate in clinical trials, to re-develop the survey question for future studies.

**Distribution of the survey**

All community groups in Wagga Wagga were approached by emails, which provided with initial information outlining the research aim and objectives and requested their support. Community groups that were approached included: rotary clubs, community parent groups, and women breakfast groups in the Wagga Wagga area. No specific ethnic or socio-economic groups were targeted and direct contact was not made with any individuals. The researcher requested to visit the group during their normal meetings to conduct an information session explaining the study and each of the survey questions and to offer the members a copy of the survey.
The researcher visited those groups that responded and provided them with a definitions fact sheet, which included information regarding clinical trials, volunteering to participate, clinical trial subjects, consent, assent, withdrawal, and new drugs; as well as study information sheets, and the poster for distribution to the participants along with the survey questions. A sealed box for the completed survey collection and copies of the survey were also provided.

The researcher returned to the community group after four weeks and collected the returned surveys. It was made clear to the potential participants, in the information sheet, that participating in the survey did not oblige them to take part in any further clinical trials or similar studies and that the collected data was unidentifiable, with neither the person nor the community group name included. Implied consent to participate was considered achieved once a participant had deposited a completed survey into the sealed box. Each community group was briefed on the trials by using the information sheet approved by the CSU ethics committee, via email and not face-to-face. No other additional information about clinical trials was provided to potential participants other than the definitions of terminologies to prevent the researcher’s influence on participants’ opinions.

It was also fully understood that the results from such a small sample would be considered as indicative and not confirmatory, but would, nonetheless, provide useful insight for undertaking further research.

Survey sample

The sample was a small convenience sample that included equal proportions of the elderly, women and parents (advocating for their children). The selection criteria for the sample was designed to be specific to people who were living with chronic disease and who understood the value of treating chronic conditions over not treating the conditions
or leaving them unmanaged. Due to the wide geographical spread of the sample collection location (rural NSW) and limited access to patients, as well as the researcher being a non-practicing overseas Pharmacist, it was not possible to use a powered sample size. The aim was to enrol 30 people in each of the three groups. To account for the likelihood of some surveys not being returned, it was decided to distribute 200 surveys. The sample was sourced from community groups in Wagga Wagga, New South Wales, Australia.

**Inclusion criteria for Phase 3**

- Australian citizen or resident
- Men or women
- At the age of 18 or above for the women group, above the age of 65 for the elderly group, or a parent of any age and gender, of a child who is under the age of 21 years.
- Participants must be diagnosed with at least one chronic disease that requires ongoing medication for the elderly or women groups, or be a parent of a child who is under the age of 21 who is diagnosed with at least one chronic condition that requires ongoing medication.

**Exclusion criteria for Phase 3**

- Have a rare medical condition where there is no other current cure
- Not able to consent (complete the survey independently).

Individuals who fitted the selection criteria were asked to enrol into one category only, as either women, the elderly or parents — no double entry was allowed. Also, no financial incentive (either in cash or in kind) was given to the participants. The survey
was completed during the participated groups’ normal scheduled meeting time to minimise inconveniences. All paper copies of the survey were then scanned and saved in electronic form; the paper copies were shredded and disposed of into a secure paper waste bin on the university campus.

**Limitations of the survey methodology**

While the response rate of surveys is known to be low, surveys are cost-effective options when a large sample is required in a shorter time than an interview. However, effective surveys must have reasonable readability scores that are suitable to the audience. Low Flesch-Kincaid grade scores and high flesh reading ease scores are most suited to members of the public aged between 8–10 to allow for higher return and to meet the general public literacy level. The readability index is less than 60%, so 4 in 10 have found the survey difficult to read. The survey sample size was also low.

**Pros and cons of the survey methodology**

Attitude changes in people can range from low to high. This behavioural trait can result in the same cohort of people exhibiting positive behaviours and culture, and can moderate many social psychological phenomena (Phil et al., 2012).

The survey methodology provides an ideal condition, which reflects and represents the general population opinion without the pressure of face-to-face interviewing (Phil et al., 2012). However, like most tools used in qualitative research; surveys also have some limitations. In particular:

- surveys based on research may be expensive when large samples or polls are required
• unconscious bias and misunderstanding of the survey questions can contribute towards unexpected results
• data entry errors of paper copy surveys contribute to misreporting
• designing a survey is a critical step to maximise the reliability and validity of the collected data.

Once a survey design has been specified, the next step is to validate it in small samples to ensure that its readability and cognitive meaning are all correctly achieved. Changes can be then made, followed by a second validation round, before finally using the survey on the main study population. Careful monitoring of the ongoing data collection permits early detection of problems. If problems relating to survey understanding are established, data collection may be ceased or the issue should be considered during data analysis.

Survey plain language statement

All individuals regardless of age, gender or ethnicity who take medicines are subjected to some potential risks; these risks are commonly known as side-effects. The severity varies in different individuals, and is based not only on personal response, but also upon gender, age group and the individual state of health.

Clinical studies conducted during the development of new medicines are generally designed to establish the new drug safety and efficacy under strict conditions. New drugs are tested in humans after they are proven not to be toxic in animals. They are then trialled in relatively carefully-selected and defined populations of healthy adults for tolerability (side-effects and to determine the dose). The next step involves testing the drug’s ability to treat or cure the disease, which is known as efficacy. This testing is usually conducted
in patients who are diagnosed with the medical condition that the medicine is intended to treat.

This study reviewed the literature with the intention to understand if the level of participation, as volunteer subjects, in clinical trials was representative of the general population. This was important for assessing the drug’s safety and efficacy in patients who intended to use it before it was registered and marketed; and thus to make the drug safer for the rest of the population after marketing. This part of the study found that there was poor representation from special groups such as older people, women and children.

The second part of the study examined the current records for clinical trials in Australia to investigate this poor participation; however, this could not be confirmed or denied as the records were somewhat incomplete.

The third part was a feasibility survey, which was developed by the researcher based on the previous studies findings on reasons that encourage or discourage people from volunteering to participate in the clinical trials. The intention of conducting this survey was to assess the feasibility of the use of the survey to gather public opinion regarding participation in clinical trials, rather than the feedback after participation similarly to that done by most of the other studies. Participants were asked to respond to questions that would require 15 minutes of their time. Consent to participate would be considered achieved once a participant had deposited the survey into the sealed box located in their community group meeting venue. As the box was sealed and the survey did not have any personal identifiers (name or address), withdrawal of entry was not possible after the deposit of the survey into the collection box. However, people who collected the form but then changed their opinion not to participate, may have either disposed of the form or deposited it into the collection box as a blank.
For a volunteer to be able to participate in this survey, he/she must have been: an Australian citizen or resident, 18 or above in age for the women group, above the age of 65 for the elderly group, or a parent of any age and gender, of a child who was under the age of 21 years and diagnosed with at least one chronic disease that required ongoing medication.

People who had a rare medical condition for which there was no other current cure, or people not able to consent (complete the survey independently) were not able to participate. Individuals who fitted the selection criteria were able to enrol in one category only, as women, the elderly or as parents. No direct financial or health benefits were provided to participants; however, the findings would constitute additional resources for future studies.

Data analysis

Data collected in Phase 2 was analysed using SAS™ version 9.4 (SAS Institute, Inc. Cary, North Carolina USA). All analyses were performed using simple frequency analysis with no inferential testing. No formula was used as the values were classified as a simple numerical count for each category using the ‘PROC FREQ’ code sequence. SAS stands for the Statistical Analysis System, a software system used for data analysis and writing up reports (Littell et al., 2006).

SAS is a group of computer programs that work together to store the values of datasets, retrieve them when needed, modify data as needed, compute simple and complex statistical analyses, and provide the outcome in the form of reports. SAS can be used through the SAS Analyst (O’Rourke et al., 2013). An individual can write code for maximum flexibility to perform complex analyses (Allison, 2010). Data should be in a SAS or Excel format in order to use SAS and should be carefully arranged to run on SAS.
SAS provides a graphic point-and-click user interface for non-technical users and more advanced options through the SAS programming language (Allison, 2010). SAS data can be published in HTML, PDF, Excel and other formats using the Output Delivery System (Scott, 2006). SAS is now applied everywhere in research, industry and government and the result is authentic, reliable and evidence-based.

Thematic analysis is the most common form of analysis in qualitative research; it emphasises the examining and recording of patterns (themes) within data (Nilay, 2004; Tuckett, 2005). Themes are patterns across datasets that are important to detail the descriptions of phenomena associated with a specific research question (Nilay, 2004). Themes are then collected together to make a complete set and a pattern emerges that forms the foundation of the theme analysis (Aronson, 1995). Patterns are then categorised into sub-themes (Aronson, 1995; Fereday & Muir-Cochrane, 2008). Each pattern is then described, and the analyses progress to explaining and interpreting those patterns and their broader meanings and implications (Baum et al., 2013; Tuckett, 2005; Braun & Clarke, 2006).

Thematic analysis allows the researcher to understand large datasets from open-ended questions including interviews. However, its reliability is of concern due to the subjectivity of both the researcher and the participants (Tuckett, 2005). In this study, thematic analysis was only used for the final question in the survey and for analysing the literature review results. Alternative approaches were not considered as the amount of data that required analysis other than statistical analysis was very limited.

**Documentation security**

The researcher ensured that data was saved onto a password protected laptop. The researcher ensured the use of an Iron Mountain key USB for back-up copies. All data
collected from the Phase 3 survey were saved in an unidentifiable electronic format only. The file was saved on the CSU server and on the researcher’s computer. Records were kept for a minimum of five years in accordance with the National Research in Human Statement.

**Chapter summary**

In this chapter, the method used to conduct this research was explained. Details on how the data be analysed would be elaborated in detail. The project was conducted over three phases starting with a review of the literature, followed by data analysis for public data published on the ANZCTR and concluded with the public opinion survey which required ethics clearance. The next chapter will outline the results of the three phases.
Chapter V – Results and data analysis

Phase 1 – Literature review

This phase formed the background section of the study and identified the limits of the existing research, enabling the development of the study concept. A literature review was conducted to identify gaps in knowledge and develop the concept of the study. A number of electronic databases (PubMed, EMBASE, the Cochrane Library, Medline and the FDA repository) were searched, from 2000 to 2015 for peer-reviewed articles, scientific publications, books, reports and clinical trial updates from academic conference proceedings. Country-specific drug regulatory internet websites (English translated version) were also searched. There was no restriction on the types of disease, treatments and success (or lack thereof) in registering medicines.


The selection criteria included that the publications:

1) were written in English

2) focused on pharmaceutical or drug safety surveillance and risk management in the elderly, women and children.

The following types of articles were excluded:

1) conference programs

2) those comprised of only the abstract

3) educational catalogues for marketing purposes

4) articles published in journals sponsored by commercial trades of medicines
5) medical experts’ interviews or blogs

6) general discussions or commentaries related to risk associated with medical devices or biotechnology.

After the removal of duplicate articles and those that were not undertaken in relation to the targeted population to be studied, the remaining articles were individually examined to check if they met the selection criteria. Table 10 shows the process adapted during the literature review.

Table 8. Adapted process for the literature search.

<table>
<thead>
<tr>
<th>Search engine</th>
<th>Keywords</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Articles selected for this research</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed, EMBASE, the Cochrane Library, Medline and the FDA repository</td>
<td>Pharmaceuticals, drugs, clinical trials, medicines, formulations, randomised clinical trials, Australian clinical trials, elderly in clinical trials, children in clinical trials, women in clinical trials, sex, age, paediatrics, pharmacovigilance</td>
<td>1) The publications were in English; and 2) they focused on pharmaceutical or drug safety surveillance and risk management in women, children and elderly.</td>
<td>Conference programs with speakers’ profile and abstract only, educational catalogues for marketing purposes, journals which deal in the commercial trading of medicines, medical experts’ interviews as well as blogs, and general discussions related to risk associated with medical devices or biotechnology.</td>
<td>Overall, 581 articles were searched online using keywords, which dealt with human study and participation of women, children and the elderly in clinical trials. Out of these, 278 articles were shortlisted, which mentioned ADR, real case studies, or evidence-based studies. These were incorporated into this thesis.</td>
</tr>
</tbody>
</table>

At the conclusion of the literature review reasons for inclusion or exclusion from clinical trials were identified and listed by study names (Table 11). Additionally, any study which included participants’ feedback was listed and the main feedback areas were included in Table 12. The comments of parents and children were combined in one section. All comments were then grouped to create a domain which could be used to develop the survey questions. The following were the top factors that can be considered
as a reason to enrol in a trial or to be excluded from a trial based on Tables 11 and 12, which formed the basis of Table 13. Table 14 lists questions and the domains that were used to develop them.
### Table 9. Reasons for exclusion or inclusion.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Elderly</th>
<th>Women</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide studies in 1960</td>
<td></td>
<td>Pregnant ladies and lactating women due to vulnerable nature</td>
<td></td>
</tr>
<tr>
<td>Women patients with pre-menopausal breast cancer trialled at two university centres and a satellite centre, Herlev, Odense, and Sonderborg</td>
<td></td>
<td>Women who suffer from Cancer</td>
<td></td>
</tr>
<tr>
<td>Treatment with inhaled corticosteroids on patients with chronic respiratory disease during 1992–2006 in Western Australia</td>
<td>Greater than or equal to 65 years of age</td>
<td>Participants who had suffered an unspecified active or recent hepatic disease</td>
<td>Participants who had suffered an unspecified active or recent hepatic disease</td>
</tr>
<tr>
<td>COX-2-selective NSAID rofecoxib trial in Western Australia during 1999–2000</td>
<td>Participants who had suffered an unspecified active or recent hepatic disease</td>
<td>Greater than or equal to 65 years of age</td>
<td>Greater than or equal to 65 years of age</td>
</tr>
<tr>
<td>Cardiac clinical trials at Duke University Medical Center (DUMC) between November 2001 and May 2004.</td>
<td>Patients with a language barrier or those whose consent was obtained from their legally authorised representatives, and patients not eligible for the cardiac trials were excluded from this study.</td>
<td>Patients with a language barrier or those whose consent was obtained from their legally authorised representatives, and patients not eligible for the cardiac trials were excluded from this study.</td>
<td></td>
</tr>
<tr>
<td>Patients with large rectal adenomas counseled between January and July 2011 for participation in an RCT comparing endoscopic mucosal resection (EMR) with trans anal</td>
<td>Patients with the actual disease were included</td>
<td>Patients with the actual disease were included</td>
<td></td>
</tr>
<tr>
<td>Study name</td>
<td>Elderly</td>
<td>Women</td>
<td>Children</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>---------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>endoscopic microsurgery (TEM) were invited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A review of protocols submitted to the FDA between 1988 and 1994 showed only 24 (16%) of 152 HIV studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A survey for 1992–1996 of INDs and NDAs revealed Inconsistency too</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kalorama information research on paediatrics participation in oncology trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>To investigate the inclusion of a placebo arm in a clinical trial of hormone replacement therapy (trial throughout UK)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuskegee Syphilis Study, an infamous clinical study conducted between 1932 and 1972 by the U.S. Public Health Service</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exclusion</td>
<td>Inclusion</td>
<td>Exclusion</td>
</tr>
<tr>
<td></td>
<td>Did not enrol Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females were excluded from 25% of the studies reviewed, and 40% of these exclusions were from Phase-I pharmacokinetic studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age of the children was not mentioned; neither was whether they were an infant or a grown up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Women aged 45–64 who had not had a hysterectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rural African-American men — no mention of age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Participants’ positive and negative feedback.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Elderly</th>
<th>Women</th>
<th>Children/Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women patients with pre-menopausal breast cancer trialled at two university centres and a satellite centre, Herlev, Odense, and Sønderborg</td>
<td>Participation is a moral obligation. Trials are necessary for further medical development. Patients originally trusted that doctors primarily pursued the interest of patients.</td>
<td>Patients expressed discomfort with randomisation. Mistrust was shown towards the pharmaceutical industry. They did not trust the adequacy of doctors or industry in maintaining self-regulation.</td>
<td></td>
</tr>
<tr>
<td>Cardiac clinical trials at Duke University Medical Center (DUMC) between November 2001 and May 2004.</td>
<td>Trust in their doctor, the benefit of being in the research study, family opinion was also associated with patients’ enrollment decisions, having participated in research studies in the past</td>
<td>Treatment in question was unproven, the possible risks involved in participating in the research study, not knowing which treatment they would be assigned and the inconvenience associated with participating in the study</td>
<td></td>
</tr>
<tr>
<td>Kalorama information research on paediatrics participation in oncology trials</td>
<td></td>
<td></td>
<td>Children participating in oncology trials did not understand what their doctor was saying to them about the trial, and that the decision was more in the hands of their parents and doctors</td>
</tr>
<tr>
<td>To investigate the inclusion of a acebo</td>
<td>Willingness to take part in a trial</td>
<td>Not wanting to take unknown or unnecessary tablets, or not</td>
<td></td>
</tr>
</tbody>
</table>

113
<table>
<thead>
<tr>
<th>Study name</th>
<th>Elderly</th>
<th>Women</th>
<th>Children/Parents</th>
</tr>
</thead>
<tbody>
<tr>
<td>arm in a clinical trial of hormone replacement therapy (trial throughout UK)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A standard periodontal examination was undertaken in a group of 66 (54 men and 12 women) in Australia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive feedback</td>
<td>Negative feedback</td>
<td>Positive feedback</td>
<td>Negative feedback</td>
</tr>
<tr>
<td>Don’t want to change treatment.</td>
<td>Too ill.</td>
<td>Possible side-effect of tests.</td>
<td>Don’t want to be a guinea pig.</td>
</tr>
</tbody>
</table>
Table 11. Domains developed to inform the design of the survey questions.

<table>
<thead>
<tr>
<th>Domain name</th>
<th>Factors and reasons included in the domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients’ own best interests — that is, personal maximised safety, confidence and trust</td>
<td>Women patients with pre-menopausal breast cancer trialled at two university centres and a satellite centre, Herlev, Odense, and Sønderborg</td>
</tr>
<tr>
<td>Perceived lack of clinical equipoise</td>
<td>Cardiac clinical trials at Duke University Medical Center (DUMC) between November 2001 and May 2004; Kalorama information research on paediatrics participation in oncology trials</td>
</tr>
<tr>
<td>Attitudes towards clinical research</td>
<td>To investigate including a placebo arm in a clinical trial of hormone replacement therapy (trial throughout UK)</td>
</tr>
<tr>
<td>Relative necessity of trials</td>
<td>To investigate including a placebo arm in a clinical trial of hormone replacement therapy (trial throughout UK)</td>
</tr>
<tr>
<td>Randomisation — unease with letting chance decide</td>
<td>Women patients with premenopausal breast cancer trialled at two university centres and a satellite centre, Herlev, Odense, and Sønderborg</td>
</tr>
<tr>
<td>Trial participation as a moral imperative</td>
<td>To investigate the inclusion of a placebo arm in a clinical trial of hormone replacement therapy (trial throughout UK); women patients with pre-menopausal breast cancer trialled at two university centres and a satellite centre, Herlev, Odense, and Sønderborg</td>
</tr>
<tr>
<td>Public and the internal control — both necessary</td>
<td>To investigate the inclusion of a placebo arm in a clinical trial of hormone replacement therapy (trial throughout UK); a standard periodontal examination was undertaken in a group of 66 (54 men and 12 women) in Australia</td>
</tr>
<tr>
<td>Motives of doctors and researchers</td>
<td>Cardiac clinical trials at Duke University Medical Center (DUMC) between November 2001 and May 2004</td>
</tr>
</tbody>
</table>

Australian Clinical Trials 2009–2013
Table 12. Questions and the domains used to develop them.

<table>
<thead>
<tr>
<th>Survey question</th>
<th>Domain/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 If you were healthy would you participate in clinical trials?</td>
<td>Patients’ own best interests — that is, personal maximised safety, confidence and trust</td>
</tr>
<tr>
<td>Q2 If you had the disease that a new medicine is treating, but you were happy with your current treatment; would you participate in clinical trials?</td>
<td>Public and the internal control — both necessary</td>
</tr>
<tr>
<td>Q3 If you had the disease the new medicine is treating, but were not happy with your current treatment; would you participate in the clinical trials?</td>
<td>Randomisation — unease with letting chance decide; attitudes towards clinical research</td>
</tr>
<tr>
<td>Q4 If you had the disease the new medicine is treating, but no other treatment was working and the new medicine was your last hope; would you participate in the clinical trials?</td>
<td>Relative necessity of trials</td>
</tr>
<tr>
<td>Q5 If you had the disease the new medicine is treating, and you were offered lifelong health insurance which covers any side-effect or damage caused by the tested medicine, regardless of if there was, or was not another treatment currently working; would you participate in the clinical trials?</td>
<td>Patients’ own best interests — that is, personal maximised safety, confidence and trust; motives of doctors and researchers</td>
</tr>
<tr>
<td>Q6 If you had the disease the new medicine is treating, and if you were offered lifelong health insurance which covers any side-effect or damage caused by the tested medicine, and there was no other treatment working; would you participate in the clinical trials?</td>
<td>Randomisation — unease with letting chance decide; motives of doctors and researchers</td>
</tr>
<tr>
<td>Q7 If you had the disease the new medicine is treating, if you were offered a payment, regardless of if there was or there was no other</td>
<td>Perceived lack of clinical equipoise; motives of doctors and researchers</td>
</tr>
<tr>
<td>Survey question</td>
<td>Domain/s</td>
</tr>
<tr>
<td>----------------</td>
<td>----------</td>
</tr>
<tr>
<td>treatment working: would you participate in the clinical trials?</td>
<td></td>
</tr>
<tr>
<td>Q8 If you had the disease the new medicine is treating, if you were offered a payment, and there was no other treatment working, would you participate in the clinical trials?</td>
<td>Public and the internal control — both necessary; motives of doctors and researchers</td>
</tr>
</tbody>
</table>
Phase 2 – ANZCTR data analysis

The following fields were considered when analysing the historical data collected from the clinical trials registered on ANZCTR during the period from 2009 to 2013:

- clinical trial registration condition codes
- clinical trial funding sources
- clinical trial locations including the location of the subject samples
- updating of clinical trials based on post-marketing Phase IV results or changes
- clinical trial sample breakdown by age and gender
- records of pregnant women participation
- records of participant withdrawal due to disease deterioration or side-effects.

Clinical trials registered between 2009 and 2013 were considered in this analysis. The data accessible in the public domain were insufficient for the purposes of this analysis; consequently, more comprehensive data was requested from ANZCTR to complete the detailed analysis. Datapharm™ was contracted to conduct the analysis of the data gathered from the ANZCTR. While the fields to be analysed comprised a simple count of cells, the complexity of the data tabulation meant that the data were not able to be analysed by the candidate. The dataset contained 3740 rows, with each row listing details of a single clinical trial over 53 columns (clinical trial identification code, study short title, study long scientific title, study abbreviation or acronym, type of intervention, medical condition that the medication proposed to treat, study type, study location, study purpose, study design: concealment, sequencing, masking, placebo, control or assignment; study design feature, study end point, statistical method used, duration of the study, sample selection, when the study was conducted, study phase, trial start date and end date including anticipated date and actual date; sample size, recruitment method,
ethics review, study summary and stage, when the dossier was submitted for registration, approval date, Australian or NZ clinical trial registration number, trial website and other notes, sample exclusion criteria and selection criteria, if any standards were used, the primary sponsor and finally, when the trial file was last updated). The dataset from ANZCTR was coded and categorised.

**Number of trials per year**

For the data analysis, trials starting in 2008 or before were excluded; hence, all trials from 2009 have been taken into consideration. On the clinical trials worksheet, there were 3739 trials registered; however, only 2946 trials (92%) were considered. Only trials that had commencement dates and closing dates were considered and counted, regardless of being completed or not or whether their subjects were enrolled or not. Figure 9 shows the number of trials registered by year during the period between 2009 and 2013. It had been noted that some trials started recruiting, but were stopped at a later stage of recruitment. Additionally, it was noted that ‘not yet recruiting’ accounted for 43.0% of all the trials. This might be because the trial had not been updated after the initial registration date, the ‘last updated date’, or because the trial update was submitted after the registry webpage was lately updated (hence, it was not captured or recorded). Such trial information would usually be updated at a later stage. Some manufacturers were approached for such information; however, the length of freedom of information documentations, additional ethics clearance and the number of abundant studies made achieving this outcome almost impossible. Additionally, with the limited time of candidature, it was impossible to follow up a meaningful or representable sample.
There was a gradual increase in the number of registered clinical trials per annum from 2009 until 2012. There was a sharp decline in 2013 from 681 to 400 clinical trials. In a statement released by the Minister of Health and Sport, the main reason given for this decline was the inability to recruit enough volunteers to participate in clinical trials.

**Funding sources**

Some trials have multiple funding sources, for example, some clinical trials have combined non-government organisation (NGO) and government funds or are funded in collaboration with research-based universities and hospital facilities (Table 15). It has been noted that government funding bodies have the highest-funding grants and account for 22.9% of the total provided funds. Government funding bodies, such as the NHRMC
and the Australia Research Council (ARC), funded most of the clinical trials registered in Australia throughout this period. Government funding was followed by funding from pharmaceutical industries at 21.5%.

Universities and Hospitals are placed third and fourth in the funding order. There are many integrated health research centres in universities that are working in collaboration and partnership with hospitals. For example, the Menzies School of Health Research at Charles Darwin University is working with the Royal Darwin Hospital.

Foundations and charities are placed fifth in the funding category followed by self-funded research. There are many organisations, such as the Cancer Council, Headspace, and Beyond Blue, that financially contribute to health research. It has also been noted that some trials that had multiple funding sources had more than one condition code registered.

Table 13. Funding for types of clinical trials from 2009 to 2013.

<table>
<thead>
<tr>
<th>Fund type</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative frequency</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charities/societies/foundations</td>
<td>475</td>
<td>13.95</td>
<td>475</td>
<td>13.95</td>
</tr>
<tr>
<td>Commercial sector/industry</td>
<td>632</td>
<td>18.57</td>
<td>1107</td>
<td>32.52</td>
</tr>
<tr>
<td>Government funding body</td>
<td>676</td>
<td>19.86</td>
<td>1783</td>
<td>52.38</td>
</tr>
<tr>
<td>Hospital</td>
<td>482</td>
<td>14.16</td>
<td>2265</td>
<td>66.54</td>
</tr>
<tr>
<td>Other</td>
<td>67</td>
<td>1.97</td>
<td>2332</td>
<td>68.51</td>
</tr>
<tr>
<td>Other collaborative groups</td>
<td>98</td>
<td>2.88</td>
<td>2430</td>
<td>71.39</td>
</tr>
<tr>
<td>Self-funded/unfunded</td>
<td>451</td>
<td>13.25</td>
<td>2881</td>
<td>84.64</td>
</tr>
<tr>
<td>University</td>
<td>523</td>
<td>15.36</td>
<td>3404</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Number of trials registered by condition code

Any registered trial can specify up to three different condition categories as indicated in the Australian New Zealand Clinical Trials Registry, 2015 (Viergever & Ghersi, 2011). Medications with ‘mental health’ listed as the medical condition were at the top of the list followed by chronic diseases, such as cancer and anesthesiology (Table 16).
There was a discrepancy between the analysis results presented in Table 16 and the top health priorities in Australia as listed by the Australian Institute of Health and Welfare (World Health Organisation, 2016) with the early results of the 2011–2012 National Health Survey:

- Cancer
- Cardiovascular health
- Injury prevention and control
- Mental health
- Diabetes mellitus
- Asthma
- Arthritis and musculoskeletal conditions
- Obesity
- Dementia.

This also suggests that the pharmaceutical industry spending may not be directed to research into diseases that constitute the greatest burden on the health system, but possibly into areas where a patent on a new treatment can be achieved.
Table 14. Clinical trials registered by condition code from 2009 to 2013.

<table>
<thead>
<tr>
<th>Condition codes</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative frequency</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative and complementary medicine</td>
<td>127</td>
<td>3.03</td>
<td>127</td>
<td>3.03</td>
</tr>
<tr>
<td>Anaesthesiology</td>
<td>292</td>
<td>6.97</td>
<td>419</td>
<td>10.01</td>
</tr>
<tr>
<td>Blood</td>
<td>55</td>
<td>1.31</td>
<td>474</td>
<td>11.32</td>
</tr>
<tr>
<td>Cancer</td>
<td>323</td>
<td>7.71</td>
<td>797</td>
<td>19.04</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>256</td>
<td>6.11</td>
<td>1053</td>
<td>25.15</td>
</tr>
<tr>
<td>Diet and nutrition</td>
<td>199</td>
<td>4.75</td>
<td>1252</td>
<td>29.90</td>
</tr>
<tr>
<td>Ear</td>
<td>21</td>
<td>0.50</td>
<td>1273</td>
<td>30.40</td>
</tr>
<tr>
<td>Eye</td>
<td>101</td>
<td>2.41</td>
<td>1374</td>
<td>32.82</td>
</tr>
<tr>
<td>Human genetics and inherited disorders</td>
<td>34</td>
<td>0.81</td>
<td>1408</td>
<td>33.63</td>
</tr>
<tr>
<td>Infection</td>
<td>184</td>
<td>4.39</td>
<td>1592</td>
<td>38.02</td>
</tr>
<tr>
<td>Inflammatory and immune system</td>
<td>104</td>
<td>2.48</td>
<td>1696</td>
<td>40.51</td>
</tr>
<tr>
<td>Injuries and accidents</td>
<td>84</td>
<td>2.01</td>
<td>1780</td>
<td>42.51</td>
</tr>
<tr>
<td>Mental health</td>
<td>441</td>
<td>10.53</td>
<td>2221</td>
<td>53.05</td>
</tr>
<tr>
<td>Metabolic and endocrine</td>
<td>203</td>
<td>4.85</td>
<td>2424</td>
<td>57.89</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>272</td>
<td>6.50</td>
<td>2696</td>
<td>64.39</td>
</tr>
<tr>
<td>Neurological</td>
<td>172</td>
<td>4.11</td>
<td>2868</td>
<td>68.50</td>
</tr>
<tr>
<td>Oral and gastrointestinal</td>
<td>168</td>
<td>4.01</td>
<td>3036</td>
<td>72.51</td>
</tr>
<tr>
<td>Other</td>
<td>77</td>
<td>1.84</td>
<td>3113</td>
<td>74.35</td>
</tr>
<tr>
<td>Physical medicine/rehabilitation</td>
<td>125</td>
<td>2.99</td>
<td>3238</td>
<td>77.33</td>
</tr>
<tr>
<td>Public health</td>
<td>111</td>
<td>2.65</td>
<td>3349</td>
<td>79.99</td>
</tr>
<tr>
<td>Renal and urogenital</td>
<td>126</td>
<td>3.01</td>
<td>3475</td>
<td>82.99</td>
</tr>
<tr>
<td>Reproductive health and childbirth</td>
<td>181</td>
<td>4.32</td>
<td>3656</td>
<td>87.32</td>
</tr>
<tr>
<td>Respiratory</td>
<td>225</td>
<td>5.37</td>
<td>3881</td>
<td>92.69</td>
</tr>
<tr>
<td>Skin</td>
<td>87</td>
<td>2.08</td>
<td>3968</td>
<td>94.77</td>
</tr>
<tr>
<td>Stroke</td>
<td>35</td>
<td>0.84</td>
<td>4003</td>
<td>95.61</td>
</tr>
<tr>
<td>Surgery</td>
<td>184</td>
<td>4.39</td>
<td>4187</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Number of trials registered by country outside Australia

Some trials had more than one country listed, which may be a consequence of the pre-registration requirements of the regulatory bodies of various countries, or of multicenter studies, or of cost saving (Table 17). Any registered trial can list up to 50 countries for recruitment as indicated in Australian New Zealand Clinical Trials Registry, 2015. It had been noted that the highest percentage of clinical trials were conducted in Australia, followed by New Zealand (NZ), but there were cases where clinical trials have taken place in developing countries in Europe and South-east Asia.
Table 15. Trials registered by country outside Australia.

<table>
<thead>
<tr>
<th>Country</th>
<th>Frequency</th>
<th>Percent</th>
<th>Cumulative frequency</th>
<th>Cumulative percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>16</td>
<td>0.45</td>
<td>16</td>
<td>0.45</td>
</tr>
<tr>
<td>Austria</td>
<td>12</td>
<td>0.33</td>
<td>28</td>
<td>0.78</td>
</tr>
<tr>
<td>Bahrain</td>
<td>1</td>
<td>0.03</td>
<td>29</td>
<td>0.81</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>5</td>
<td>0.14</td>
<td>34</td>
<td>0.95</td>
</tr>
<tr>
<td>Belgium</td>
<td>21</td>
<td>0.58</td>
<td>55</td>
<td>1.53</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>1</td>
<td>0.03</td>
<td>56</td>
<td>1.56</td>
</tr>
<tr>
<td>Botswana</td>
<td>1</td>
<td>0.03</td>
<td>57</td>
<td>1.59</td>
</tr>
<tr>
<td>Brazil</td>
<td>72</td>
<td>2.00</td>
<td>129</td>
<td>3.59</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>3</td>
<td>0.08</td>
<td>132</td>
<td>3.67</td>
</tr>
<tr>
<td>Cambodia</td>
<td>4</td>
<td>0.11</td>
<td>136</td>
<td>3.79</td>
</tr>
<tr>
<td>Canada</td>
<td>46</td>
<td>1.28</td>
<td>182</td>
<td>5.07</td>
</tr>
<tr>
<td>Chile</td>
<td>6</td>
<td>0.17</td>
<td>188</td>
<td>5.23</td>
</tr>
<tr>
<td>China</td>
<td>50</td>
<td>1.39</td>
<td>238</td>
<td>6.62</td>
</tr>
<tr>
<td>Colombia</td>
<td>3</td>
<td>0.08</td>
<td>241</td>
<td>6.71</td>
</tr>
<tr>
<td>Comoros</td>
<td>1</td>
<td>0.03</td>
<td>242</td>
<td>6.74</td>
</tr>
<tr>
<td>Congo</td>
<td>1</td>
<td>0.03</td>
<td>243</td>
<td>6.76</td>
</tr>
<tr>
<td>Congo, The Democratic Republic of</td>
<td>1</td>
<td>0.03</td>
<td>244</td>
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</table>

* denotes name of the countries that were not mentioned and clustered as one
Number of trials where recruitment inside Australia occurred

The number of trials is marked against the Australian state where each clinical trial took place (Figure 10). Out of all registered trials, 76.8% did not identify the state.

![Counts of trials in Australian states and territories by year where indicated](image)

Figure 10. Studies conducted within Australia.

When trials across states were compared (Figure 11), Victoria had the highest rate of clinical trial recruitments and also the highest number of research centres, hospitals, universities and research outputs.
Figure 11. Number of trials recruited in the various states of Australia by year.

Number of trials with other countries of recruitment

Fewer clinical trials were conducted outside Australia (65.6%) compared with those recruiting within Australia (34.6%) (Table 18).

Table 16. Clinical trials with multiple countries recorded.

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<td>3</td>
<td>18 (0.6)</td>
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<td>5</td>
<td>50 (1.7)</td>
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Number of trials registered by recruitment status

The Intention to Treat (ITT) principle assumes that all subjects allocated at random to the ‘treatment’ arm of a study will take all of the prescribed medicine. It has been reported that a proportion of subjects will generally not comply with the trial regime or
are by nature more tolerant and do not report side-effects, which may lead to inaccurate findings (Kelman et al., 2007).

Only 11.3% of all trials included in this analysis showed a completed status (Table 19). Observation: The table showed that the follow-ups of some of the trials have not been updated and shockingly, that 43% of the clinical trials had already been registered without commencing the recruitment of volunteers. This indicates that either the trial information has not been updated, or that the trials experienced problems sourcing participants.

Table 17. Number of trials registered by recruitment status.

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<th>Cumulative frequency</th>
<th>Cumulative percent</th>
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<td>8</td>
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<td>103</td>
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**Correspondence between the anticipated starting date and the actual starting date**

This analysis was conducted to investigate whether there was a discrepancy between the actual status of clinical trials and the status made public. Actual start dates and both the anticipated and actual end-dates were converted from character to numeric data; ‘today’s date’ was used where there were ‘NULL’ entries for any of those dates. Out of the 3739 trial entries, 3547 (94.86%) listed the last update as before the actual start date. There were 185 (4.95%) entries updated between the actual start date and the anticipated end date; one (0.03%) was updated between the anticipated end date and the actual end date, and six (0.16%) were last updated after the actual end date.
Those with a sample size for credible data (seven studies) constituted less than 0.2% of the original sample. A sample of 30 records is shown in Table 20, indicating 100% discrepancy between the three fields.

Table 18. Records of sets of data accrued for the study by date of submission.

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<td>15/09/2008</td>
<td>02/02/2009</td>
<td>15/09/2008</td>
</tr>
<tr>
<td>83165</td>
<td>15/09/2008</td>
<td>01/01/2009</td>
<td>28/02/2013</td>
</tr>
<tr>
<td>83180</td>
<td>19/09/2008</td>
<td>16/01/2009</td>
<td>18/09/2008</td>
</tr>
<tr>
<td>83189</td>
<td>24/09/2008</td>
<td>01/02/2009</td>
<td>19/09/2008</td>
</tr>
<tr>
<td>83190</td>
<td>20/05/2009</td>
<td>31/07/2009</td>
<td>19/09/2008</td>
</tr>
<tr>
<td>83199</td>
<td>24/09/2008</td>
<td>02/01/2009</td>
<td>24/09/2008</td>
</tr>
</tbody>
</table>

Number of trials by age and gender of subjects recruited

There were only four trials that commenced after 1 January 2009, which were updated on or after the anticipated trial end date. All four trials recruited adult (21+ years) females and males. A total of 587 subjects were to be enrolled. There was no data on actual enrolment — only the sample size provided by the ANZCTR second-hand data
supplied to the researcher. Figure 12 shows the results of the trials, which indicate that both males and females of all ages were enrolled (21 years and over).

![Counts of trials by Age groups and year recruitment started](image)

**Figure 12.** Trials that indicate that both males and females of all ages were enrolled.

Table 21 shows the number of trials that stipulated age and gender in their selection criteria. Out of all registered clinical trials, only 605 (20%) did not have age limits. While 83% of all trials required participants to be 21 or over from any gender, 2.85% of trials required people under the age of 21 years, of which 2.58% were under the age of one. Trials that required the elderly (over 65 years of age) to participate comprised 2.2% of all clinical trials. Additionally, clinical trial selection criteria that indicated women only from all ages constituted only 9.64% of all trial selection criteria, while those that required only men constituted 5.63% (Figure 13).
Table 19. Number of trials by age group and gender of subjects.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age group</th>
<th>Elderly (65 years minimum)</th>
<th>Entire age span</th>
<th>Very elderly (75 years minimum)</th>
<th>Very young (&lt;1 year)</th>
<th>Young (&lt;21 years)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both males and females</td>
<td>Adult (21+ years)</td>
<td>1824</td>
<td>52</td>
<td>532</td>
<td>4</td>
<td>76</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>61.91</td>
<td>1.77</td>
<td>18.06</td>
<td>0.14</td>
<td>2.58</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73.08</td>
<td>2.08</td>
<td>21.31</td>
<td>0.16</td>
<td>3.04</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>83.06</td>
<td>91.23</td>
<td>87.93</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td>226</td>
<td>4</td>
<td>54</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td>7.67</td>
<td>0.14</td>
<td>1.83</td>
<td>0.00</td>
<td>0.00</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>79.58</td>
<td>1.41</td>
<td>19.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.29</td>
<td>7.02</td>
<td>8.93</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td>146</td>
<td>1</td>
<td>19</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
<td>4.96</td>
<td>0.03</td>
<td>0.64</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>87.95</td>
<td>0.60</td>
<td>11.45</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6.65</td>
<td>1.75</td>
<td>3.14</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>2196</td>
<td>57</td>
<td>605</td>
<td>4</td>
<td>76</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74.54</td>
<td>1.93</td>
<td>20.54</td>
<td>0.14</td>
<td>2.58</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Figure 13. Level of participation of both sexes in the trials.
Phase 3 – Data analysis and results

The survey questions were framed to get the opinion of the community about participating in a clinical trial if they ever needed to do so. None of the survey participants were currently enrolled in any clinical trials.

The researcher distributed 200 surveys into community groups based at Wagga Wagga, New South Wales Australia. Only 150 surveys were returned (75% return). Furthermore, 47 surveys out of the 150 surveys deposited in the collection boxes were incomplete or blank and thus were excluded. Only 103 surveys were included in the final analysis (68.7% of all returned surveys).

The completed survey forms received consisted of 42 from the elderly population, 38 from women population and 39 from parents’ population. When the forms were scrutinised only 33 forms from the elderly, 36 from the women and 34 from the parent cohorts were completed and met the selection criteria.

Demographic information, which cannot be used to identify the participants or their community group, such as age and gender, were collected. Information on participants’ current total medical conditions and medications were also collected as part of the selection criteria. The survey contained eight closed-ended questions and one open-ended question (do you have further comments?).

Participants were informed via the information sheet provided with the survey that the return of the completed survey to the researcher was considered as their consent to participate.

Coding of the survey questions

The eight closed-ended questions were abbreviated as Q1–Q8 for ease in graphical representation during data analysis (Table 22).
Table 20. Survey questions.

<table>
<thead>
<tr>
<th>Code</th>
<th>Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>If you are healthy would you participate in clinical trials?</td>
</tr>
<tr>
<td>Q2</td>
<td>If you had the disease that a new medicine is treating, but you were happy with your current treatment, would you participate in clinical trials?</td>
</tr>
<tr>
<td>Q3</td>
<td>If you had the disease the new medicine is treating, but were not happy with your current treatment, would you participate in the clinical trials?</td>
</tr>
<tr>
<td>Q4</td>
<td>If you had the disease the new medicine is treating, but no other treatment was working and the new medicine was your last hope, would you participate in the clinical trials?</td>
</tr>
<tr>
<td>Q5</td>
<td>If you had the disease the new medicine is treating, and you were offered lifelong health insurance which covers any side-effect or damage caused by the tested medicine, regardless of if there was, or was not another treatment currently working, would you participate in the clinical trials?</td>
</tr>
<tr>
<td>Q6</td>
<td>If you had the disease the new medicine is treating, and if you were offered lifelong health insurance which covers any side-effect or damage caused by the tested medicine, and there was no other treatment working, would you participate in the clinical trials?</td>
</tr>
<tr>
<td>Q7</td>
<td>If you had the disease the new medicine is treating, and if you were offered a payment, regardless of if there was or was not another treatment working, would you participate in the clinical trials?</td>
</tr>
<tr>
<td>Q8</td>
<td>If you had the disease the new medicine is treating, and if you were offered a payment, and there was no other treatment working, would you participate in the clinical trials?</td>
</tr>
</tbody>
</table>

Initial survey analysis

Responses to the survey

In this section the results are presented as percentages or proportions of the group total sample. There were three subsets of responses for each of the questions; those were the elderly group, women group and parents group. Each group was analysed separately; then the three groups were compared.

The elderly group survey results

There were 33 participants who agreed to voluntarily participate in the study and accepted that the collected data be used as population data for this study purpose by returning their completed survey to the researcher. The survey sample was a convenience sample, with the intention being to detect trends to inform future studies rather than to represent the entire Australian elderly, women and children populations (as this would have required a larger budget and larger sample based on power calculations).
The number of respondents in the age group’s 65–69, 70–74, 75–79 and 80 years and above were in the ratio of 7:12:10:4 respectively, is shown in Figure 14.

![Age of the elderly participants](image1)

Figure 14. Age categories of the elderly participants.

Out of the enrolled 33 participants, there were 15 males, 17 females and 1 other (Figure 15).

![Gender of the elderly population](image2)

Figure 15. Gender of the elderly participants.
Out of 33 participants, two had one medical condition but were taking no medication, six had one medical condition and were taking one medicine daily, 15 had one medical condition and were taking multiple medications daily, and 10 had more than one medical condition and were taking multiple medicines daily (Figure 16).

![Figure 16. Medical conditions of the elderly participants.](image)

The elderly group responses to the survey closed-ended questions are shown in Figure 17. Fifteen participants of this group strongly agreed, 11 agreed and seven disagreed that if they were healthy, they would participate in clinical trials (Q1). Eleven participants of this group strongly agreed, 13 agreed and nine disagreed that if they had a disease that a new medicine was treating, but were happy with their current treatment, they would participate in clinical trials (Q2).
Fourteen participants of this group strongly agreed and 19 agreed that if they had the disease the new medicine was treating, but were not happy with their current treatment, they would participate in the clinical trials (Q3).

Seventeen participants of this group strongly agreed, 13 agreed and three disagreed that if they had the disease the new medicine was treating, but no other treatment was working and the new medicine was their last hope, they would participate in the clinical trials (Q4). Reasons for disagreement were not disclosed to the researcher; however, this might have been due to their personal wish to cease active treatment or fears of the potential to become worse.

Thirteen participants of this group strongly agreed, 15 agreed and five disagreed that if they had the disease the new medicine was treating, and they were offered lifelong health insurance which covered any side-effect or damage caused by the tested medicine, regardless of if there was, or was not another treatment currently working, they would participate in the clinical trials (Q5).

Eleven participants of this group strongly agreed, 17 agreed and five disagreed that if they had the disease the new medicine was treating, and if they were offered lifelong health insurance which covered any side-effect or damage caused by the tested medicine, and there was no other treatment working, they would participate in the clinical trials (Q6).

Only six participants of this group strongly agreed, 14 agreed, nine disagreed and four strongly disagreed that if they had the disease the new medicine was treating, and if they were offered a payment, regardless of if there was or was not another treatment working, they would participate in the clinical trials (Q7).

Fifteen participants of this group strongly agreed, 13 agreed and 5 disagreed that if they had the disease the new medicine was treating, and if they were offered a payment,
and there was no other treatment working, they would participate in the clinical trials (Q8).

![Responses of elderly - If they had the disease which the new medicine was treating and there is no other treatment working, would they participate in the clinical trials

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Q8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly agree</td>
<td>45.5%</td>
<td>33.3%</td>
<td>42.4%</td>
<td>51.5%</td>
<td>39.4%</td>
<td>33.3%</td>
<td>18.2%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Agree</td>
<td>33.3%</td>
<td>39.4%</td>
<td>57.6%</td>
<td>39.4%</td>
<td>45.5%</td>
<td>51.5%</td>
<td>42.4%</td>
<td>39.4%</td>
</tr>
<tr>
<td>Disagree</td>
<td>21.2%</td>
<td>27.3%</td>
<td>9.1%</td>
<td>15.1%</td>
<td>15.2%</td>
<td>27.3%</td>
<td>15.1%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Strongly disagree</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 17. The elderly participants’ responses.

Six out of 33 participants in this category responded to the open-ended question. The individual responses were:

1. *I would consider after receiving feedback about the medication and side-effects.*
2. *I will take part after talking to my GP.*
3. *I would only participate if I thought there was some benefit to me or other people suffering.*
4. *I should know the side-effects of the new medication.*

5. *Participating for the future generation.*

6. *It will benefit the society.*

Thematically, 33.3% of respondents were happy to participate in a clinical trial if they received feedback about the medication and side-effects; 16.7% of respondents felt that the role of a GP (General Practitioner) was important in influencing volunteers to participate in a clinical trial and 50% respondents felt that participating in a clinical trial benefitted the society.

### The women-only group survey results

There were 36 women that voluntarily agreed to participate in the study. Due to the small sample size, some bands were not represented as shown in Figure 18.

![Age of the women participants](image)

Figure 18. Age of the women participants.
Out of 36 enrolled in this group, there were 11 women who had one medical condition but were taking no medication, 18 had one medical condition and were taking one medicine daily, four had one medical condition and were taking multiple medications daily and three had more than one medical condition and were taking multiple medicines daily as shown in Figure 19.

![Medical conditions of the female respondents](image)

Figure 19. Medical conditions of the women participants.

The women group responses to the survey questions are presented in Figure 20.

Ten participants of this group strongly agreed, eight agreed, 11 disagreed and seven strongly disagreed that if they were healthy, they would participate in clinical trials (Q1).

Eleven participants of this group strongly agreed, 11 agreed, 10 disagreed and four strongly disagreed that if they had the disease that a new medicine was treating, but were happy with their current treatment, they would participate in clinical trials (Q2).
Twenty-four participants of this group strongly agreed, 11 agreed and one disagreed that if they had the disease the new medicine was treating, but were not happy with their current treatment, they would participate in the clinical trials (Q3).

Twenty-eight participants of this group strongly agreed, six agreed and two disagreed that if they had the disease the new medicine was treating, but no other treatment was working and the new medicine was their last hope, they would participate in the clinical trials (Q4).

Twenty-one participants of this group strongly agreed, nine agreed and six disagreed that if they had the disease the new medicine was treating, and they were offered lifelong health insurance that covered any side-effects or damage caused by the tested medicine, regardless of if there was, or was not another treatment currently working, they would participate in the clinical trials (Q5).

Twenty participants of this group strongly agreed, 13 agreed, two disagreed and one strongly disagreed that if they had the disease the new medicine was treating, and if they were offered lifelong health insurance which covered any side-effects or damage caused by the tested medicine, and there was no other treatment working, they would participate in the clinical trials (Q6).

Sixteen participants of this group strongly agreed, nine agreed, 10 disagreed and one strongly disagreed that if they had the disease the new medicine was treating, and if they were offered a payment, regardless of if there was or there was no other treatment working, they would participate in the clinical trials (Q7).

Seventeen participants of this group strongly agreed, 14 agreed and five disagreed that if they had the disease the new medicine was treating, and if they were offered a payment, and there was no other treatment working, they would participate in the clinical trials (Q8).
Eight of the 36 people that participated in this group responded to the additional comments question. Their responses were:

1. *I think having a disease that had no treatments that work for you, I would jump at the chance to try a new medication.*

2. *I will participate in a clinical trial if I am a control subject.*

3. *If I was dying from the condition I would take any trial medications so they could learn as much as possible before I died.*

4. *I will participate if I get the full information.*

5. *I think it’s risky to participate.*

6. *I don’t want to be a scape-goat.*

7. *Would love to know more before participating.*

8. *I would love to be part of the future research.*
Thematically, 25% of respondents were happy to participate in a clinical trial on condition when there was no alternative to survive except for participating in a new drug trial; 12.5% of respondents felt that if they were made a control then they would participate; 25% respondents feared participating; and 37.5% responded that they would love to participate if given more information.

Parents group survey results

There were 34 parent (one of the two parents not both) participants that agreed to voluntarily participate in the study.

Out of 34 individual parents, 12 had one child, 10 had two children, four had three children and eight had four children or more (Figure 21).

![Number of children per parent](image-url)

Figure 21. Number of children per parent.

There were 15 males, 17 females and two others in the parents’ group (Figure 22). They had a total of 33 male children and 41 female children (Figure 23).
Out of the reported 74 children in total, 29 had one medical condition but were taking no medication, 36 had one medical condition and were taking one medicine daily, six had one medical condition and were taking multiple medications daily, and three had more than one medical condition and were taking multiple medicines daily as shown in Figure 24.
Figure 24. Medical condition of the children of parents that participated in the survey.

In this group (Figure 25), six participants strongly agreed, nine agreed, 16 disagreed and three strongly disagreed that if they were healthy, they would participate in clinical trials (Q1).

Seven participants recorded ‘strongly agree’, zero agreed, 14 disagreed and three strongly disagreed that if they had the disease that a new medicine was treating, but were happy with their current treatment, they would participate in clinical trials (Q2).

Out of the 34 parents, 12 strongly agreed, 16 agreed, four disagreed and two strongly disagreed that if they had the disease the new medicine was treating, but were not happy with their current treatment, they would participate in the clinical trials (Q3).

Twenty-three parents strongly agreed, five agreed and six disagreed that if they had the disease the new medicine was treating, but no other treatment was working and the new medicine was their last hope, they would participate in the clinical trials (Q4).

Fourteen parents strongly agreed, eight agreed, 10 disagreed and two strongly disagreed that if they had the disease the new medicine was treating, and they were
offered lifelong health insurance that covered any side-effects or damage caused by the tested medicine, regardless of if there was, or was not another treatment currently working, they would participate in the clinical trials (Q5).

Sixteen participants strongly agreed, 10 agreed and eight disagreed that if they had the disease the new medicine was treating, and if they were offered lifelong health insurance that covered any side-effects or damage caused by the tested medicine, and there was no other treatment working, they would participate in the clinical trials (Q6).

Twenty-two parents strongly agreed, 10 agreed and two disagreed that if they had the disease the new medicine was treating, and if they were offered a payment, regardless of if there was or there was no other treatment working, they would participate in the clinical trials (Q7).

Eighteen parents strongly agreed, nine agreed and seven disagreed that if they had the disease the new medicine was treating, and if they were offered a payment, and there was no other treatment working, they would participate in the clinical trials (Q8).
Four out of 34 individuals that participated in the parents group responded to the additional comment question. Their responses were:

1. *I don’t want my child to be a participant in a clinical trial.*
2. *I will consult my doctor before participation.*
3. *That will be my child’s worst nightmare.*
4. *I have never thought about my children’s participation.*

Thematically, 25% of the respondents showed trust in their health professional and would consult them before participating in a trial; 25% of respondents said that they may or may not let their children participate as it had never occurred to them; and 50% were clear in their mindset that they would not allow their child/children to participate as volunteers in a clinical trial.
Comparing the three groups

The following is a comparison among the three groups’ opinions. This was conducted to try to establish the participants’ perception of the level of risk in each of the three categories.

Question 1 – Q1

There was no one in the elderly group who strongly disagreed to the question, and the majority (45.5%) strongly agreed. The other two groups (women and parents) responded similarly for the strongly agreed (50%) and agreed (44.1%) responses, and for the strongly disagreed (50%) and disagreed (55.9%)’ responses (Figure 26). This may have been related to the involvement of children (or foetuses).

Figure 26. Question 1, comparison among the three groups.
Question 2 – Q2

There was no one in any group who strongly disagreed to the question; however, the majority of the parents (41.2%) disagreed. The other two groups (women and elderly) responded in the similar manner to strongly agree (30.6% and 33.4%, respectively) and agree (30.6% and 39.4%, respectively) (Figure 27).

![Question 2 - Q2 Comparison](image)

Figure 27. Question 2, comparison among the three groups.

Question 3 – Q3

There was lesser disagreement on Question 3. Parents strongly agreed (66.7%) that they would love to be involved in a clinical trial of a drug if it was treating the medical condition that their child/children had and they were unhappy with the current treatment. The other two groups (women and elderly) responded in the similar manner (strongly agree and agree as 42.4% and 57.6%, respectively, and 35.3% and 47.1%, respectively) (Figure 28).
Figure 28. Question 3, comparison among the three groups.

**Question 4 – Q4**

All three cohorts of the study participants (elderly, women, parents) strongly agreed (51.5%, 67.6%, and 77.8%, respectively) that they would participate in a clinical trial if they had the disease the new medicine was treating and no other treatment was working for them and this new medicine was their last hope of survival. However, 91% of the elderly population disagreed to participate, which might highlight the fact that the elderly level of awareness of benefits versus risk needs to be addressed in future trials (Figure 29).
Figure 29. Question 4, comparison among the three groups.

**Question 5 – Q5**

Women strongly agreed (58.3%) that they would participate in a clinical trial of a drug if they had the disease the new medicine was treating and if they were offered lifelong health insurance that covered any side-effects or damage caused by that medicine, regardless of the presence or absence of another treatment (Figure 30).

Figure 30. Question 5, comparison among the three groups.
**Question 6 – Q6**

There was more disagreement than agreement on Question 6. Overall, 55% of women and 59% of parents disagreed, while 55.3% of women strongly agreed and 47.1% of parents agreed to be involved in a clinical trial of a drug if they had the disease the new medicine was treating, and if they were offered lifelong health insurance that covered any side-effects or damage caused by the tested medicine, and there was no other treatment working. The elderly strongly agreed to participate in the trials (Figure 31).

![Question 6 - Q6 Comparison](image)

Figure 31. Question 6, comparison among the three groups.

**Question 7 – Q7**

Overall 44.5% of women and 64.7% of parents strongly agreed to participate in a clinical trial of a drug if they were are offered a payment, regardless of if there was or was no other treatment working. In comparison, 59% of parents disagreed in participating in a clinical trial. Of the elderly, 18.2% strongly agreed and 42.4% agreed to participate in clinical trials; which shows that financial incentive is a factor to motivate the
participants to participate more in further studies (Figure 32). Reasons for disagreement were not disclosed to the researcher, but they might have been influenced by poor awareness of the benefits of participation and fears of suffering additional disease complications as a consequence of the unknown new drug.

![Question 7 - Q7 Comparison](image)

Figure 32. Question 7, comparison among the three groups.

**Question 8 – Q8**

For Question 8, 45.5% of the elderly, 47.25% of women and 52.9% of parents strongly agreed and 39.4% of the elderly, 38.9% of women and 26.5% of parents agreed to participate in a clinical trial of a drug if they had the disease the new medicine was treating and they were offered a payment, and there was no other treatment working. A lower proportion of the respondents disagreed and there were none who strongly disagreed to participate. This indicated that financial incentive is a factor to motivate the participants to participate more in clinical trials (Figure 33). Reasons for disagreement were not disclosed to the researcher, but they might have been influenced by poor
awareness of the benefits of participation and fears of suffering additional disease complications as a consequence of the unknown new drug.

Figure 33. Question 8, comparison among the three groups.

**Thematic comparison**

Out of the 103 participants in all groups, only 52% responded to the open-ended questions.

Based on the respondents’ comments, it was found that there was no common theme between the three groups, with the exception of the elderly and women groups (33.3% and 37.5%, respectively) responding that they would love to participate if given more information. However, that 50% of the parent respondents were clear in their mindset that they would not allow their child/children to participate as volunteers in clinical trials.

**Survey statistical analysis**

Statistical analysis was conducted by the professional statistician to further understand the results.
Based on the scale used for this survey, the best category to use for comparison was the percentage of people who ‘**Strongly agree**’ with the statement. This was usually the most discriminating point in attitudinal scales. Based on this approach, there were three comparison tests per question:

- Elderly versus women
- Elderly versus parents
- Parents versus women

The numbers of respondents in each group were as follows:

- Women: 36
- Parents: 34
- Elderly: 33

A two-sample proportions test was conducted for each comparison. As three tests were conducted per question, there was a need to adjust the alpha level. Instead of \( p=0.05 \), the \( p=0.05/3 = 0.0166 \) was used. P-values less than 0.0166 were required to claim that there was a significant difference.

The following is a summary of the analysis of all questions; more details are in Appendix 8.

**Table 21. Q1: If you were healthy would you participate in clinical trials?**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>1.008</td>
<td>0.313</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>-1.526</td>
<td>0.127</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>-2.453</td>
<td>0.014</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Elderly people seemed to strongly agree with Q1 more than parents (at a statistically significant level).
Table 22. Q2: If you had the disease that a new medicine was treating, but you were happy with your current treatment, would you participate in clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>0.954</td>
<td>0.340</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>-0.247</td>
<td>0.805</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>-1.177</td>
<td>0.239</td>
<td>No</td>
</tr>
</tbody>
</table>

There was no statistical difference among the groups for Q2.

Table 23. Q3: If you had the disease the new medicine was treating, but were not happy with your current treatment, would you participate in the clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>2.625</td>
<td>0.009</td>
<td>Yes</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>2.022</td>
<td>0.043</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>-0.599</td>
<td>0.549</td>
<td>No</td>
</tr>
</tbody>
</table>

Women seemed to strongly agree with Q3 more than parents (at a statistically significant level).

Table 24. Q4: If you had the disease the new medicine was treating, but no other treatment was working and the new medicine was your last hope, would you participate in the clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>0.953</td>
<td>0.341</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>2.289</td>
<td>0.022</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>1.346</td>
<td>0.178</td>
<td>No</td>
</tr>
</tbody>
</table>

There was no statistical difference among the groups for Q4.

Table 25. Q5: If you had the disease the new medicine was treating, and you were offered lifelong health insurance that covered any side-effects or damage caused by the tested medicine, regardless of if there was, or was not another treatment currently working, would you participate in the clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>1.435</td>
<td>0.151</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>1.572</td>
<td>0.116</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>0.148</td>
<td>0.882</td>
<td>No</td>
</tr>
</tbody>
</table>

There was no statistical difference among the groups for Q5.

Table 26. Q6: If you had the disease the new medicine was treating, and if you were offered lifelong health insurance that covered any side-effects or damage caused by the tested medicine, and there was no other treatment working, would you participate in the clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>0.711</td>
<td>0.477</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>1.854</td>
<td>0.064</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>1.145</td>
<td>0.252</td>
<td>No</td>
</tr>
</tbody>
</table>
There was no statistical difference among the groups for Q6.

Table 27. Q7: If you had the disease the new medicine was treating, and if you were offered a payment, regardless of if there was or was no other treatment working, would you participate in the clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>-1.701</td>
<td>0.089</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>2.338</td>
<td>0.019</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>3.860</td>
<td>0.000</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Parents seemed to strongly agree with Q7 more than the elderly (at a statistically significant level).

Table 28 - Q8: If you had the disease the new medicine was treating, and if you were offered a payment, and there were no other treatments working, would you participate in the clinical trials?

<table>
<thead>
<tr>
<th></th>
<th>Z-value</th>
<th>P-value</th>
<th>Significant difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women vs. Parents</td>
<td>-0.478</td>
<td>0.632</td>
<td>No</td>
</tr>
<tr>
<td>Women vs. Elderly</td>
<td>0.147</td>
<td>0.883</td>
<td>No</td>
</tr>
<tr>
<td>Parents vs. Elderly</td>
<td>0.613</td>
<td>0.540</td>
<td>No</td>
</tr>
</tbody>
</table>

There was no statistical difference among the groups for Q8.

Findings

At a statistically significant level; elderly people seemed to strongly agree with Q1 more than parents, women seemed to strongly agree with Q3 more than parents and parents seemed to strongly agree with Q7 more than the elderly. There was no statistical difference among the groups for Q2, 4, 5, 6 and 8.
Chapter VI – Discussion and limitations

Participating in a clinical trial inevitably imposes some burden upon participants (Flood & Lemmens, 2013). Burdens can range from the experience of side-effects to the logistics of participation itself (Glasser et al., 2007).

The researcher undertook two days of training from 7–8 April 2014 at the TGA headquarters in Canberra to understand more about the Australian pharmaceutical industry. It was funded by the researcher’s CSU operating fund. At the TGA, the staff provided an overview of the TGA process and how dossiers for new drugs registration are usually made.

The candidate made an observation as an employee of a well-known and established company with a strong corporate culture in India, that there were insufficient efforts made in attracting women and the elderly to take part in clinical trials, despite the elderly being the major treatment target group for the drugs being tested. Enrolled patients had minimal knowledge of adverse or expected side-effects of those trials. This situation influenced the candidate’s interest in investigating the reasons behind the ‘perceived’ level of participation of older people, women and children in clinical trials.

When the efficacy and safety of a new drug in the group of which it is licensed is well established, this encourages prescribers to use off-label in other groups for which the drug may not be indicated for. Most off-label prescribing is applied to the children and the elderly population. The following are some examples of where a product has been used for populations, other than those it was indicated for in the drug licensing document:

- Johnson & Johnson (J&J) agreed to settle criminal and civil allegations involving off-label promotion of its widely-used Risperdal antipsychotic, a
drug for treating schizophrenia, to treat psychosis in Alzheimer’s patients (Gøtzsche, 2012).

- The influenza vaccine, Fluvax, which can be dangerous to children under 5, was given to children under 5 years of age, off-label, due to a shortage of other suitable vaccines in Australia, despite serious side-effects detected in a clinical trial (Natasha, 2013). However, after a fatality, a safety alert was sent to all prescribers and advertised in the media.

The following are examples of research misconduct that became known to the public and possibly affected attitudes towards participation in clinical trials relating to unknown risks:

- Following a trial of a drug to treat psoriasis in the US, the claimants argued that the experiment was unethical because the subjects who were randomised into the placebo arm were not receiving treatment and were being subjected to the risk of suffering significant harm (Fiscus, 2009b).

- In the early 1960s, a connection between thalidomide and severe birth defects was observed, which worked as a catalyst for healthcare professionals to consider a system or framework for monitoring drug safety (Kelman et al., 2007).

- The Tuskegee Syphilis Study resulted in the unethical treatment of African Americans in research, and is another example of the mistreatment of an ethnic group in a clinical trial (Herrera et al., 2010).

In the last ten years, over a dozen high-profile brand-name drugs, including rofecoxib, troglitazone, cisapride, and cerivastatin, were withdrawn from the market (Guo et al., 2010) due to them causing significant side-effects.
The researcher chose this topic to discuss the participation in clinical trials outside the USA and Europe. The researcher approached various agencies in Australia and overseas. There was a great level of difficulty in sourcing trusted and up-to-date data, since only general statistical and information are usually made available in the public domain.

The FDA response was: ‘The specific information you are requesting is not collected by the FDA in a readily retrievable format. Records and data are available through private organisations (available from: http://www.imshealth.com or http://www.phrma.org/ or http://www.clinicaltrials.gov’), and ‘Be aware that the FDA does not endorse any of the information contained on non-government sites.’

The UK Database Manager of Current Controlled Trials responded to say: ‘We do not have the data readily broken down the way you need. You will need to make some assumptions, using the info that is freely available (including participant details). Please note that the ISRCTN register — like all public trials registers — does not claim to be comprehensive.’

The researcher contacted the TGA first to know more about the clinical trials in Australia. The TGA directed the researcher towards ANZCTR for further reference. ANZCTR agreed to share the clinical trial data with the researcher on a condition that it should be acknowledged wherever the students presented findings that were related to the data provided. The data given by ANZCTR were analysed and interpreted by the researcher, supervisory team and DataPharm™.

While many global studies analysed the final participants’ demographics, the data sourced from the ANZCTR public-portal did not include the final participant numbers and their breakdown by demographics (such as age and gender). Hence, it was not possible to analyse these data in this study and to make comparisons against the findings.
from the literature review as was initially planned. Additionally, seeking new data from
the ANZCTR was not feasible, since until a new medicine is registered, all information
remains confidential and even after that the request would have to be made to the
individual trial research teams and not through the registry. The researcher signed a
confidentiality agreement with the ANZCTR, which prohibited the researcher from using
the provided data to contact manufacturers or sponsors. Accordingly, it was not possible
to contact any of the manufacturers to release any additional or the missing data.

There is a genuine demand for the public and consumers to be able to view historical
results from previous clinical trials to understand the actual consequences and benefits to
individuals and society after the conclusion of the trial and the marketing of the new drug
(Madsen et al., 1999). However, pharmaceutical industries have expressed concern that
free access to data and updated trials information before the completion of the study,
registering the patent, publishing the findings and registering the new medicine will
provide competitors with confidential proprietary information into which financially they
have heavily invested (Nardini, 2014). To identify if the concept of this study was sound
or if it was only the researcher’s opinion, a short survey was conducted by the researcher
in Wagga Wagga, NSW Australia. The participants were given eight closed-ended
questions and an open-ended question regarding their view towards participation in
clinical trials. However, it was acknowledged that this opinion may have changed if they
were at the stage where they were offered an actual opportunity to participate in clinical
trials or they were diagnosed with an illness that had no other treatment available.
Additionally, the survey was validated for content and its psychological effect prior to
being used, in order to confirm the significance of the results. The survey questions’
cognitive meanings and readability were tested in a small group from the local
community, students and academics, and the comments from these three groups were
used to amend the questions. The survey was then critiqued by the additional academics group ‘research group, PhD and Masters candidates’ and then subjected to the ethics committee members’ approval. However, it should be noted that the survey questions should be validated in future studies, in different samples to ensure the results’ reproducibility.

The Australian New Zealand Clinical Trial Register

According to a recent FDA report, the most commonly identified compliance offences by clinical investigators were: failure to follow the investigational plan that was prepared before the start of the clinical trial, protocol deviations from the standard path, inadequate record keeping of recruitment processes and follow-ups, inadequate accountability for the investigational product, and inadequate subject protection — including informed consent issues relating to the recruited subjects (Corporate Sustainability Performance Measurement Systems: A Review and Research Agenda, 2012).

When the data from the public portal supplied by the ANZCTR was analysed, the datasets from only four out of 3000 studies were found to be complete. This indicates that the records are not updated frequently or at the least, after the new medication or the new indication is registered and patent is obtained.

The National Health and Medical Research Council, which is the highest national ethics committee in Australia, should enforce random inspections of the ANZCTR records to ensure the completion, quality and integrity of data entered into the public portal of the ANZCTR.

Not only do the public have the need to know, for awareness purposes, but also the researchers needs to have access, considering that data mining studies are on the rise. This
should not depend solely upon published papers that are not freely available to the public, or the manufacturer. Rather, the ANZCTR and TGA should allocate sufficient resources to ensure the database is frequently updated.

If this was to occur, the public would be able to make informed decisions based on knowledge of the benefits and risks in previous clinical trials. Registering of clinical trials through the ANZCTR is not mandatory. Accordingly, the number of current registered trials is not a true representation of clinical trials conducted in Australia and NZ for any period. Additionally, as stated by the ANZCTR, the register is not responsible for any data inaccuracies, which raises the question of the value of having such a register.

A legislative requirement to register all clinical trials relating to medications intended for human treatment is required for transparency and future research.

Pharmacovigilance audits

Pharmacovigilance audits should become part of the post-marketing new medication management plan, or at the closure of a study if the medication is deemed unsuitable for registration, to ensure that clinical trial data is updated and complete. Confirmatory studies conducted to test the reproducibility of findings from previous studies require researchers to access the records of such studies. While it may be possible to access some information from published papers, information are usually not published on other aspects, such as reasons for withdrawals or the death of participants, or studies which were not completed due to safety issues or flaws in their methods or designs.

Risks to participants in clinical trials may arise due to many factors, such as poor study design, poor methodology or the sample selection criteria.

During the designing of clinical trials, researchers should consider the following questions:
• How complex is the study design?
• Does the study population include a vulnerable population or subset?
• Are sites located where there are differences in the regulations?
• How experienced is the clinical investigator?
• What is the sponsor’s experience working with the clinical investigator?
• Does the investigational product have any safety concerns?

After asking and answering the questions above, risks are identified. Other issues might include:

• study sites with insufficient staff to perform all the necessary tasks required for the trial
• unsatisfactory compliance with patient dietary requirements.

While these types of commonplace issues vary in significance, they all have the potential to pose a degree of risk. The list of such risks for a particular trial forms the basis for the risk management plan.

**Health insurance cover during and after participation in clinical trials**

Australia’s NHMRC asks researchers running trials whether they have included equal numbers of men and women, but there is little enforcement of such requests (Gerathy, 2010). Extrapolating the effectiveness of a drug from one population to another may lead to possible unexpected and even unwanted effects.

Clinical trials risk management plans usually include the responsibility to cover health care expenses for if the person did not tolerate the tested treatment or withdrew due to side-effects, only until they are stabilised on their previous treatment or the side-effects subside. However, delayed effects are usually not included. On the other hand,
health insurance covers withdraw their cover and support if the person is participating in clinical trials of a new drug, as the consequences are usually unknown and can be costly.

Participants will have confidence participating in clinical trials and will maintain their involvement until the end of the study if they are well informed about the potential side-effects of the drug and who will cover the treatment cost during and after the study until either they are cured, or for life if a disability or permanent damage to health occurs.

The phrase ‘health insurance providers’ role in clinical trials’ was used to search for papers that explored the Australian health insurance providers’ role in clinical trials. Twenty articles were found; however, none of those studies were conducted in Australia or were referring to the meaning of private insurance cover, as it is defined in Australia. The information on the availability of private health insurance cover will protect both the participant and the public health system from carrying the cost of any potential adverse events associated with clinical trials, in either the short- or long-term context (Miller & Pearson, 2011).

It is a difficult concept for the public that participation is of benefit to the society but might cause life-long consequences for those who are volunteering to participate. There is a greater need for educating the public about interpreting the risks. It should not just be the benefits or risks involved but also the benefits of exploring a possible cure of a medical condition where no treatment is available. There is also a possibility of cure versus a definite cure in others — to allow them to make an informed decision.

While the need to reduce the cost of clinical trials is fully understood, it should not be on the expense of participants’ rights. It should be noted that health insurance usually does not cover the participants during their participation in clinical trials, which discourages many volunteers with other comorbidities from participating in such trials (Hartford et al., 2006).
To alleviate out-of-pocket costs and to increase the participation of volunteers in a clinical trial, a growing number of USA states have passed legislation that requires health plans to pay for the routine medical care of clinical trial patients — a good practice which should be used as a guide for other countries (Herrera et al., 2010). Phase 3 of the survey of this study showed that parents, women and the elderly were willing to participate if they were offered life-long insurance that covered side-effects and damage caused by the tested medicine.

**Trust in health professionals**

There is a need to engage more with the parents of infants and children who may benefit from the participation in the clinical trials; however, there remains a valid challenge of ethical clearance to justify the inclusion of these subjects in a clinical trial. More motivational tools, with clear and complete information, should be provided to the parents of the children. The survey showed that the parents of the children had trust in the health professionals. They were willing to participate and engage more once they consulted their health professionals and got all of the relevant information.

**Incentive payment for participation**

Phase 3 of the survey of this study showed that payment in kind or in cash to the clinical trial participant was another factor that increased the participation in a clinical trial.

The survey found that 18.2% of the elderly, 44.5% of women and 64.7% of parents strongly agreed to participate in a clinical trial of a drug if they were offered a payment, regardless of if there was or was not another treatment working.
Inclusion of the elderly population in a clinical trial

Communication with the elderly requires a different effort than that for the rest of the population. Considering that access to information might be limited, familiarisation with technology, level of health literacy, and understanding of medical terminology might also be factors contributing to a lack of understanding about clinical trials. Consent can also be an issue, as most trials will insist on the person’s ability to consent or the carer to consent on their behalf and this might exclude a number of potential participants who may benefit from participation. Having comorbidities, other than the disease treated (which is more common in the elderly), is another reason for possible under-participation.

While equal representation in the clinical trial is desirable, it is understood that without the ability to purposefully invite eligible participants and provision of life-long health cover, the situation may not change or improve. The results from the survey indicate that in contrast to women and parents (advocating for their children), the elderly were more willing to participate in clinical trials irrespective of whether they were paid or not paid, if there was no other treatment working. The data received from ANZCTR showed that the elderly were included in the clinical trials; however, it was found that male elders participated more than female elders when counted separately.

Both safety and efficacy require the continued monitoring of subjects after approval. Each year, the lives of elderly patients are improved with the introduction of new drugs, but a significant number of them experience serious side-effects that could have been prevented if their demographic sample was genuinely included in clinical trials. These findings suggest that the number of patients studied before approval is sufficient to determine the short-term efficacy of new medicines, but is insufficient to determine safety or long-term efficacy, which develops at a later phase.
Inclusion of the children population in a clinical trial

The data received from ANZCTR showed that children were included in the clinical trials, but were not segregated in their age group bracket. Age groups need to be well defined based on life stages, since age corresponds to each stage, where medications are affected by the body system’s maturity, e.g. neonate, infants, toddlers, children, adolescents, young adults, adults and older adults.

The high prevalence of off-label and unlicensed drug use in children needs to be addressed. Various studies have shown that prescribing unlicensed or off-label medication is more frequent for children than for adults (Pritchard & Kenner, 2012). Many medicines prescribed for children and adolescents are not licensed for under the age of 18 years (for example, tricyclic antidepressants), or the route or formulation of administration is not the one for which it has been approved (for example, oral midazolam or omeprazole solution), or the product is not licensed at all (for example, caffeine) (Pritchard & Kenner, 2012). In addition, there are also compounds that are licensed for children, but not for adults (for example, methylphenidate) (Pritchard & Kenner, 2012).

Limitations

Study design limitations

The study was designed to compare the findings from a systematic review of the literature to the findings from a historical data desktop analysis. However, neither the available literature nor the data sourced from the ANZCTR were sufficient to achieve this aim. The Australian clinical trials records are not captured by a single body, but rather a number of government organisations, institutions ethics committees and subcommittees. Additionally, registration in the ANZCTR is not compulsory. As a result, the design was then varied by adding a survey element, to gather public opinion on participation in
clinical trials. While the additional element concept is sound, the low budget available for the project, when compared to the resources of larger analytical companies such as KPMG or Price Waterhouse Coopers, imposed another limitation on the level of sophistication of the survey and the number of participants that could be reached.

The use of historical data

This research only involved the data provided by ANZCTR; detailing information about clinical trials, but not the opinions or verdicts of the healthcare personnel who conducted the trials and who were an integral part of the service chain. In addition, the data (Excel worksheet) received from ANZCTR was condensed and complex and was difficult to understand with respect to each code in the documented data. High-level statistical knowledge was required to be able to analyse the received data, and as such, the researcher made a choice based on cost and available funding to use a commercial statistician rather than to undertake a 6-month professional statistical analysis course. However, at the stage of submission, this course of action was regrettable. None of the manufacturers were contacted. The ANZCTR instructed the researcher not to pass on any of the content of the supplied data to a second person or to use them to contact suppliers. Additionally, contacting researchers or study sponsors directly was over-looked by the researcher.

Ability to answer the research question

As a result of the inability to identify information to answer the research question based on the data sourced from the ANZCTR, the researcher applied for variation of the initial proposal. The variation included a survey element in order to complement the data from ANZCTR and the literature. A convenience sample was chosen, to assess the
feasibility of the use of a survey to gather public opinion regarding participation in clinical trials to inform future studies. The selection criteria for the sample were very limiting, and required people who were living with chronic disease. Due to the wide geographical spread of the sample collection location (rural NSW) and limited access to patients, and the researcher being a non-practicing overseas pharmacist, it was not possible to use a powered sample size. The aim was to enrol 30 people in each of the three groups. Two hundred people were approached, and the sample saturation of 50 in each group was achieved from the 150 surveys returned. However, during data entry, 47 surveys had to be excluded as a result of being either incomplete or blank. This left only 103 completed surveys, which still satisfied the study sample of 90. The survey results should be considered as indicative and not confirmatory, but provide useful insight for further research. The extension of this research should be powered based on the national population with chronic diseases, with adequate funding. The data would be collected through polled surveys, to identify the barriers that prevent the vulnerable sections of the society in participating in a clinical trial, as well as the enablers to achieve an equitable level of participation.

The following additional result limitations were experienced:

1. The researcher did not have clinical or practical pharmacy experience in Australia or India, and instead only had industrial pharmacy experience, and on selected topics within the area or practice.

2. The sample of all three components, the literature review, the ANZCTR historical data and the survey were smaller than expected due to there only being a small number of Australian studies on the topic, incomplete data in the ANZCTR, and limited funding to undertake a large sample in the survey.
Accordingly, the finding might not represent the entire population of the elderly, women and parents of children.

3. The survey participants were not subjected to the psychological and emotional need of participating in a clinical trial, which might have influenced their opinion.

4. The researcher was an overseas pharmacist. Hence, learning the Australian system required greater effort, but her placement in the TGA added to her knowledge, although the placement was short and limited to only three days. Additionally, the details of the three days’ placement could not be included in the thesis, as they were deemed by the TGA as being confidential and the researcher was asked to sign a confidentiality declaration form.
Chapter VII - Conclusion and recommendations

Healthcare systems are constantly changing across the globe, and thus supporting clinical research in developing countries and delivering good quality and safe medicines to populations is both critical and challenging. This thesis discussed the participation of the elderly, women and parents of children in clinical trials. The objectives of this thesis were to (1) review the literature related to clinical trials sample selection and the inclusion of the elderly, women and children in clinical trials; (2) review a block of ANZCTR historical clinical trial public access data; and (3) to gather the opinions of a small sample of each of the elderly, women and parents with respect to their participation in clinical trials. The aim was to compare the findings from the three phases to provide insights about the probable causes of the level of participation of the elderly, women and children in clinical trials and to recommend ways forward.

Regulatory agencies should continue to encourage unbiased gender and race participation in clinical trials. Australia’s NHRMC asks researchers running trials whether they will include equal numbers of men and women, but there is little enforcement of this request. It is recommended that sponsors conduct sex-based analysis of the subjects enrolled in clinical trials. Prospective design of clinical trials to include sex and gender analysis would provide more relevant statistical information.

The National Statement of Ethics in Human Research identified the main five principles of research: merit, integrity, justice, beneficence and respect. All ethics committees apply the national statement requirements when considering a research application and approving its commencement. Annual reports from the researcher or the organisation under which they are operating within the approved boundaries are also required.
However, the actual conduct of the research is not monitored unless an adverse event occurs or a participant or outside party complains. In addition, participation rates are rarely prospectively measured, and privacy and confidentiality requirements frequently mean that it is not known if low participation is due to the selection criteria, the selection and advertising process, or the personal choice of the elderly, women, and parents on behalf of their children.

This study had limited resources, and access only to data already in the public domain. It aimed to investigate the participation level of the elderly, women and children as volunteers in clinical trials, and whether that level represented equitable participation compared to men under the age of 65 years. The time taken to conduct the literature review and to analyse the data from the ANZCTR register (which was found to be very far from complete) meant that it was not possible at that point to redesign the methodology.

A condition of access to the ANZCTR was that the researcher would not pass on any of the content of the supplied data to any third party. Additionally, contacting researchers or study sponsors directly was not attempted by the researcher. The aim of this study was not achieved, but the identification of the extent of incomplete records in the ANZCTR is an important finding that needs to be addressed. Additionally, the public survey that was developed, and its findings warrant validation in future studies. Greater clarity on risk versus benefit, the risk profile of the insurance cover during and after participation in clinical trials and life-long health cover insurance cover, require further investigation with wider discussion in the public domain, rather than amongst the researchers only.
Recommendations

1. A better health insurance cover system is required to assure participants that any damage to their health that might occur during the clinical trials will not cause them financial burden and that the researchers will take all possible risk mitigation measures before conducting such trials.

2. Communicating and making historical data accessible will improve participants’ confidence that their rights will be protected and that either them individually or the wider society will benefit from their participation.

3. Improving the awareness of benefits and risks experienced by previous participants may provide the public with a better understanding of aspects of clinical trials.

4. An incentive of extending patents for drugs trialled on the elderly, women and children may act as a catalyst in the long term.

Benefit to current practice and body of knowledge

This study provided some insight on the status of the current deficiency in the local literature on evaluating participation in clinical trials by the elderly, women and children. The study brought the issue of inadequacy of information held by the ANZCTR for public access to the spotlight. The elderly, women and children (through their parents) expressed willingness to participate, if their participation is the only available treatment which may inform future planning for promoting participation for reasons other than active treatment.

Future research

Future research should aim to gather the public opinion on barriers and enablers to participate in clinical trials and also to investigate health insurance issues during clinical trials participation.
References


Australian Bureau of Statistics. (2008). *One in four Australians aged 65 years and over by 2056: ABS.*


Australian New Zealand Clinical Trials Registry. (2015)


Database System: Basic Facts.


Henderson, I., Scott, S., Bennett, C., & Plibersek, T. (2013). Drug trial: The Federal Health Minister says he’s prepared to consider setting up an independent body to oversee scientific research in Australia. *ABC News Victoria.*


http://www.kpmg.com/au/en/about/Pages/default.aspx

factors work together? Mediators, moderators, and independent, overlapping,


Krishna, K., & Kumar, A. (2014). Ethics in clinical research: Indian scenario. *Journal
of Research in Medical Education & Ethics, 4*(1), 14–22.

Kummar, S., Rubinstein, L., Kinders, R., Parchment, R. E., Gutierrez, M. E., Murgo, A.


Li, J. S., Eisenstein, E. L., Grabowski, H. G., Reid, E. D., Mangum, B., Schulman, K.
under the pediatric exclusivity program. *JAMA, 297*(5), 480–488.


409–419.

Littell, R. C., Stroup, W. W., Milliken, G. A., Wolfinger, R. D., & Schabenberger, O.


NHMRC. (n.d.). *Australian clinical trials.*


NordForsk. (2014). *Apply for funding for Nordic clinical research projects.*


PTNA. (2014). *The Paediatric Trials Network Australia*. 191


TGA. (2015a). What’s on a medicine label?


Appendices

Appendix 1 – Ethics approval letter

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Ms Saba Nabi  
SBMS  
10/81 - 85 Ziegler Ave  
Kooringal  
NSW 2650  

20 June 2016  

Dear Saba,  

The Faculty of Science Ethics in Human Research Committee has reviewed your proposal “Risk and Benefit of the Inclusion of Women, Children and Elderly in Clinical Trials” and has approved your proposal for a twelve month period from 20 June 2016.  

The protocol number issued with respect to this project is 400/2016/18. Please be sure to quote this number when responding to any request made by the Committee.  

Please note the following conditions of approval:  

- All consent forms and information sheets are to be displayed on CSU letterhead. Students should liaise with their Supervisor to arrange to have these documents printed where necessary.  
- You must notify the Committee immediately in writing should your research differ in any way from that proposed;  
- You must notify the Committee immediately if any serious or unexpected adverse event or outcomes occur associated with your research, that might affect the participants and therefore ethical acceptability of the project;  
- Amendments to the research design must be reviewed and approved by the Faculty Human Ethics Committee.  
- You are required to submit a final report by 20 June 2017. If an extension of the approval period is required, a request form must be submitted to the Faculty Human Ethics Committee prior to this date;  

You are reminded that an approval letter from the Science FHEC constitutes ethical approval only. If your research involves the use of radiation, biological materials or chemicals then a separate approval is required from the appropriate University Committee.
The Committee wishes you well in your research and please do not hesitate to contact Ingrid Stuart on telephone 6885 7327 or email scienceFHEC@csu.edu.au if you have any enquiries.

Yours sincerely,

Dr. Patricia Logan

Chair Faculty of Science Low Risk Human Ethics Committee
Senior Lecturer - Health Sciences
Appendix 2 – Email to the ANZCTR, a request to release data for Phase 2

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From: ACTR - Info [mailto:actr@ctc.usyd.edu.au]
Sent: Thursday, 27 June 2013 3:33 PM
To: Nabi, Saba
Subject: RE: information regarding Clinical Trial [SEC=UNCLASSIFIED]

Dear Saba,

Thank you for your patience.

We have just finished processing your data request. The results of your data request has been attached to this email as a zip file (due to the size of the original file). Once you unzip the attached zip file, you will see a MS Excel spreadsheet. This MS Excel spreadsheet contains every trial registered on that ANZCTR that are:

- Interventional,
- Related to treatment using drugs, surgery, devices and other (miscellaneous), and
- Registered on the ANZCTR from 1st January 2008 until 27th June 2013.

We did not include trials related to diagnosis/diagnostic tests as we were unsure if you required these trials. Please let us know if you do.

Please note that the MS Excel spreadsheet contains all information provided in the record for each trial meeting the above mentioned criteria. The reason for this is because we thought that you may want to review the entire trial record for trials you may be unsure of in regards to their relevancy to your project. However, columns containing the information (data fields) on each trial’s key inclusion criteria, key exclusion criteria, age range and gender have been highlighted in yellow. This information can be found in the first worksheet named ‘Trials’ within the spreadsheet.

We hope this helps.

Kind regards,

ANZCTR Staff

-----Original Message-----
From: Nabi, Saba [mailto:snabi@csu.edu.au]
Sent: Monday, 24 June 2013 2:25 PM
To: ACTR - Info
Subject: RE: information regarding Clinical Trial [SEC=UNCLASSIFIED]

Dear Concerned,

Thanks for the positive response.
The purpose of using this data is that my PhD Research involves looking at the Clinical trials at Australia and New Zealand and my University (Charles Sturt University) has no commercial interest in it. Since it's my Research topic and my University has backed me with the scholarship and the resources which all the Research students need.

In addition, as advised in sections 4.1 and 4.2, I also assure that I as well as my University will appropriately acknowledge the ANZCTR as the source of this data.

In your earlier email, I would confirm the following what criteria (data fields) which I would like to include in my data request such as:

- Trials conducted/recruiting in Australia and New Zealand as well as Trials conducted/recruiting in all countries
- Was there any specific health condition you wanted (e.g. breast cancer trials only; etc)? and/or No want all the medication related clinical trials
- Was there any specific time period that you are interested in (e.g. only trials registered with the ANZCTR from 2010 – 2013; etc)? Yes from 2008-13
- Did you want both observational and interventional studies? No just want the interventional studies

When we retrieve the data, we will ensure that the data fields relevant to participants (e.g. inclusion and exclusion criteria, gender and age range; etc) will be included. Thank you for this piece of information.

If you need any clarification, please don't hesitate to call me on 0435472995.

Have a lovely day ahead

With Regards

Saba Nabi
PhD Scholar
School of Biomedical Sciences
Faculty of Science
Charles Sturt University
Wagga Wagga NSW 2678 Australia

Phone +61 2 6933 4569
Mobile: +61 435472995

Email: snabi@csu.edu.au or nabisaba@gmail.com
Dear Saba,

In order for us to formally finalise this data request, we would like to inform you of the ANZCTR’s terms of approval.

As stated in the ANZCTR Access Policy document (http://www.anzctr.org.au/docs/ANZCTR%20Access%20policy%20-%20V3%2023Apr08.pdf) in section 2.2, please disclose the purpose of your request for this specific data and what your organisation will be using it for.

In addition, as advised in sections 4.1 and 4.2, please write back to us stating in writing that your organisation will appropriately acknowledge the ANZCTR as the source of this data. The suggested wording that should be used when citing a data from the ANZCTR is:

“Australian New Zealand Clinical Trials Registry (ANZCTR) [database on the internet]. Sydney (NSW): The University of Sydney (Australia); 2005 [cited year month day]. Available from http://www.anzctr.org.au”.

Once these terms have been met we can then proceed with your data request.

In your reply email, could you please also confirm that what criteria (data fields) you would like to include in your data request? As discussed earlier in our phone conversation, we can retrieve all drug and device trials registered with the ANZCTR. However, were there any other criteria you would want included such as:

- Trials conducted/recruiting in Australia and New Zealand only; and/or
- Trials conducted/recruiting in Australia only; and/or
- Trials conducted/recruiting in all countries; and/or
- Was there any specific health condition you wanted (e.g. breast cancer trials only; etc)? and/or
- Was there any specific time period that you are interested in (e.g. only trials registered with the ANZCTR from 2010 – 2013; etc)? and/or
- Did you want both observational and interventional studies?

When we retrieve the data, we will ensure that the data fields relevant to participants (e.g. inclusion and exclusion criteria, gender and age range; etc) will be included.
Kind Regards

ANZCTR Staff

-----Original Message-----
From: Nabi, Saba [mailto:snabi@csu.edu.au]
Sent: Tuesday, 18 June 2013 12:15 PM
To: ACTR - Info
Subject: RE: information regarding Clinical Trial [SEC=UNCLASSIFIED]

Dear Concerned,

Please don't apologize, I know you guys are really busy.

Through my request which I placed earlier "I mean all the drug and device trials which got registered on the ANZCTR". I am specifically looking for the number of men, women, children and elderly which were the subjects in the clinical trials which got registered from 2005-2013.

I saw the Statistics Report which was there on "Australian and New Zealand Clinical Trial Registry" website but it says the total number of trials. I actually want the breakup of the participants in the clinical trials.

If you need any clarification, please don't hesitate to call me on 0435472995.

Have a lovely day ahead.

With Regards

Saba Nabi
PhD Scholar
School of Biomedical Sciences
Dear Sabi,

Thank you for your email.

First of all, we would like to apologise for our late response.

Before we proceed with your data request, we will need to confirm what is meant by “clinical trials which got registered in TGA”. The reason we ask is because we do not ask trialists who register their trials with us whether or not their trial was also registered with the TGA. Therefore, it would be hard to identify which trials meet your criteria. However, we could try and retrieve trials with the following criteria:
• Trials that have TGA or a TGA contact person listed as a Funding Source, Primary Sponsor, Secondary Sponsor, Collaborator, and/or Contact Person.

• All drug and device trials registered on the ANZCTR.

In your reply email, please confirm whether or not these criteria would be sufficient and/or if there are any other criteria you think may be useful for retrieving the trials you need.

Kind regards,

ANZCTR Staff

-----Original Message-----

From: Nabi, Saba [mailto:snabi@csu.edu.au]
Sent: Tuesday, 11 June 2013 3:30 PM
To: info@actr.org.au
Dear Australian and New Zealand Clinical Trial Registry,

I am a PhD student in the School of Biomedical Sciences at Charles Sturt University.

My PhD Research topic involved assessing the subjects enrolled in the clinical trials from 2005-2013.

I am specifically looking for the number of men, women, children and elderly which were the subjects in the clinical trials which got registered in TGA from 2005-2013.

Can you please provide me the data for my Research.

With Regards

Saba Nabi

PhD Scholar
Appendix 3 - Invitation Letter to community groups

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Risk and benefit of the Inclusion of Women, Children and Elderly in Clinical Trials

Researcher: SABA NABI, B. Pharm & MBA (Pharmaceutical Management), Charles Sturt University for the degree of Doctor of Philosophy.

Supervisors: Professor Patrick Ball**, Mr George John*, Dr Hana Morrissey**
*School of Biomedical Sciences, Faculty of Science, Charles Sturt University, Wagga Wagga, NSW, Australia
** School of Physiological and Clinical Sciences, Faculty of Engineering Health Science & Environment, Charles Darwin University, Darwin, Northern Territory 0909 Australia

Parent project title: Risk and benefit of the Inclusion of Women, Children and Elderly in Clinical Trials

Ethics approval number: 400/2016/18
Dear President of ..........group/club/committee

Saba Nabi is currently pursuing her PhD in the School of Biomedical Sciences at Charles Sturt University, Wagga Wagga. This study is part of Saba’s PhD Research, data and information collected upon completion of this study will form part of her PhD Thesis and will also contribute towards formal scientific publications.

All individuals regardless of age, gender or ethnicity who take medicines are subjected to some potential risks such as side effects.

Clinical studies conducted during the development of new medicines are generally designed to show safety and efficacy before marketing, then again after marketing. However, public participation as volunteers in those trials is generally poor.

This study is a survey aiming to gather public perception on how individuals would feel about participation in clinical trials as volunteers, including the things that may motivate them to participate or the concerns and barriers that stop them from participating.

She will be recruiting participants who are:

1. 65 years old or over, from any gender who has one or more medical condition that requires ongoing use of medications.
2. Women 18 years and over, who has one or more medical condition that requires ongoing use of medications.
3. Parent of child/children (0-18 years of age) who has one or more medical condition that requires ongoing use of medications.

Individuals who fit in more than one of the above criteria can only participate once under the most appropriate group to their current state.

She is inviting your group/club/committee to take part in the study and complete a short survey which will require 15 minutes of their time regarding their opinion about the participation in clinical trials.

This is only a small survey; all data will be collected as anonymous, neither the person nor the community group name, location or their affiliation will be identified or disclosed at any time or in any future publications.
If in agreement she will provide you with a poster which has my contact details for members who are willing to voluntarily participate to contact me to meet and complete the survey at time and place of their convenience.

If you have any questions regarding this study, please contact the researcher by email on (snabi@csu.edu.au) or her supervisor on (pball@csu.edu.au).

If you have any complaint regarding this study please contact the Faculty of Science Human Ethics Low Risk Committee, Locked Bag 49, 8 Tony McGrane Place, Dubbo, NSW 2830, Australia
Tel: +61 2 6885 7327 Email: scienceFHEC@csu.edu.au

Yours sincerely

Prof. Patrick Ball
Appendix 4 - Marketing Poster for community groups, to invite their members

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Risk and benefit of the Inclusion of Women, Children and Elderly in Clinical Trials

Do you know that:
All individuals regardless of age, gender or ethnicity who take medicines may experience some side effects.
Clinical studies conducted during the development of new medicines require the participation of healthy people first to determine the medication safety then require people who have the condition that new medicine intended to treat, to test its effectiveness. However, participation in those trials is generally poor.

This study aims to gather public opinion on how people feel about participating in clinical trials, including the things that may motivate them to participate or the concerns and the barriers that stop them from participating.

All data will be anonymous, neither the person nor the community group name, location or their affiliation will be identified or disclosed at any time or in any future publications.

If in agreement please inform your community group President or leader for more information on date, time and place when the researcher will visit your group.

We are inviting you to take part in this short survey which will require 15 minutes of your time regarding your opinion about the participation in the clinical trials
You can participate if you are:
- 65 years old or over, from any gender who has one or more medical condition that requires ongoing use of medications,
  OR
- Women 18 years and over, who has one or more medical condition that requires ongoing use of medications
  OR
- Parent of child/children who has one or more medical condition that requires ongoing use of medications

Individuals who fit in more than one of the above criteria can only participate once.

Ethics approval number: 400/2016/18

If you have any complaint regarding this study please contact
Faculty of Science Human Ethics Low Risk Committee, Locked Bag 49, 8 Tony McGrane Place, Dubbo, NSW 2830. Tel: +61 2 6885 7327 Email: scienceFHEC@csu.edu.au
Appendix 5 - Public Survey

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Risk and benefit of the Inclusion of Women, Children and Elderly in Clinical Trials

Researcher: SABA NABI, B. Pharm & MBA (Pharmaceutical Management), Charles Sturt University student for the degree of Doctor of Philosophy.

Supervisors: Professor Patrick Ball *, **, Mr George John*, Dr Hana Morrissey**

*School of Biomedical Sciences, Faculty of Science, Charles Sturt University, Wagga Wagga, NSW, Australia
** School of Physiological and Clinical Sciences, Faculty of Engineering Health Science & Environment, Charles Darwin University, Darwin, Northern Territory 0909 Australia

Parent project title: Risk and benefit of the Inclusion of Women, Children and Elderly in Clinical Trials

Ethics approval number: 400/2016/18
Dear Participant,

Saba Nabi is currently pursuing her PhD in the School of Biomedical Sciences at Charles Sturt University, Wagga Wagga. This study is part of Saba’s PhD Research, data and information collected upon completion of this study will form part of her PhD Thesis and will also contribute towards formal scientific publications.

All individuals regardless of age, gender or ethnicity who take medicines are subjected to some potential risks. All medications have potential safety concerns, which vary in severity in different individuals based upon gender, age group and state of health.

Clinical studies conducted during the development of new medicines are generally designed to show safety and efficacy under strict conditions. They are trialled in relatively carefully selected and defined populations of healthy subjects in phase one studies, then are required to be tested for efficacy in patients having the medical condition for which the medicine is targeted.

This small component of an overall study is aiming to inform the balance between commercial risk and societal risk arising from the levels of participation in phase 4 clinical trials from the elderly, woman and children, and gather some information on consumer opinions about the participation of such groups in clinical trials as volunteers, examining the motivations that may persuade them to participate or the barriers that prevent them from taking part. The results from this survey will be compared to the data extracted from the Australia/New Zealand Clinical Trials Register to compare the participation levels with public perceptions found from this survey.

Participation in this study does not oblige the participants to take part in any further study. All data will be collected de-identified, neither the person nor the community group name, location or affiliation will be identified or disclosed at any time of the study or in any future publications. Each form will have a unique serial number which the participant will be asked to record so that if they later decide to withdraw from the study, their form can be identified and destroyed. Participants will be asked to respond to questions which will require 15 minutes of their time.

Consent to participate will be considered achieved once a participant has completed and handed over the completed survey to the researcher.

For a volunteer to be able to participate in this study they must be:

1. 65 years old or over, from any gender who has one or more medical condition that requires ongoing use of medications

2. Women 18 years and over, who have one or more medical condition that requires ongoing use of medications.

3. Parent of a child/children who have one or more medical condition that requires ongoing use of medications.

Individuals who fit more than one of the above criteria can only participate once.

All individuals who complete the survey need to drop the survey sheet in a sealed envelope in the box.

She will be keeping the information generated from the research for 5 years as a scanned document which is password protected. Hard copies are kept in a closed cupboard. The information will be properly disposed off after 5 years.
If you have any questions regarding this study, please contact the research by email on (snabi@csu.edu.au) or her supervisor on (pball@csu.edu.au).

If you have any complaint regarding this study, please contact the Charles Sturt University ethics committee Executive Officer, Human Ethics, Low Risk Committee, Charles Sturt University, Locked Bag 49, 8 Tony McGrane Place, Dubbo, NSW, 2830. 02 6885 7327. Email: ScienceFHEC@csu.edu.au

If you are experiencing high levels of stress, get help. Talk to your GP, a Counsellor or call Lifeline on 13 11 14.

This page is for you to keep
Part 2 – Surveys

Please complete the section APPLICABLE to your situation only (see pages 2-3).

You can participate only under one category.

Please Tick (√) ONE correct answer
A- The Elderly participation in clinical trial survey

(Please complete pages 5 and 6 only)

Study serial number:

Do you:

Have a dependant relationship with the researcher

Wish to voluntarily participate

Accept that the collected data be used as population data for this study purpose which will be published unidentified

Age

65-69 years old

70-74 years old

75-79 years old

80 years old and over

Gender

Male

Female

Others

Health status

One medical condition and taking no daily medication

One medical condition and taking one medication daily

One medical condition and taking multiple medications daily

More than one medical condition and taking multiple medications daily
<table>
<thead>
<tr>
<th>Question - The Elderly participation in clinical trial survey</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you are healthy would you participate in clinical trials?</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>If you had the disease that a new medicine is treating, but you were happy with your current treatment; would you participate in clinical trials?</td>
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</tr>
<tr>
<td>If you had the disease the new medicine is treating, but were not happy with your current treatment; would you participate in the clinical trials?</td>
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</tr>
<tr>
<td>If you had the disease the new medicine is treating, but no other treatment is working and the new medicine were your last hope; would you participate in the clinical trials?</td>
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</tr>
<tr>
<td>If you had the disease the new medicine is treating, and you were offered lifelong health insurance which covers any side effect or damage caused by the tested medicine, regardless of if there is, or is not another treatment currently working; would you participate in the clinical trials?</td>
<td></td>
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<tr>
<td>If you had the disease the new medicine is treating, and if you were offered lifelong health insurance which covers any side effect or damage caused by the tested medicine, and there is no other treatment working; would you participate in the clinical trials?</td>
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<tr>
<td>If you had the disease the new medicine is treating, if you are offered a payment, regardless of if there is or there is no other treatment working; would you participate in the clinical trials?</td>
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<tr>
<td>If you had the disease the new medicine is treating, if you were offered a payment, and there is no other treatment working, would you participate in the clinical trials?</td>
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</tbody>
</table>

Further comments about participation in clinical trials which involve administration of medication:

Please return these two pages to the researcher
Thank you for your participation
B- Women participation in clinical trial survey
(Please complete pages 7 and 8 only)

Study serial number:

Do you:

- Have a dependant relationship with the researcher
- Wish to voluntarily participate
- Accept that the collected data be used as population data for this study purpose which will be published unidentified

Age

- 18-24 years old
- 25-34 years old
- 35-44 years old
- 45-54 years old
- 55-64 years old
- 65-69 years old
- 70-74 years old
- 75-79 years old
- 80 years old and over

Gender

- Female

Health status

- One medical condition and taking no daily medication
- One medical condition and taking one medication daily
- One medical condition and taking multiple medications daily
- More than one medical condition and taking multiple medications daily
<table>
<thead>
<tr>
<th>Question - The Women participation in clinical trial survey</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you are healthy would you participate in clinical trials?</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>If you had the disease that a new medicine is treating, but you were happy with your current treatment; would you participate in clinical trials?</td>
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</tr>
<tr>
<td>If you had the disease the new medicine is treating, but were not happy with your current treatment; would you participate in the clinical trials?</td>
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<tr>
<td>If you had the disease the new medicine is treating, but no other treatment is working and the new medicine were your last hope; would you participate in the clinical trials?</td>
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<tr>
<td>If you had the disease the new medicine is treating, and you were offered lifelong health insurance which covers any side effect or damage caused by the tested medicine, regardless of if there is, or is not another treatment currently working; would you participate in the clinical trials?</td>
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<tr>
<td>If you had the disease the new medicine is treating, and if you were offered lifelong health insurance which covers any side effect or damage caused by the tested medicine, and there is no other treatment working; would you participate in the clinical trials?</td>
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<tr>
<td>Further comments about participation in clinical trials which involve administration of medication:</td>
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</table>

Please return these two pages to the researcher
Thank you for your participation
C – Parents of child/children participation in clinical trials survey

(Please complete pages 9 and 10 only)

Study serial number:

Do you:

Have dependant relationship with the researcher
Wish to voluntarily participate
Accept that the collected data be used as population data for this study purpose which will be published unidentified

Number of children

One child
2 children
3 children
4 or more than 4 children

Your gender

Male
Female
Others

Your child's gender (please write the number against each gender)

Male………..
Female………..
Others ……..

Health status of your children (please write the number against each gender)

One medical condition and taking no daily medication
One medical condition and taking one medication daily
One medical condition and taking multiple medications daily
More than one medical condition and taking multiple medications daily
<table>
<thead>
<tr>
<th>Question - The Parent’s participation in clinical trial survey</th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you are healthy would you participate in clinical trials?</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>If you had the disease that a new medicine is treating, but you were happy with your current treatment, would you participate in clinical trials?</td>
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</tr>
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<td>If you had the disease the new medicine is treating, but were not happy with your current treatment; would you participate in the clinical trials?</td>
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<tr>
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<td>Further comments about participation in clinical trials which involve administration of medication:</td>
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Please return these two pages to the researcher
Thank you for your participation
Appendix 6 – Raw Data Electronic

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Appendix 7 – Conference Abstracts

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Clinical trials: Australian prospective view

Saba Nabi1, Parikshit Basu1, George John1 and Patrick Ball2

1Charles Sturt University, Australia
2Charles Darwin University, Australia

The regulatory agencies need to have pro-active approach in handling clinical trials throughout the globe. FDA as well as other regulatory bodies should continue to encourage unbiased gender and race participation in the clinical trials. Australia’s National Health and Medical Research Council does ask researchers running trials whether they’ll include equal numbers of men and women, but there’s little follow up to enforce the guidelines. The sponsors should conduct sex analysis of the subjects enrolled at the clinical trial sites. Prospective design of clinical trials for sex analysis would provide more relevant statistical information. Trust, communication, education, and building a presence within the community are successful means to increasing diversity in clinical trials. Collaborative efforts are essential across all sectors of medical product research and development. Regulatory and review bodies must focus on patients’ needs and facilitate the clinical trial process. Phase III trials are not powered to assess trends in subgroups. In order to make an impact, analysis should be done in Phase III, not just post marketing studies. Manufacturers still want to make one-size-fits-all, and also don’t want to have to make many different dosages. There is a high prevalence of off-label and unlicensed drug use confirming that it is a widespread phenomenon. It is important for both the marketing authorization holder and national and international regulatory authorities to monitor for any consequential safety concerns and to take appropriate measures to address them, as well as to identify research priorities and mandate clinical studies to resolve important questions. Regulatory authorities should use existing clinical evidence on the use of off-label and unlicensed drugs in decision making and support conducting rigorous clinical trials only when necessary in order to fill the gaps in pediatric pharmacotherapy.

It is recommended to the clinical trial sponsors that researchers use consent forms, promotional materials, and other study forms in age-appropriate formats and adjusted literacy levels. There are many tools and promotional items like large-print, third-to fifth-grade reading level materials, accompanying audiovisuals for the hearing- and vision impaired, and other clinical teaching aids that are appropriate to culture and literacy level (e.g., videos, charts, and diagrams). It’s the duty of the Liaison Committee for Medical Education, which addresses education regarding clinical research, amend medical education requirements and curricula objectives to sensitize future practitioners to the special needs of older and elderly clinical trial subjects or volunteers.

There is a need for the regulators, policy makers and the stakeholders to analyze the bitter truth of conducting clinical trials impartially. The stakeholders as well as the clinical trial experts should plan their strategy in age-appropriate formats. Therapeutic good administration (TGA), National health and medical research council (NHMRC) and clinical trial action group (CTAG) Australia should work coherently to develop simplified ethical and legal procedures and constantly monitor the progress of the trials with no age-related barriers. The health care system in Australia has to successfully manage an increasing absolute number of frail older people with multiple co-morbidity and disability.

snabi@csu.edu.au
PARTICIPATION OF WOMEN, CHILDREN AND ELDERLY IN THE CLINICAL TRIALS: AUSTRALIAN PROSPECTIVE VIEW

Collaborative efforts are essential across all sectors of medicinal product development. Nabi, Saba, Charles Sturt University, Wagga Wagga, NSW, Australia

Ball, Patrick, School of Psychological and Clinical Sciences, Charles Darwin University, Northern Territory, Australia

Basu, Parikshit, Charles Sturt University, Wagga Wagga, NSW, Australia

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ABSTRACT

Life expectancy in Australia is 79.3 years for men and 83.9 years for women. Australia is predicted to see a substantial increase in the number of frail older people. An essential component of medical care is Pharmacotherapy and it’s estimated that around two-thirds of Australians over the age of 60 use four or more drugs. Exclusion of older adults as clinical trial participants is highly problematic because they suffer high rates of Cancer, Cardiovascular Disease, Dementia, Arthritis and Parkinson’s disease. The health care system in Australia has to successfully manage an increasing absolute number of frail older people with multiple co-morbidity and disability

It has been documented for years that female have been underrepresented in the clinical trials in the New Drug Application (NDA) and Investigational New Drug Application (INDA) which are being approved before the marketing.

The issue of the underprivileged position of children with respect to the drug therapies or their participation in the clinical trials was raised years ago, but the situation remains inadequate. Children are routinely given drugs that basically lack the specific pediatric information because of facing the difficulty in carrying out clinical trials in this population, such as practical difficulties and ethical considerations arising from the involvement of children.

The regulatory agencies require a Pro-active approach in handling clinical trials throughout the globe. The FDA and other regulatory bodies should continue to encourage unbiased gender and race participation in trials. Australia’s National Health and Medical Research Council does ask researchers running trials whether they’ll include equal numbers of men and women, but there’s little follow up to enforce the guidelines. The sponsors should conduct analysis of distribution of the sexes of subjects enrolled in clinical trials. The prospective design of clinical trials for analysis of gender would provide more relevant statistical information. The pillars of increasing diversity in the Clinical trials are Trust, communication, education, and building a presence within the community. Collaborative efforts are essential across all sectors of medicinal product research and development. Regulatory and review bodies must focus on patients’ needs and initiate the clinical trial process. Phase III trials are currently not powered to assess trends in subgroups. In order to make an impact, analysis should be done in Phase III, not just post marketing studies. Manufacturers still want to make one-size-fits-all, and also don’t want to have to make many different dosages. There is a high prevalence of off-label and unlicensed drug use confirming that it is a widespread phenomenon. It is important for both the marketing authorization holder and national and international regulatory authorities to monitor for any consequential safety concerns and to take appropriate measures to address them, as well as to identify research priorities and mandate clinical studies to resolve important questions.

Regulatory authorities should use existing clinical evidence on the use of off-label and unlicensed drugs in decision making and support conducting rigorous clinical trials only when necessary in order to fill the gaps in pediatric as well as geriatrics pharmacotherapy.

It is recommended to sponsors that clinical trial researchers use consent forms, promotional materials, and other study forms in age-appropriate formats and adjusted literacy levels. There are many tools and promotional items like large-print, third- to fifth-grade reading level materials, accompanying audiovisuals for the hearing- and vision impaired, and other clinical teaching aids that are appropriate to culture and literacy level (e.g., videos, charts, and diagrams). It’s the duty of the Liaison Committee for Medical Education, which addresses education regarding clinical research, to amend medical education requirements and curricula objectives to inform future practitioners of the special needs of older and elderly clinical trial subjects or volunteers.
There is a need for the regulators, policy makers and the stakeholders to analyze the risk balance between the industry and society. When a medication becomes licensed and marketed, the whole of society shares the risk of use in the elderly children and other special groups. Extending trials to include these groups would increase costs, and delay the release of new medicines. This paper asks whether the current balance is optimal. The stakeholders as well as the clinical trial experts should plan their strategy in age-appropriate formats. The Therapeutic Good Administration (TGA), National Health and Medical Research Council (NHMRC) and Clinical Trial Action Group (CTAG) Australia should work coherently to develop guidelines to balance the risk between the innovator and society to ensure the balance is correct.
Appendix 8 – Statistical Analysis of Survey

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Q1: If you are healthy would you participate in clinical trials?

Parents vs Elderly (x=Parents, y=Elderly)

Women vs Parents (x=Women, y=Parents)

Women vs Elderly (x=Women, y=Elderly)

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|   | [95% Conf. Interval] |
|----------|--------|-----------|--------|-------|----------------------|
| x        | 0.2777778 | 0.0746505 | 0.1314654 | 0.4240901 |
| y        | 0.1764706 | 0.0653787 | 0.0483307 | 0.3046105 |
| diff     | 0.1013072 | 0.0992324 | -0.0931848 | 0.2957992 |

Pr(Z < z) = 0.8435  Pr(|Z| > |z|) = 0.3131  Pr(Z > z) = 0.1565

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|   | [95% Conf. Interval] |
|----------|--------|-----------|--------|-------|----------------------|
| x        | 0.2777778 | 0.0746505 | 0.1314654 | 0.4240901 |
| y        | 0.1764706 | 0.0653787 | 0.0483307 | 0.3046105 |
| diff     | -0.1767677 | 0.1143934 | -0.4009746 | 0.0474393 |

Pr(Z < z) = 0.0635  Pr(|Z| > |z|) = 0.1270  Pr(Z > z) = 0.9365

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|   | [95% Conf. Interval] |
|----------|--------|-----------|--------|-------|----------------------|
| x        | 0.1764706 | 0.0653787 | 0.0483307 | 0.3046105 |
| y        | 0.1545455 | 0.0866784 | 0.2046589 | 0.621432 |
| diff     | -0.2706749 | 0.1085704 | -0.4908689 | 0.0652809 |

Pr(Z < z) = 0.0071  Pr(|Z| > |z|) = 0.0142  Pr(Z > z) = 0.9929
8. *Q2: If you had the disease that a new medicine is treating, but you were happy with your current treatment; would you participate in clinical trials?

9. *Women vs Parents (x=Women, y=Parents)

10. prtesti 36 11 33 11, count

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|  | [95% Conf. Interval] |
|----------|--------|-----------|--------|-----|----------------------|
| x        | .3055556 | .0767737  | .1550818 | .4560293 |
| y        | .2058824 | .0693446  | .0699695 | .3417952 |
| diff     | .0996732 | .1034547  | -.1030943 | .3024407 |

Diff = prop(x) - prop(y) under Ho: diff = 0, Ha: diff < 0, Ha: diff != 0, Ha: diff > 0
Pr(Z < z) = .8299, Pr(|Z| > |z|) - .3403, Pr(Z > z) = .1701

11. *Women vs Elderly (x=Women, y=Elderly)

12. prtesti 36 11 33 11, count

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|  | [95% Conf. Interval] |
|----------|--------|-----------|--------|-----|----------------------|
| x        | .3055556 | .0767737  | .1550818 | .4560293 |
| y        | .3333333 | .082061   | .1724967 | .4941699 |
| diff     | -.0277778 | .1123753  | -.2480293 | .1924738 |

Diff = prop(x) - prop(y) under Ho: diff = 0, Ha: diff < 0, Ha: diff != 0, Ha: diff > 0
Pr(Z < z) = .4023, Pr(|Z| > |z|) - .8047, Pr(Z > z) = .5977

13. *Parents vs Elderly (x=Parents, y=Elderly)

14. prtesti 34 7 33 11, count

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|  | [95% Conf. Interval] |
|----------|--------|-----------|--------|-----|----------------------|
| x        | .2058824 | .0693446  | .0699695 | .3417952 |
| y        | .3333333 | .082061   | .1724967 | .4941699 |
| diff     | -.127451 | .1074369  | -.3380233 | .0831214 |

Diff = prop(x) - prop(y) under Ho: diff = 0, Ha: diff < 0, Ha: diff != 0, Ha: diff > 0
Pr(Z < z) = .1197, Pr(|Z| > |z|) - .2393, Pr(Z > z) = .8803
15. *Q3: If you had the disease the new medicine is treating, but were not happy with your current treatment; would you participate in the clinical trials?

16. *Women vs Parents (x=Women, y=Parents)

17. prtesti 36 24 34 12, count

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|----------|--------|-----------|-------|------|----------------------|
| x        | .6666667 | .0785674 | .5126774 | .820656 |
| y        | .3529412 | .0819565 | .1923093 | .513573 |
| diff     | .3137255 | .1135329 | .0912051 | .5362458 |

under Ho: .1195229 2.62 0.009

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<td>Ha: diff != 0</td>
<td>Ha: diff &gt; 0</td>
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<td>Pr(</td>
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<tr>
<td>Pr(Z &gt; z)</td>
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18. *Women vs Elderly (x=Women, y=Elderly)

19. prtesti 36 24 33 14, count

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|----------|--------|-----------|-------|------|----------------------|
| x        | .6666667 | .0785674 | .5126774 | .820656 |
| y        | .4242424 | .086034 | .255619 | .5928659 |
| diff     | .2424242 | .1165104 | .014068 | .4707805 |

under Ho: .1198781 2.02 0.043

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<tr>
<td>Pr(Z &gt; z)</td>
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</tbody>
</table>

20. *Parents vs Elderly (x=Parents, y=Elderly)

21. prtesti 34 12 33 14, count

Two-sample test of proportions

| Variable | Mean   | Std. Err. | z     | P>|z| | [95% Conf. Interval] |
|----------|--------|-----------|-------|------|----------------------|
| x        | .3529412 | .0819565 | .1923093 | .513573 |
| y        | .4242424 | .086034 | .255619 | .5928659 |
| diff     | -.0713012 | .1188222 | -.3041885 | .161586 |

under Ho: .1190816 -0.60 0.549

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<tr>
<td>Pr(Z &lt; z)</td>
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<td>Pr(</td>
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<tr>
<td>Pr(Z &gt; z)</td>
<td>0.7253</td>
<td></td>
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</tbody>
</table>
Ho: \( \text{diff} = 0 \)

```
 diff = \text{prop}(x) - \text{prop}(y)

H_0: \text{diff} = 0
H_1: \text{diff} < 0 \quad H_1: \text{diff} \neq 0 \quad H_1: \text{diff} > 0
```

**Two-sample test of proportions**

```
prtesti 34 23 33 17, count
*x* Parents vs Elderly (x=Parents, y=Elderly)
```

```
Pr(Z < z) =
Ho: \text{diff} = 0
diff = \text{prop}(x) - \text{prop}(y)
```

```
| Variable | Mean   | Std. Err. | z     | P>|z| | (95% Conf. Interval) |
|----------|--------|-----------|-------|------|----------------------|
| x        | 0.7702 | 0.06923   | 1.127 | .261 | [0.6150, 0.9253]     |
| y        | 0.6764 | 0.08023   | 0.860 | .388 | [0.5175, 0.8352]     |
| diff     | 0.1013 | 0.106009  | 0.95  | .340 | [-0.106468, 0.3090828] |
```

22. **Q4:** If you had the disease the new medicine is treating, but no other treatments are working and the new medicine were your last hope; would you participate in the clinical trials?

Q4 is unrecognized r(199);

23. **Q4:** If you had the disease the new medicine is treating, but no other treatments are working and the new medicine were your last hope; would you participate in the clinical trials?

24. **Women vs Parents (x=Women, y=Parents)**

25. `prtesti 36 28 34 23, count`

```
Two-sample test of proportions
x: Number of obs = 36
y: Number of obs = 34
```

```
| Variable | Mean   | Std. Err. | z     | P>|z| | (95% Conf. Interval) |
|----------|--------|-----------|-------|------|----------------------|
| x        | 0.7778 | 0.06928   | 1.127 | .261 | [0.6146, 0.9410]     |
| y        | 0.6764 | 0.08023   | 0.860 | .388 | [0.5175, 0.8352]     |
| diff     | 0.1013 | 0.10601   | 0.95  | .340 | [-0.106468, 0.3090828] |
```

26. **Women vs Elderly (x=Women, y=Elderly)**

27. `prtesti 36 28 34 17, count`

```
Two-sample test of proportions
x: Number of obs = 36
y: Number of obs = 34
```

```
| Variable | Mean   | Std. Err. | z     | P>|z| | (95% Conf. Interval) |
|----------|--------|-----------|-------|------|----------------------|
| x        | 0.7778 | 0.06928   | 1.127 | .261 | [0.6146, 0.9410]     |
| y        | 0.5156 | 0.08699   | 0.576 | .566 | [0.3607, 0.6705]     |
| diff     | 0.2626 | 0.11223   | 2.316 | .023 | [0.0446, 0.4806]     |
```

28. **Parents vs Elderly (x=Parents, y=Elderly)**

29. `prtesti 34 23 33 17, count`

```
Two-sample test of proportions
x: Number of obs = 34
y: Number of obs = 33
```

```
| Variable | Mean   | Std. Err. | z     | P>|z| | (95% Conf. Interval) |
|----------|--------|-----------|-------|------|----------------------|
| x        | 0.6764 | 0.08023   | 0.860 | .388 | [0.5175, 0.8352]     |
| y        | 0.5156 | 0.08699   | 0.576 | .566 | [0.3607, 0.6705]     |
| diff     | 0.1613 | 0.11836   | 1.35  | .178 | [0.0703, 0.3932]     |
```

29. **Q4:** If you had the disease the new medicine is treating, but no other treatments are working and the new medicine were your last hope; would you participate in the clinical trials?

Friday March 24 14:30:53 2017   Page 4
Pr(Z < z) = \Pr(Z > z) = 0.0892

Ha: diff < 0       Ha: diff ≠ 0       Ha: diff > 0
Pr(Z < z) = 0.9108  Pr(|Z| > |z|) = 0.1783  Pr(Z > z) = 0.8819

30. *Q5: If you had the disease the new medicine is treating, and you were offered a treatment which covers any side effect or damage caused by the medicine, regardless of if there is, or is not another treatment currently working; would you participate in the clinical trials?

31. *Women vs Parents (x=Women, y=Parents)
32. prtesti 36 21 34 13, count
Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|    | [95% Conf. Interval] |
|----------|--------|-----------|--------|--------|----------------------|
| x        | 0.58333 | 0.08217 | 0.422 | 0.674 | 0.422275 - 0.744392  |
| y        | 0.41177 | 0.08440 | 0.246 | 0.807 | 0.246368 - 0.577192  |
| diff     | 0.171 | 0.11779 | -0.593 | 0.559 | -0.059304 - 0.402442 |

under Ho: \text{diff} = \text{prop(x)} - \text{prop(y)}
Ho: \text{diff} = 0

Pr(Z < z) = 0.9243  Pr(|Z| > |z|) = 0.1513  Pr(Z > z) = 0.0757

33. *Women vs Elderly (x=Women, y=Elderly)
34. prtesti 36 21 33 13, count
Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|    | [95% Conf. Interval] |
|----------|--------|-----------|--------|--------|----------------------|
| x        | 0.58333 | 0.08217 | 0.422 | 0.674 | 0.422275 - 0.744392  |
| y        | 0.39398 | 0.08505 | 0.227 | 0.807 | 0.227285 - 0.560652  |
| diff     | 0.190 | 0.11826 | -0.042 | 0.968 | -0.042397 - 0.421187 |

under Ho: \text{diff} = \text{prop(x)} - \text{prop(y)}
Ho: \text{diff} = 0

Pr(Z < z) = 0.9420  Pr(|Z| > |z|) = 0.1160  Pr(Z > z) = 0.0580

35. *Parents vs Elderly (x=Parents, y=Elderly)
36. prtesti 34 14 33 13, count
Two-sample test of proportions

| Variable | Mean   | Std. Err. | z      | P>|z|    | [95% Conf. Interval] |
|----------|--------|-----------|--------|--------|----------------------|
| x        | 0.41177 | 0.08440 | 0.246 | 0.807 | 0.246368 - 0.577192  |
| y        | 0.39398 | 0.08505 | 0.227 | 0.807 | 0.227285 - 0.560652  |
| diff     | 0.018 | 0.11983 | -0.217 | 0.827 | -0.217034 - 0.252684 |

under Ho: \text{diff} = \text{prop(x)} - \text{prop(y)}
Ho: \text{diff} = 0

Pr(Z < z) = 0.5591  Pr(|Z| > |z|) = 0.8818  Pr(Z > z) = 0.4409
37. *Q6: If you had the disease the new medicine is treating, and if you were offered a red lifelong health insurance which covers any side effect or damage caused by the tested medicine, and there is no other treatment working; would you participate in the clinical trials?

38. *Women vs Parents (x=Women, y=Parents)

```
> prtesti 36 20 34 16, count
Two-sample test of proportions
x: Number of obs = 36
y: Number of obs = 34

| Variable | Mean   | Std. Err. | z     | P>|z|  | [95% Conf. Interval] |
|----------|--------|-----------|-------|------|---------------------|
| x        | .555556| .0828173  | .3932366 | .7178745 |
| y        | .4705882 | .0856008 | .3028137 | .6383627 |
| diff     | .0849673 | .1191059 | -.1484759 | .3184105 |
```

under Ho: diff = 0

Ha: diff < 0
Ha: diff != 0
Ha: diff > 0

Pr(Z < |z|) = 0.7109
Pr(|Z| > |z|) = 0.2891

40. *Women vs Elderly (x=Women, y=Elderly)

```
> prtesti 36 20 33 11, count
Two-sample test of proportions
x: Number of obs = 36
y: Number of obs = 33

| Variable | Mean   | Std. Err. | z     | P>|z|  | [95% Conf. Interval] |
|----------|--------|-----------|-------|------|---------------------|
| x        | .555556| .0828173  | .3932366 | .7178745 |
| y        | .3333333 | .082061 | .1724967 | .4941699 |
| diff     | .2222222 | .1165878 | -.0062857 | .4507301 |
```

under Ho: diff = 0

Ha: diff < 0
Ha: diff != 0
Ha: diff > 0

Pr(Z < |z|) = 0.9681
Pr(|Z| > |z|) = 0.0319
Pr(Z > |z|) = 0.0638

42. *Parents vs Elderly (x=Parents, y=Elderly)

```
> prtesti 34 16 33 11, count
Two-sample test of proportions
x: Number of obs = 34
y: Number of obs = 33

| Variable | Mean   | Std. Err. | z     | P>|z|  | [95% Conf. Interval] |
|----------|--------|-----------|-------|------|---------------------|
| x        | .4705882 | .0856008 | .3028137 | .6383627 |
| y        | .3333333 | .082061 | .1724967 | .4941699 |
| diff     | .1372549 | .1185812 | -.09516 | .3696698 |
```

under Ho: diff = 0

Ha: diff < 0
Ha: diff != 0
Ha: diff > 0

Pr(Z < |z|) = 0.8739
Pr(|Z| > |z|) = 0.2522
Pr(Z > |z|) = 0.1261
**Q7:** If you had the disease the new medicine is treating, if you are offered a payment, regardless of if there is or there is no other treatment working; would you participate in the clinical trials?

46. `prtesti 36 16 34 22, count`

| Variable | Mean | Std. Err. | z     | Pr>|z|   | [95% Conf. Interval] |
|----------|------|-----------|-------|-------|---------------------|
| x        | .4444444 | .0828173  | .2821255 | .6067634 |
| y        | .6470588  | .0819565  | .486427  | .8076907  |
| diff     | -.2026144 | .1165143  | -.4309782 | .0257495 |

47. *Women vs Elderly (x=Women, y=Parents)*

| Variable | Mean | Std. Err. | z     | Pr>|z|   | [95% Conf. Interval] |
|----------|------|-----------|-------|-------|---------------------|
| x        | .4444444 | .0828173  | .2821255 | .6067634 |
| y        | .61818182 | .0671408  | .502246  | .3134118  |
| diff     | .2626263  | .1066143  | .0536662 | .4715864  |

48. `prtesti 36 16 33 6, count`

| Variable | Mean | Std. Err. | z     | Pr>|z|   | [95% Conf. Interval] |
|----------|------|-----------|-------|-------|---------------------|
| x        | .4444444 | .0828173  | .2821255 | .6067634 |
| y        | .61818182 | .0671408  | .502246  | .3134118  |
| diff     | .2626263  | .1066143  | .0536662 | .4715864  |

49. *Parents vs Elderly (x=Parents, y=Parents)*

| Variable | Mean | Std. Err. | z     | Pr>|z|   | [95% Conf. Interval] |
|----------|------|-----------|-------|-------|---------------------|
| x        | .6470588  | .0819565  | .486427  | .8076907  |
| y        | .61818182 | .0671408  | .502246  | .3134118  |
| diff     | .4652406  | .105947   | .2575884 | .6728929  |

50. `prtesti 34 22 33 6, count`

| Variable | Mean | Std. Err. | z     | Pr>|z|   | [95% Conf. Interval] |
|----------|------|-----------|-------|-------|---------------------|
| x        | .6470588  | .0819565  | .486427  | .8076907  |
| y        | .61818182 | .0671408  | .502246  | .3134118  |
| diff     | .4652406  | .105947   | .2575884 | .6728929  |

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51. *Q8: If you had the disease the new medicine is treating, if you were offered a payment, and there are no other treatments working; would you participate in the clinical trials?

52. *Women vs Parents (x=Women, y=Parents)

```
. prtesti 34 18 33 15, count
Two-sample test of proportions
Variable | Number of obs | Count
----------|---------------|---------------------
x | 36            | 4722222             |
y | 34            | 5294118             |
```

```
Pr(Z < z) = 0.3091441 0.653003
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Ho: diff = 0          Pr(|Z| > |z|) = 0.6324 0.1767821
```

```
diff = prop(x) - prop(y)
Ho: diff = 0
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Pr(Z < z) = 0.3162     Pr(|Z| > |z|) = 0.6324 0.1767821
```

53. prtesti 36 17 34 18, count

```
Two-sample test of proportions
Variable | Number of obs | Count
----------|---------------|---------------------
x | 36            | 4722222             |
y | 34            | 5294118             |
```

```
Pr(Z < z) = 0.3091441 0.653003
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Ho: diff = 0          Pr(|Z| > |z|) = 0.6324 0.1767821
```

```
diff = prop(x) - prop(y)
Ho: diff = 0
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Pr(Z < z) = 0.3162     Pr(|Z| > |z|) = 0.6324 0.1767821
```

54. *Women vs Elderly (x=Women, y=Elderly)

```
. prtesti 36 17 34 18, count
Two-sample test of proportions
Variable | Number of obs | Count
----------|---------------|---------------------
x | 36            | 4722222             |
y | 34            | 5294118             |
```

```
Pr(Z < z) = 0.3091441 0.653003
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Ho: diff = 0          Pr(|Z| > |z|) = 0.6324 0.1767821
```

```
diff = prop(x) - prop(y)
Ho: diff = 0
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Pr(Z < z) = 0.3162     Pr(|Z| > |z|) = 0.6324 0.1767821
```

55. prtesti 36 17 33 15, count

```
Two-sample test of proportions
Variable | Number of obs | Count
----------|---------------|---------------------
x | 36            | 4722222             |
y | 33            | 5294118             |
```

```
Pr(Z < z) = 0.3091441 0.653003
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Ho: diff = 0          Pr(|Z| > |z|) = 0.6324 0.1767821
```

```
diff = prop(x) - prop(y)
Ho: diff = 0
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Pr(Z < z) = 0.3162     Pr(|Z| > |z|) = 0.6324 0.1767821
```

56. *Parents vs Elderly (x=Parents, y=Elderly)

```
. prtesti 34 18 33 15, count
Two-sample test of proportions
Variable | Number of obs | Count
----------|---------------|---------------------
x | 34            | 4722222             |
y | 33            | 5294118             |
```

```
Pr(Z < z) = 0.3091441 0.653003
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Ho: diff = 0          Pr(|Z| > |z|) = 0.6324 0.1767821
```

```
diff = prop(x) - prop(y)
Ho: diff = 0
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Pr(Z < z) = 0.3162     Pr(|Z| > |z|) = 0.6324 0.1767821
```

57. prtesti 34 18 33 15, count

```
Two-sample test of proportions
Variable | Number of obs | Count
----------|---------------|---------------------
x | 34            | 4722222             |
y | 33            | 5294118             |
```

```
Pr(Z < z) = 0.3091441 0.653003
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Ho: diff = 0          Pr(|Z| > |z|) = 0.6324 0.1767821
```

```
diff = prop(x) - prop(y)
Ho: diff = 0
Ha: diff < 0          Ha: diff != 0          Ha: diff > 0
Pr(Z < z) = 0.3162     Pr(|Z| > |z|) = 0.6324 0.1767821
```
58 . log close
   name: <unnamed>
   log: C:\PSY2017\IDrive-Sync\PS1723 - Saba\Analysis\Statistical outputs.s
> mcl
   log type: smcl
   closed on: 24 Mar 2017, 14:00:21