# Title

*A glint or a squint should make you think! A double-blind, randomised controlled study to evaluate the impact of a paediatric eye-health awareness pamphlet for new parents.*

# 2a. Trial identifier

Australia and New Zealand Clinical Trials Registry (ANZCTR) <https://anzctr.org.au>

Registration number: ACTRN12617001431314p

# 2b. World Health Organization Trial Registration Data Set UTN: U1111-1203-0485

|  |  |
| --- | --- |
| **Data Category** | **Information** |
| Primary registry and trial identifying number | Aust. Clinical Trials Registration Number: ACTRN12617001431314p |
| Date of registration in primary registry | 9/10/2017  |
| Secondary identifying numbers | Royal Women’s Hospital Human Research Ethics Committee # (pending approval) |
| Source(s) of monetary or material support | NHMRC Public Health Post-Graduate Scholarship #1114932Australian Government Research Training Program (RTP) Scholarship NHMRC CRE #1116360William Angliss (Victoria) Charitable Fund |
| Primary sponsor | Centre for Eye Research Australia |
| Secondary sponsor | n/a |
| Contact for public queries | Sandra Staffieri sandra.staffieri@unimelb.edu.au |
| Contact for scientific queries | Sandra Staffieri sandra.staffieri@unimelb.edu.auDr Gwyneth Rees grees@unimelb.edu.auA/Prof Alex Hewitt hewitt.alex@gmail.com |
| Public title | Evaluating a children’s eye health awareness pamphlet for new parents |
| Scientific Title | A glint or a squint should make you think. A double-blind randomised controlled study to evaluate the impact of a paediatric eye-health awareness pamphlet for parents |
| Countries of recruitment | Australia |
| Health condition(s) or problem(s) studied | Early diagnosis of paediatric eye diseases with a presenting sign of strabismus or leukocoria |
| Intervention | Information pamphlet  |
| Key inclusion and exclusion criteria | Ages eligible for study: ≥18 years Sexes eligible for study: female Accepts healthy volunteers: not applicable *Inclusion criteria:* English-speaking; adult pregnant women ≥18 years of age; active email address; 2nd or 3rd trimester of pregnancy*Exclusion criteria:* inactive email address; unable to read and/or understand written English; ≤18 years of age; 1st trimester of pregnancy |
| Study type | Interventional Allocation: randomised Intervention model: parallel assignment Masking: double blind Primary purpose: early diagnosisPhase III |
| Date of first enrolment | To be determined following HREC approval – aim for 5/2/18 |
| Target sample size | 520 - 200 control; 200 intervention + 30% allowance for attrition\*\*[non-return of follow-up survey] |
| Recruitment status | Yet to commence |
| Primary outcome | Parents’ increased understanding that a white pupil (leukocoria) and/or crossed/turned eye (strabismus) in their child as a significant cause for concern |
| Secondary outcome | Increased help-seeking behavioural intention to seek help or advice if a white pupil (leukocoria) and/or crossed/turned eye (strabismus) were to be observed in their child |

# Protocol version

Glint-or-Squint\_Research Protocol\_v1\_Nov17

# Funding sources

Costs for all materials including pamphlets (control and intervention), postage, development of the web-based questionnaire and hosting will be funded by William Angliss (Victoria) Charitable fund and NHMRC CRE grant #1116360. Research assistants for recruitment are funded by NHMRC CRE #1116360. Principal Investigator SS is funded by an NHMRC Public Health Post-Graduate Scholarship #1114932 and an Australian Government Research Training Program (RTP) Scholarship. The sponsor site, the Centre for Eye Research Australia (CERA) receives Operational Infrastructure Support from the Victorian Government.

# Roles and responsibilities

### 5a Names, affiliations, and roles of protocol contributors

**Ms Sandra Staffieri**

*Affiliations:*

1. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital
2. Ophthalmology, University of Melbourne, Department of Surgery
3. Department of Ophthalmology, Royal Children’s Hospital

*Role:*

* *Principal Investigator*
* *Co-ordinate recruitment by research assistants, conduct and oversight of the study*
* *Recruitment of participants, obtain consent and administer Baseline survey*
* *Data analysis and interpretation*
* *Manuscript preparation*
* *Preparation and submission of all annual reports and governance requirements*
* *Oversight of 2 research assistants named in this protocol*

**Ms Lisa Kearns**

*Affiliations:*

1. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital
2. Ophthalmology, University of Melbourne, Department of Surgery

*Role:*

* *Research assistant*
* *Recruitment of participants, obtain consent and administer Baseline survey*
* *Revision of manuscript*

**Ms Linda Clarke**

*Affiliations:*

1. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital
2. Ophthalmology, University of Melbourne, Department of Surgery

*Role:*

* *Research assistant*
* *Recruitment of participants, obtain consent and administer Baseline survey*
* *Revision of manuscript*

**Dr Gwyneth Rees**

*Affiliations:*

1. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital
2. Ophthalmology, University of Melbourne, Department of Surgery

*Role:*

1. *Supervision, research student - PhD Candidate Sandra Staffieri*
2. *Review of materials used in trial*
3. *Review and interpretation of data analysis*
4. *Revision of manuscript*

**A/Prof. Stephen Cole**

*Affiliations:*

1. Royal Women’s Hospital Melbourne
2. Epworth Freemasons private hospital

*Role:*

1. *Liaison with Royal Women's Hospital personnel for conduct of the research project*
2. *Revision of manuscript*

**A/Prof. Alex Hewitt**

*Affiliations:*

1. *Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital*
2. *Ophthalmology, University of Melbourne, Department of Surgery*
3. *Department of Ophthalmology, Royal Children’s Hospital*
4. *Menzies Institute for Medical Research, University of Tasmania*

*Role:*

1. *Supervisor, graduate research student - PhD Candidate Sandra Staffieri*
2. *Review of materials used in trial*
3. *Review and interpretation of data analysis*
4. *Revision of manuscript*

**Dr Paul Sanfilippo**

*Affiliations:*

1. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital
2. Ophthalmology, University of Melbourne, Department of Surgery

*Role:*

1. *Supervisor, graduate research student - PhD Candidate Sandra Staffieri*
2. *Review of materials used in trial*
3. *Data analysis support and interpretation*
4. *Revision of manuscript*

**Prof. David Mackey**

*Affiliations:*

1. Lions Eye Institute, University of Western Australia
2. Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital
3. Ophthalmology, University of Melbourne, Department of Surgery

*Role:*

1. *Supervisor, graduate research student - PhD Candidate Sandra Staffieri*
2. *Review of materials used in trial*
3. *Review and interpretation of data analysis*
4. *Revision of manuscript*

### 5b Name and contact information for the trial sponsor

**Centre for Eye Research Australia**

Level 7, Peter Howson Wing, Royal Victorian Eye and Ear Hospital

32 Gisborne Street, East Melbourne, 3002 VICTORIA

+61 3 9929 8713

### 5c Role of study sponsor and funders

The study sponsor, Centre for Eye Research Australia will provide support to PhD Candidate Sandra Staffieri, as well as oversee and provide additional governance support regarding the ethical conduct of this project.

The conduct of this study is financially supported by:

* NHMRC Public Health Post-Graduate Scholarship #1114932
* Australian Government Research Training Program (RTP)
* Scholarship NHMRC CRE #1116360
* William Angliss (Victoria) Charitable Fund

The funding supporters have no direct authority over the study design, management, analysis, interpretation of data or publication.

### 5d Composition, roles and responsibilities of the coordinating centre

As a single-centre, double-blind randomised placebo-controlled trial, a co-ordinating centre will not be required. The research team will meet on a regular basis to discuss study progress and adverse events, if any, as they arise.

**INTRODUCTION**

# 6a. Research question and justification

Retinoblastoma is the most common paediatric eye cancer with an incidence of 1:17 500 births in Victoria.1 Single or multiple tumours can develop in one or both eyes, leading to blindness, loss of the affected eye, or in some cases, death.2 Treatment for RB can include any one or a combination of systemic chemotherapy, intra-ocular chemotherapy and focal treatments (freezing or heating the tumours directly). For advanced disease, the only option is enucleation (removal of the eye) to save the child’s life.3 The most common presenting sign for retinoblastoma is leukocoria (white pupil – seen with the naked eye or in photographs), followed closely by strabismus (turned or crossed eye).2 Delays in diagnosis of retinoblastoma are widely-reported in the literature and occur in part due to parents not recognising or acting on the symptoms and signs of the disease.4-6

Pilot data collected from the Victorian Retinoblastoma Database1 has shown that parents often do not recognise or ignore these presenting signs, leading to devastating consequences. Because retinoblastoma is a rare eye disease that develops anytime from birth to 5 years of age, a national screening program would be neither efficient nor effective. It is important to note however that idiopathic strabismus is common in the paediatric population7 and screening for retinoblastoma can ‘ride on the shoulders’ of this more commonly seen paediatric eye disease. The earliest diagnosis and treatment of paediatric eye diseases such as strabismus ensures the best possible outcome for the development of normal vision and depth perception (3D vision).

**SIGNIFICANCE AND TRANSLATIONAL OUTCOMES:**

 As we await further advances in globe and sight-saving treatments for children with retinoblastoma, all we can offer **immediately** is earlier diagnosis by increasing awareness of the early signs of the disease. Leander and co-workers showed that by educating parents to promptly report leukocoria in their child to health workers resulted in earlier diagnosis and intervention for retinoblastoma with a significant improvement in mortality.8 Whilst the low mortality rate from retinoblastoma in Victoria1 continues to compare favourably with other developed countries9-11 by presenting earlier, it is hoped that children with non-familial retinoblastoma will present at a point where potentially globe-salvage (eye-saving) rather than life-saving treatment (enucleation) will be the appropriate and achievable goal. Demonstrating that a relatively inexpensive ocular health educational intervention can positively influence reported health behaviour, will support an evidence-based change in policy regarding newborn health care and infant screening.

**Consequences of late presentation and the critical role of parents:**

 Paediatric ophthalmic conditions can range from the innocuous (e.g congenital nasolacrimal duct obstruction [blocked tear duct] and chalazia [eyelid cyst] to potentially blinding (e.g. cataract [cloudy lens of the eye], glaucoma [raised eye pressure] or even possibly fatal (e.g. retinoblastoma) diseases.

 Parents are generally the first to observe any direct clinical sign that their child could have a significant eye disease or disorder. Visual behaviour will typically only be impaired when both eyes are affected, and as such, unilateral eye conditions are often initially ignored or missed. It is important to note that there are clear clinical signs that can be observed and alert an informed parent to the manifestation of a potentially significant eye disease in an otherwise healthy child. Ensuring that paediatric eye diseases are identified and treated in a timely manner requires parents to be aware of signs that can occur during their child’s early infancy and childhood. Parents should also know where and when to seek eye health care advice.

 Strabismus in most cases is idiopathic in nature but is commonly associated with eye disease. Undiagnosed and untreated, idiopathic strabismus will lead to poor vision development in one eye (amblyopia) and abnormal development of 3-D vision.12 Often enough however, strabismus can also be a **sign of a more sinister ocular pathology**13 including cataract or retinoblastoma (Table 1). Whilst intermittent or even constant strabismus is a common finding in healthy newborns, normal eye co-ordination should be evident by approximately 4 months of age.14 Any persisting strabismus after this age should be investigated to rule out any serious eye disease in the first instance, or to commence appropriate management to minimise the development of amblyopia.14

**Current paediatric eye screening in Victoria:**

 In Victoria, newborns are screened at birth for potentially blinding congenital eye disease or malformations by a gross inspection of the neonate’s eyes and examination of the red reflex (determining the presence or absence of disease within the eye such as cataract). The second opportunity for formal screening is not until 3½ years of age, when the Maternal and Child Health Nurse (MCHN) assesses vision and ocular alignment at the tenth ‘Key Ages and Stages’ visit.15 To minimise delays in diagnosis and capitalise on early treatment, parents need to be aware of ocular symptoms and signs they should be alert to between these chronologically disparate, scheduled screening opportunities.

 Upon discharge from hospital, the ‘My Health and Development Book’ is provided to parents of newborns as a source of information and a chronicle of their child’s health and development. At some visits, very general questions such as: “Does your baby make eye contact?”; “Does your baby smile at you?” are included and designed not only to prompt the parents to discuss any concerns they might have regarding their child’s vision but to assess social development in order to identify early possible autism spectrum disorder. **Currently, there is no information or guidance formally provided to parents regarding the signs that should alert them to the presence of significant eye disease or barriers to optimal vision development.**

 Whilst very early screening for congenital ocular malformations or disease at birth are in place, the initial absence of obvious eye disease does not preclude an infant from developing such disease in the months or years that follow. Other than in-hospital neonatal/newborn screening for congenital eye anomalies, there are limited opportunities for children to be diagnosed early with significant, potentially blinding or even fatal eye conditions.

 Thus, it is incumbent on the parent to not only **notice** any ocular symptoms or signs in their child, but also to **recognise** that such signs are significant and warrant further investigation**. It is therefore essential that parents are aware of the potential symptoms and signs of poor vision or binocular development and potentially blinding or fatal eye disease.**

**Table 1. Eye conditions requiring timely, appropriate diagnosis.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Eye condition** | **Incidence in Australia** | **Key signs / symptoms** | **Prognosis and importance of early detection** |
| Strabismus | 2.8% children7\* | Crossed/turned eye (strabismus) | Good, if diagnosed and treated earlyLoss of sight |
| Retinoblastoma | 1:17,5001 | LeukocoriaStrabismus | Poor if diagnosed lateLoss of sightEnucleationLoss of life |
| Cataract | 2.2:10,00016 | LeukocoriaStrabismus | Poor if diagnosed lateLoss of sight |

\*Prevalence data only available

**PILOT DATA:**

**The cost of parents not recognising ophthalmic signs:**

 Using the Victorian Retinoblastoma Database, we have undertaken a project investigating retinoblastoma awareness, delay in diagnosis and treatment outcomes (Royal Children’s Hospital, Parkville HREC #33046A). To date, 34 parents of children with non-familial retinoblastoma have been invited to retrospectively complete a semi-structured telephone interview describing their child’s pathway to diagnosis and any delays to diagnosis experienced. Pilot data has been collected on 27 respondents. 51.8% of respondents had a tertiary qualification.

 Consistent with the literature, the most common presenting sign for retinoblastoma in this small cohort was leukocoria (62.9%; 17/27) followed by strabismus (25.9%; 7/27). Remarkably, four (23.5%) children presenting with leukocoria also had strabismus that was not regarded as significant thus their presentation was delayed, resulting in enucleation as the only treatment to control their disease. In addition, four cases of leukocoria were observed by the parent and not considered significant and did not present until strabismus was noted. 59.2% of respondents noted leukocoria as a primary sign or retrospectively in photographs.

 Comments from parents completing the questionnaire revealed strabismus was considered ‘normal’ – “I didn’t think anything of it”; and reports of leukocoria in photos were ignored or disregarded as a trick of the light or camera – “A white pupil was not enough to make me worry”.

 This pilot data demonstrated parents were unaware of the significance of strabismus or leukocoria in their child at an early age. Despite numerous articles in digital and print media about children with retinoblastoma, **no** parent reported being aware of the signs that should have raised suspicion. To date, **no awareness programs in Australia have been trialled or implemented** to overcome these problems.

**Earlier diagnosis could save the child’s sight, eye or life.**

# 6b. Explanation for choice of comparators

**PRELIMINARY RESEARCH – DEVELOPMENT OF AN EYE-HEALTH AWARENESS PAMPHLET:**

An exploratory qualitative study to identify knowledge gaps and determine factors that influence parents’ help-seeking advice for ocular symptoms in young children has been completed. [RVEEH HREC 15/1244H] Using an inductive thematic analysis approach,17 data from focus groups was thematically analysed to inform the content of a paediatric eye-health awareness pamphlet for parents. The development of this pamphlet was grounded in an evidence-based approach to develop health promotion materials18 and the ‘**I**nformation-**M**otivation-**B**ehavioural skills’ (IMB) model.19 This theoretical framework specifies that effective health promotion material needs to: address information gaps [information]; provide arguments that motivate behaviour [motivation]; and provide instruction and explanation to perform behaviour [behaviour skills].19

A cognitive interview process was utilized as an opportunity to test and refine the Baseline and Follow-up surveys and pamphlet [intervention] to be used in the proposed RCT. Cognitive interviews were conducted with 17 women with children or of child-bearing age, following which the pamphlet was modified for content, layout and comprehension. Analysis of data from preliminary testing in this cohort demonstrated statistically significant changes in participants’ knowledge of infant vision development (p<0.005); important early signs of eye disease (p<).009) and a change in their behavioural intentions following review of the pamphlet (p<0.003).

The revised pamphlet will be scored by key stake holders (ophthalmologists, orthoptists, Maternal Child Health Nurses and General Practitioners) using the Suitability Assessment of Material (SAM) Score Sheet (Appendix B). Developed by Doak, Doak and Root20 this validated tool aids in the development of purposeful health education materials. Six evaluation criteria are included to assess the content, readability, graphics, layout, learning stimulations and motivation, and where appropriate, cultural appropriateness. Scores of ‘0’ (not suitable) to ‘2’ (superior) are given for each criterion and calculated to provide an overall percentage score confirming the suitability of the material being assessed. This process allows for valuable input by the proposed key stakeholders providing the opportunity to ‘tailor’ the health education material to the target audience and maximise its effectiveness.

# Objectives/hypothesis

Using a randomised controlled trial (RCT), the specific aims for this project are to evaluate the impact of the pamphlet on parents’ awareness; their understanding of early signs or paediatric eye disease; and their behavioural help-seeking intentions if signs of paediatric eye disease were observed in their child.

The hypotheses for this project are that compared to the control group, those parents who receive and read the intervention pamphlet will demonstrate:

1. Increased knowledge of leukocoria
2. Increased intention to seek health advice if leukocoria is observed
3. Increased knowledge of strabismus
4. Increased intention to seek health advice if strabismus is observed

# Trial design

 Single-centre, double-blind randomized placebo-controlled trial, of parallel groups, with an allocation ratio of 1:1 within an exploratory framework. Randomisation will be stratified by whether participants already have children or not [pertains to previous experience and exposure to paediatric eye health information] and whether English is spoken as their first language [to identify any differences that may exist between these two groups].

**METHODS: Participants, interventions and outcomes**

# Study setting

This study will be conducted on pregnant women aged ≥ 18 years, in their 2nd or 3rd trimester of pregnancy (13-28 weeks or 29 – 40 weeks respectively) recruited from the Ante-natal clinics at The Royal Women’s Hospital, Melbourne, Australia.

A researcher nominated in this application will be seated at the entrance to the ante-natal clinic waiting room and distribute the fliers to the women as they arrive, advising if they are interested, they can take a PICF to read and consider.

Upon reading the PICF, if they are happy to proceed on the day, they can sign the consent form, complete the Baseline survey and be given their research envelope whilst they are waiting for their regular ante-natal appointment. Alternatively, if they wish to think about participation, they can take the PICF home to discuss with family and contact the researchers to arrange enrolment at their next scheduled visit if they decide to proceed.

#  Eligibility criteria

The written intervention, Baseline and Follow-up surveys will only be available in English.

*Inclusion criteria:*

* literate, pregnant women
* 2nd or 3rd trimester of first or subsequent pregnancy
* ≥ 18 years of age
* Active email account

*Exclusion criteria:*

* illiterate or non-English speaking pregnant women
* 1st trimester of first or subsequent pregnancy
* ≤ 18 years of age

# 11a. Intervention

There will be two arms to the RCT – intervention and control. The intervention group will receive the information pamphlet (Appendix C) which includes messages addressing deficits in knowledge, motivation and behavioural skills as described in 6b. With the slogan “A Glint or a Squint should make you Think!” the two key messages contained in the pamphlet are:

1. awareness of eye turns in children (“squint‟/strabismus) and;
2. awareness of white pupils – either with the naked eye or in a photograph (“glint‟/leukocoria).

The control group will receive an identical sealed, opaque envelope containing an information pamphlet for parents about ‘Playing with your Baby’. (Appendix D) This pamphlet is used in this study with permission from the Department of Education and Training and can be readily downloaded from: <http://www.education.vic.gov.au/Documents/childhood/parents/mch/2015_PLG_postcard_newborn_web.PDF>

Sealed, opaque research envelopes will be prepared in advance and labelled either GROUP A or GROUP B. The researchers undertaking recruitment, consent and administration of the baseline survey will be masked to the Group allocation for the intervention or control.

Upon completion of their Baseline survey, participants will be electronically randomised to either Group A or Group B by the REDCap data collection software, used under licence and hosted by the University of Melbourne. The participant will be provided their corresponding Group A or Group B sealed, opaque research envelope. Research staff providing the research envelope will remain masked to the Group allocation of the intervention or control. Participants will be instructed to not open the envelope until they have left the hospital at the conclusion of their ante-natal visit. Participants will be asked to read and retain the information pamphlet, and store in a place of prominence. (ie: front of refrigerator or noticeboard at home)

At the conclusion of the study, all participants in both groups will be sent a letter of thanks for participation and an explanation for the project. A suggested answer sheet to the clinical scenarios in the surveys will also be provided. (Appendix M). To ensure no participant is disadvantaged, participants in the control group will be so advised and subsequently provided with the information pamphlet originally provided only to the intervention group. The pamphlet has been designed to conform to the dimensions of the pages contained in the “My Health and Development Book” which is provided to parents at discharge, following the birth of their baby. This purposeful pamphlet design will enable participants to be instructed to file the pamphlet for future reference in their baby’s health record once their baby is born.

# 11b. Criteria for discontinuing or modifying allocated intervention

Substantial effort has been expended in developing the intervention with the input of parents as the end-users. The cognitive interview process during the development stage identified changes that were required to maximise comprehension and minimise any distress relating to the content. The information contained within the intervention pamphlet is freely available on the internet if parents were to search for information on eye disease in infants and children. It is not expected the intervention will need to be discontinued or modified during the course of the study.

# 11c. Strategies to improve adherence

Apart from clear instructions in the research envelope for participants, no specific strategies for adherence will be utilised. It is important to identify whether participants actually read the information if it is provided. Their engagement with the intervention will help guide strategies for implementation should the RCT prove successful. Questions in the Follow-up survey will explore exposure and uptake of the intervention.

# 11d. Relevant concomitant care and interventions that are permitted or prohibited.

Participants will not be actively encouraged or discouraged to seek out or resist additional research from books, promotional material or the internet. However, the study will explore whether, upon completing the Baseline survey and receiving the intervention or control, prompted any additional information-seeking behaviour.

# Outcomes

*Intervention exposure:* Initial questions in the Follow-up survey will determine if the participant received the intervention, read it – in detail or briefly, and if they kept the pamphlet, as directed, for future reference. All participants will be asked if they undertook any extra reading or research following completion of the Baseline survey to account for any other sources of information that may have contributed to their knowledge or help-seeking behaviour intentions.

*Intervention outcomes:*Single item True/False questions will assess the impact of the intervention on knowledge of signs of paediatric eye disease. Likert scale items will assess the participant’s confidence in being able to recognise signs of paediatric eye disease, intentions to monitor their child’s ocular health, intentions to seek professional advice and perceived urgency in responding to ocular signs if observed.

*Correlation of Health Literacy and intervention outcomes:*Health literacy (HL) is an important consideration in the development and measurement of the effectiveness of health information. To explore the participants’ level of HL on their participation or impact on the outcomes of the RCT, the 5 questions from Domain 9 of the Health Literacy Questionnaire21 have been embedded in the Baseline survey.

# Participant timeline

Appendix E includes a flowchart which clearly outlines the participant recruitment, provision of the intervention or control, distribution of the Follow-up survey, strategies to maximise completion of the Follow-up survey and conclusion of the study.

# Sample size

The degree of the effect size in an RCT is calculated either by: 1) previous literature 2) pilot data or 3) clinical expectation.22 The published literature examining the effect of a health intervention, by convention, seeks to demonstrate a 10% effect with 80% power, with an alpha of p=0.05. Sample size calculations were performed assuming two-sided testing, as we cannot be certain of the direction of the intervention effect. Therefore the required sample size for this RCT can be calculated thus:

Estimated sample sizes for a two-sample proportions test, using Pearson's chi-squared test where:

Ho: p2 = p1 versus Ha: p2 ≠ p1

Planned study parameters:

        alpha =   0.0500 (p=0.05)

        power =    0.8000 (80%)

        delta =    0.1000 (effect size 10%)

           p1 =     0.1000

           p2 =    0.2000

Using these planned study parameters, the estimated sample size required for this RCT using STATA was calculated as: N = 398, where n=199 per group (intervention and control). To allow for a 30% attrition of non-return of the follow-up survey, 520 participants will be recruited.

# Recruitment

A3-sized posters advertising the study will be displayed in the waiting room of the Ante-natal clinics the Royal Women’s Hospital. [Appendix F] Smaller, identically worded, A6-sized flyers will also be provided to women at clinic check-in. Pregnant women in the waiting room of the Ante-natal clinic will be approached by a research assistant [nominated in this protocol and experienced in the enrolment and consent to participate in research studies] will be verbally invited to participate in the study. The HREC approved Patient Information Sheet and Consent Form (PICF) (Appendix G) will be provided to each potential participant, the study explained, and the opportunity given to answer any questions about the study before agreeing to participate. If the woman agrees to participate, a unique study identifier will be allocated, and the consent form will be signed. If the woman would prefer more time to consider the PICF and their participation, the researcher will invite the participant to contact the research office to arrange enrolment and consent at their next scheduled ante-natal visit if the study is still open. Difficulty reaching the target sample size is not anticipated, given the intervention is not invasive nor onerous in time commitment on behalf of the participant.

**METHODS: Assignment for intervention**

# 16a. Allocation Sequence Generation

Allocation Sequence Generation for randomisation will be automated within the REDCap (Research Electronic Data Capture) web-based application, hosted on the secure, University of Melbourne data centre infrastructure. Randomisation will be stratified according to native-English speakers and non-native-English speakers; and first or subsequent pregnancy.

16b Allocation concealment mechanism

Opaque research envelopes labelled either Group A or Group B will be prepared by a research assistant from CERA not directly associated with this study. Each envelope will contain either the intervention or control pamphlet. All researchers associated with this study will be masked to the Group allocation of the envelope contents. Following enrolment of each participant, randomisation will automatically be determined using the REDCap randomisation module. The recruiting research assistant will select the corresponding research envelope – Group A or B – and record the participant’s Unique Identifier on the envelope. The participant will be instructed not to open their research envelope until the conclusion of their ante-natal appointment and they have left the hospital grounds.

16c Implementation

The research envelopes will be prepared by a CERA researcher not involved in participant recruitment. Participants will be enrolled, consented and provided their research envelopes following completion of the Baseline survey and randomization by either: Sandra Staffieri (PI) Lisa Kearns (research assistant) or Linda Clarke (research assistant).

 17a Blinding (masking)

All researchers named in this study will remain masked to group allocation until the conclusion of the study.

17b Circumstances for un-blinding

Un-masking of a participant will be permissible only if a complaint is made to the RWH Consumer Advocate in order that the complaint may be addressed. Given the non-invasive nature of the intervention, it is not anticipated that the need for un-masking would be required.

**METHODS: Data collection and Management**

18a Data collection methods

Baseline and Follow-up surveys will be completed via a secure, password protected web-based interface REDCap – Research Electronic Data Capture tool [REDCap 7.2.2© 2017 Vanderbilt University] hosted on the secure, research data centre infrastructure at the University of Melbourne.

Completion of the Basic Demographics, (Appendix H) will record demographic data. The Baseline survey, (Appendix I), will include health literacy measures and base-line data on participant’s current knowledge and help-seeking intentions in response to observing signs of eye disease in their baby. To mask the specific purpose of this study, similar questions regarding their knowledge of high fever in a child with a rash; breast redness, pain and fever in the mother [mastitis]; and diarrhoea in an infant will also be included. Two weeks’ following their enrolment to the study and completion of the Baseline survey, participants will be sent via email the Follow-up survey to determine the impact, if any, of the intervention on their knowledge, motivation and help seeking intentions. The Follow-up survey (Appendix J) will include questions to examine participant engagement with the pamphlet, whether the content of the pamphlet caused any distress or anxiety and whether they were prompted to seek additional information about any of the clinical scenarios that were presented. The remainder of the Follow-up survey questions will be identical to the Baseline survey to measure any change in knowledge or help-seeking intention. Two final questions will explore whether the participant referred to their pamphlet or the internet to answer their Follow-up survey.

18b Promotion of study completion

If the Follow-up survey is not completed within 2 weeks of the participant being sent the single-use link by email, a reminder will be sent via email to the participant to prompt the completion of the Follow-up survey using a prescribed script. (Appendix K) If the Follow-up survey remains uncompleted after 1 week, a research assistant nominated in this protocol will make ONE follow-up telephone call to encourage completion of the survey following a prescribed script. (Appendix L) If the follow-up survey remains incomplete following a further 1 week, the participant will be recorded as ‘lost to follow up’. Participants are free to withdraw from the study at any time without prejudice, this is clearly stated in the PICF.

19 Data management

*Consent forms:* Signed hard-copy consent forms will be scanned and stored electronically on an access restricted computer at the Centre for Eye Research Australia (CERA), East Melbourne. The hard-copy of the consent form will be stored in a locked filing cabinet on the access-restricted premises at CERA. A scanned copy of the signed consent will be sent by email to the participant.

*Survey responses:* At enrolment, Baseline survey responses will be completed by the participant on an iPAD using the REDCap mobile app provided by the research team during their Ante-natal clinic visit. A single-use link to the Follow-up survey will be sent securely to the participant via their nominated email address. At the conclusion of the study, all survey responses will be exported from REDCap to EXCEL and stored as a password protected electronic file on a password protected computer on the access restricted premises at CERA.

20 Statistical analysis

All analyses will be performed on an “intention-to-treat” method i.e. regardless of whether those in the intervention group read the leaflet or not. Response of the two groups of parents (intervention and control) will be compared initially using non-parametric tests given the ordinal nature of the data (such as Mann-Whitney test). Rasch analysis will be performed on appropriate outcome assessment to ensure that study-specific assessment tools are psychometrically sound. Confounding variables such as age, English as a second language and educational status will be explored and adjusted for, as appropriate in multiple logistic regression analysis. Additionally, all available participant information will be used to screen for factors that could moderate the outcome of the intervention i.e. does the intervention only have an effect in those with higher levels of education?

21 Data monitoring

The proposed intervention in this study [information pamphlet] is considered low-risk and non-invasive. As such a formal data monitoring committee is not deemed necessary. However, the research team will meet on a regular basis to report progress in recruitment, data collection, compliance and any adverse events that may arise. No interim analyses will be conducted during this study.

22 Harms

During the design and development phase of the surveys and intervention, women who completed the cognitive interviews did not report any distress experienced as a result of reading the intervention. The proposed intervention in this study is not anticipated to cause any harm. However, the regular meetings of the researchers named in this study will ensure that any adverse event(s) is reviewed by the research group and immediately reported to the RWH HREC with a plan for restitution and future mitigation.

23 Auditing

Remaining sealed opaque envelopes allocated to Group A or Group B will be audited periodically during the course of the study against the envelopes that have been distributed to enrolled participants.

**ETHICS AND DISSEMINATION**

24 Ethics approval

Ethical approval to conduct this study is sought through the Royal Women’s Hospital (RWH) Human Research Ethics Committee (HREC) by completing the NHMRC approved Human Research Ethics Application, Victorian Specific Module and submitting peer-review.

25 Protocol amendments

Any recommended changes to the protocol will be determined by the research group. Any such amendments that are deemed necessary during the course of the study will be submitted to the RWH HREC for approval prior to implementation. Recruitment will be suspended until such amendments are approved in writing by the RWH HREC.

26 Consent Process

The researchers named in this protocol: Sandra Staffieri, Lisa Kearns and Linda Clarke will consent the participants to the study. Participants who are: under the age of 18 years; unable to consent for self; or have insufficient grasp of the English language to reliably consent to the study will be excluded from the study.

Participants will be invited to consider consent to being contacted regarding future research projects that may directly arise from this study.

27 Confidentiality

*Consent forms:* Identifiable information will be recorded on the consent forms. Signed consent forms will be securely held as described in Item 19 – Data Management.

*Surveys:* Each participant will be allocated a Unique Study Identifier. Only the researchers named in this protocol will have access to the secure, password protected database (REDCap) that connects individual identifiable information and the Unique Study Identifier.

Each of the researchers involved in the recruitment and administration of the surveys are trained in Good Clinical Practice, Research Integrity, Privacy of Health Information laws and are familiar with the NHMRC *National Statement on Ethical Conduct in Human Research (2007)*.

All data will be held at the secure premises of CERA for 15 years. After this time period lapses, all databases and electronic copies of data will be deleted from the servers. Any paper records will be disposed of using commercially available destruction methods for sensitive materials.

28 Declaration of interests

None of the researchers named in this protocol, nor the sponsor institution (CERA) have any conflicts of interest to declare. This study, does however, form a major component of a PhD project being conducted by the Principal Investigator – Sandra Staffieri, enrolled at the University of Melbourne.

29 Access to data

Only the researchers named in this protocol will have access to the data obtained in this trial.

30 Ancillary and Post-trial Care

It is not anticipated that any participants will suffer any harm as a result of participating in this study. Completing the surveys and reading the intervention may prompt the participant to access further information that is freely and publicly available on the internet. However, the PICF provided to the participants includes contact details for the Principal Investigator should they have any further questions regarding information contained in the intervention or the study. Contact details for the Consumer Advocate at the Royal Women’s Hospital are also provided in the PICF if any concerns arise regarding the conduct of the researchers.

31 Dissemination policy

Individual responses or results will not be provided to participants. However, at the conclusion of this study, participants will be sent 1) suggested answers to survey clinical scenarios (Appendix M); and 2) an e-newsletter outlining the overall results and outcomes of the study. The study results will be submitted for publication in a relevant, peer-reviewed scientific journal. It is anticipated the results will be presented at relevant scientific conferences or public forums. In the event that this study demonstrates providing parents with appropriate health information improves parent knowledge and help-seeking intention, a report will be prepared and submitted to the Department of Education and Training, Victorian Department of Health.

All researchers nominated in this protocol will be eligible for authorship in any publications that may arise from this research. Public access to the full protocol, participant-level dataset and statistical code will be uploaded as part of registration of this trial with the Australian New Zealand Clinical Trials Registry. (ACTRN ACTRN12617001431314p)

**Appendices**

Appendix B\_SAM\_SuitabilityAssessmentofMaterials

Appendix C\_Pamphlet\_Intervention \_v1\_1Sept17

Appendix D\_Pamphlet\_Control\_v1\_1Sept17.pdf

Appendix E\_Study timeline flowchart\_v1\_1Nov17

Appendix F\_recruitment poster\_RCT\_v1\_1Nov17

Appendix G\_PICF\_RCT\_v1\_1Nov17

Appendix H\_Demographics\_v1\_1Nov17

Appendix I\_BaselineSurvey\_v1\_1Sept17

Appendix J\_FollowupSurvey\_v1\_1Sept17

Appendix K\_Script email followup\_v1\_1Nov17

Appendix L\_Script telephone followup\_v1\_1Nov17

Appendix M\_ClinicalScenario ANSWER SHEET\_v1\_1Nov17

**References**

1. Dondey JC, Staffieri S, McKenzie J, Davie G, Elder J. Retinoblastoma in Victoria, 1976-2000: changing management trends and outcomes. *Clin Experiment Ophthalmol* 2004; **32**: 354-9.

2. Abramson DH. Retinoblastoma: diagnosis and management. *CA Cancer J Clin* 1982; **32**: 130-40.

3. Ghassemi F KA. Risk definition and management strategies in retinoblastoma: current perspectives. *Clinical Ophthalmology* 2015; **9**: 985-94.

4. Goddard AG, Kingston JE, Hungerford JL. Delay in diagnosis of retinoblastoma: risk factors and treatment outcome. *Br J Ophthalmol* 1999; **83**: 1320-3.

5. Butros LJ, Abramson DH, Dunkel IJ. Delayed diagnosis of retinoblastoma: analysis of degree, cause, and potential consequences. *Pediatrics* 2002; **109**: E45.

6. Wirix M, Parys-Vanginderdeuren R, Casteels I, Uyttebrouck A. Delayed diagnosis of retinoblastoma. *Bulletin de la Societe Belge d Ophtalmologie* 2000: 37-41.

7. Robaei D, Rose KA, Kifley A, Cosstick M, Ip JM, Mitchell P. Factors associated with childhood strabismus: findings from a population-based study. *Ophthalmology* 2006; **113**: 1146-53.

8. Leander C, Fu LC, Pena A, Howard SC, Rodriguez-Galindo C, Wilimas JA, Ribeiro RC, Haik B. Impact of an education program on late diagnosis of retinoblastoma in Honduras. *Pediatr Blood Cancer* 2007; **49**: 817-9.

9. Kaatsch P. Epidemiology of Childhood Cancers. *Cancer Treatment Reviews* 2010; **36**: 277-85.

10. Desandes E, Guissou S, Ducassou S, Lacour B. Neonatal Solid Tumors: Incidence and Survival in France. *Pediatr Blood Cancer* 2016; **63**: 1375-80.

11. Basta NO, James PW, Gomez-Pozo B, Craft AW, McNally RJ. Survival from childhood cancer in northern England, 1968-2005. *Br J Cancer* 2011; **105**: 1402-8.

12. McKee SP, Levi DM, Movshon JA. The pattern of visual deficits in amblyopia. *Journal of vision* 2003; **3**: 380-405.

13. Berk TA, Oner HF, Saatci OA. Underlying pathologies in secondary strabismus. *Strabismus* 2000; **8**: 69-75.

14. Horwood AM. Maternal observations of ocular alignment in infants. *J Pediatr Ophthalmol Strabismus* 1993; **30**: 100-5.

15. Maternal and Child Health Service Visits. In: Training DoEa, ed.*Maternal and Child Health Service Visits*, Victoria, 2013.

16. Wirth MG, Russell-Eggitt IM, Craig JE, Elder JE, Mackey DA. Aetiology of congenital and paediatric cataract in an Australian population. *Br J Ophthalmol* 2002; **86**: 782-6.

17. Braun V, & Clarke, V. . Using thematic analysis in psychology. *Qualitative Research in Psychology* 2006; **3**: 77-101.

18. Abraham C. Developing evidence-based content for health promotion materials. In: M AC, Kools, eds.*Developing evidence-based content for health promotion materials*, London, UK: Sage Publications, 2012.

19. Fisher JFW. The information-motivation-behavioral skills model. In: DiClemente Rj CRAKMC, ed.*The information-motivation-behavioral skills model*: John Wiley and Sons, 2002.

20. Doak CC DL, and Root JH. *Teaching patients with low literacy skills.* , 2nd Ed. edn. Philadelphia, PA: J.B. Lippincott, 1996.

21. Osborne RH, Batterham RW, Elsworth GR, Hawkins M, Buchbinder R. The grounded psychometric development and initial validation of the Health Literacy Questionnaire (HLQ). *BMC Public Health* 2013; **13**: 658.

22. Chan YH. Randomised Controlled Trials (RCTs) – Sample Size:The Magic Number? *Singapore Medical Journal* 2003; **44**: 172-74.