Full study title:

Vision and balance changes after bilateral implantation of Toric *versus* non-Toric intraocular lenses in Cataract patients with astigmatism

Short study title:

Vision and balance changes after bilateral implantation of Toric IOLs

This protocol has regard to the HRA guidance and order of content

RESEARCH REFERENCE NUMBERS

IRAS project ID: 286913

R&D Reference No: 21/OPH/606

Clinicaltrials.gov number: pending

Version: Toric IOL 1.2 (1st September 2022)

OTHER RESEARCH REFERENCE NUMBERS

PEOS ID: 2669

UOP Grant number: RR2 04499/101

SPONSOR

Study Sponsor: University Hospitals Plymouth NHS Trust

Study funder: Carl Zeiss AG

KEY TRIAL CONTACTS

Chief Investigator	**Professor Phillip Buckhurst** Room SF17, School of Health Professions, Peninsula Allied Health Centre, University of Plymouth, PL6 8BH Phone: +44 1752 588884 phillip.buckhurst@plymouth.ac.uk
Principal investigator	**Professor Nabil Habib** Consultant Ophthalmologist, Royal Eye Infirmary, Derriford Hospital Phone: +44 (0)1752 439353 nabil.habib@nhs.net
Sponsor	**University Hospitals Plymouth NHS Trust** **Dr Chris Rollinson (representative)** Research Governance Manager The Research Office Level 2 MSCP, Bircham Park Offices 1 Roscoff Rise, Derriford Plymouth, PL6 5FP +44 1752 432842 Plh-tr.RD-Office@nhs.net
PhD student and Trial Co-ordinator	**Ms Sherrie Choy** Chartered Physiotherapist, PhD student Room FF01, School of Health Professions, Peninsula Allied Health Centre, University of Plymouth, PL6 8BH Phone: 07903692005 sherrie.choy@plymouth.ac.uk
Co-investigators	**Dr Catriona MacLennan (Lecturer)** Department of Vision Sciences University of Glasgow Caledonian University, G4 0BA Phone: +44 1412731261 Catriona.maclennan@gcu.ac.uk

	Dr Hetal Buckhurst (Associate Professor) Department of Optometry, School of Health Professions, University of Plymouth Phone: +44 1752 588886 Hetal.buckhurst@plymouth.ac.uk **Prof Gary Shum** School of Sport, Health and Wellbeing Plymouth Marjon University Phone: +44 1752 636700 Gshum@marjon.ac.uk
Funder(s)	**Carl Zeiss Meditec AG** **En Gyung Kim (**Product Manager Refractive IOL) Carl Zeiss Meditec AG Max-Dohrn-Str. 8-10 10589 Berlin, Germany Phone: +49 30 8540 01 214 Mobile: +49 151 20015278 engyung.kim@zeiss.com www.zeiss.com/med
Key Protocol Contributors	**Ms Sherrie Choy** Chartered Physiotherapist, PhD student Phone: +44 1752 588800 sherrie.choy@plymouth.ac.uk
Statistician	**Prof Victoria Allgar** Professor of Medical Statistics and Director of Peninsula Clinical Trials Unit Peninsula Medical School, Faculty of Health University of Plymouth +44 1752764437 medstats@plymouth.ac.uk

i. LIST of CONTENTS

KEY TRIAL CONTACTS 2
i. LIST of CONTENTS 4
ii. LIST OF ABBREVIATIONS 5
iii. TRIAL SUMMARY 7
iv. FUNDING AND SUPPORT IN KIND 8
v. ROLE OF TRIAL SPONSOR AND FUNDER 8
vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS 8
vii. **STUDY CONTRIBUTORS** 9
viii. KEY WORDS: 10
ix. TRIAL FLOW CHART 11
1. BACKGROUND 12
2. RATIONALE 13
3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS 17
4. TRIAL DESIGN 19
5. TRIAL SETTING 20
6. PARTICIPANT ELIGIBILITY CRITERIA 20
7. TRIAL PROCEDURES 21
8. TRIAL TREATMENTS 29
9. SAFTEY REPORTING 32
10. STATISTICS AND DATA ANALYSIS 37
11. DATA MANAGEMENT 43
12. MONITORING, AUDIT & INSPECTION 44
13. ETHICAL AND REGULATORY CONSIDERATIONS 45
14. DISSEMINIATION POLICY 49
15. REFERENCES 51
16. APPENDICIES 52

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial.

Maintain alphabetical order for ease of reference.

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CAT-PROM	Cataract surgery patient-reported outcome measures
CI	Chief Investigator
CRF	Case Report Form
FES	Fall Efficacy Scale
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IOLs	Intraocular lens
IPR	Intellectual Property Right
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
LRI	Limbic relaxing incision
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NICE	The National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIMP	Non-Investigational Medicinal Product
PAHC	Peninsula Allied Health Centre
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information

SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
TUG	Timed Up and Go Test
UHP	University Hospitals Plymouth NHS Trust
UOP	University of Plymouth

iii. TRIAL SUMMARY

Trial Title	Vision and balance changes after bilateral implantation of Toric *versus* non-Toric intraocular lenses in Cataract patients with astigmatism	
Internal ref. no. (or short title)	Vision and balance changes after bilateral implantation of Toric IOLs	
Clinical Phase	Pre and post operation comparison	
Trial Design	Randomised controlled trial	
Trial Participants	Ambulatory adult aged over 50 years with bilateral cataract patients and astigmatism >1.0D awaiting intraocular lens replacement surgery	
Planned Sample Size	140 participants	
Treatment duration	Up to 12 months after first eye surgery	
Follow up duration	12 months after second eye surgery	
Planned Trial Period	3 years	
	Objectives	Outcome Measures
Primary	• Dynamic balance in functional activities	• Centre of mass and head movement by accelerometer in crossing obstacles, turning and stair walking
Secondary	• Eye tracking characteristics • Visual function • Risk of fall • Vision related quality of life	• Area of interest (heatmap) and gaze duration by eye tracking (Tobii pro2) during level ground obstacle crossing and stair walking • Duration of Timed up and go test Visual acuity • IOL rotation • Fall efficacy scale and fear of falling • CAT-PROM 5 questionnaire
Investigational Medicinal Product(s)	Monofocal Toric and non-Toric intraocular lens	
Formulation, Dose, Route of Administration	Artificial intraocular lens implantation during cataract correction surgery	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON FINANCIALSUPPORT GIVEN
Carl Zeiss Meditec AG **En Gyung Kim (**Product Manager Refractive IOL) Carl Zeiss Meditec AG Max-Dohrn-Str. 8-10 10589 Berlin, Germany Phone: +49 30 8540 01 214 Mobile: +49 151 20015278 engyung.kim@zeiss.com www.zeiss.com/med	1. All Zeiss Toric and non-Toric IOLs needed for this project (bilateral eyes of 140 participants plus spare) 2. Research grant to University of Plymouth grant number: RR2 04499/101 for full-time PhD studentship, participant travel subsidy and research conference subsidy

v. ROLE OF TRIAL SPONSOR AND FUNDER

Carl Zeiss Meditec AG is the trial funder. It funds the study by providing both the Toric and non-Toric monofocal intraocular lenses needed in the cataract correction surgery for all participants in this study and a research grant to the University of Plymouth covering a full-time PhD studentship, travel subsidy for patients' study visits and related expenses required for presentation of this research in conferences. University Hospitals Plymouth NHS Trust (UHP) is the sponsor. The Research and Development (R&D) Office of UHP provides support for research approval process and implementation to ensure it is compliant to the Health Research Authority (HRA) guidelines. The Consultant Ophthalmologist Prof. Nabil Habib of UHP provides collaboration as Principal Investigator to lead and provide intraocular lens replacement surgery to selected Cataract patients, as well as review of data analysis and report of result. UHP also provides research support with input from the R&D team to support the implementation of this project.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

The University of Plymouth (UoP) is the provider of the PhD studentship and the related training. The supervisory team holds weekly meetings with the PhD student Ms. Choy to monitor the study progress and to discuss any issues arise. The PhD student, the supervisory team, PI and study Sponsor also has regular meeting to update progress of the study and to discuss any issue that impact on the research

project. The study is also required to comply with the UoP Research Ethics Policy and the Code of Good Research Practice and Research Data Policy (https://www.plymouth.ac.uk/research/governance/research-ethics-policy).

Ethical approval is not required by the University, but this study is also registered on the Plymouth Ethics Online System of University of Plymouth for record purpose.

vii. STUDY CONTRIBUTORS

Prof Phillip Buckhurst of UoP is the Chief Investigator (CI) of this study. He is a chartered optometrist and takes primary responsibility for the conduct of this research project from research design, the three study visits at the University of Plymouth (PAHC building) and result generation. He will act as the contact person for University of Plymouth, overseeing the management and research conduct throughout the trial period, and coordinating the personnel with sponsor and co-investigators. He is also responsible for the overall conduct of the research project to meet the standard as set in the UK Policy Framework of Health and Social Care Research.

Prof. Habib is the Principal Investigator (PI) and the clinical lead of this study. He is the Consultant Ophthalmologist at Royal Eye Infirmary (REI) of UHP and has responsibility for the conduct of the research at UHP. He will supervise the participant recruitment, screening for inclusion/exclusion criteria and the implementation of the intervention with his clinical team at the REI. He will coordinate with the sponsor (UHP) to ensure this project meet the required regulatory requirements. He and his ophthalmologist team are responsible for the cataract clinic pathway and post-operation care of the participants recruited for this study.

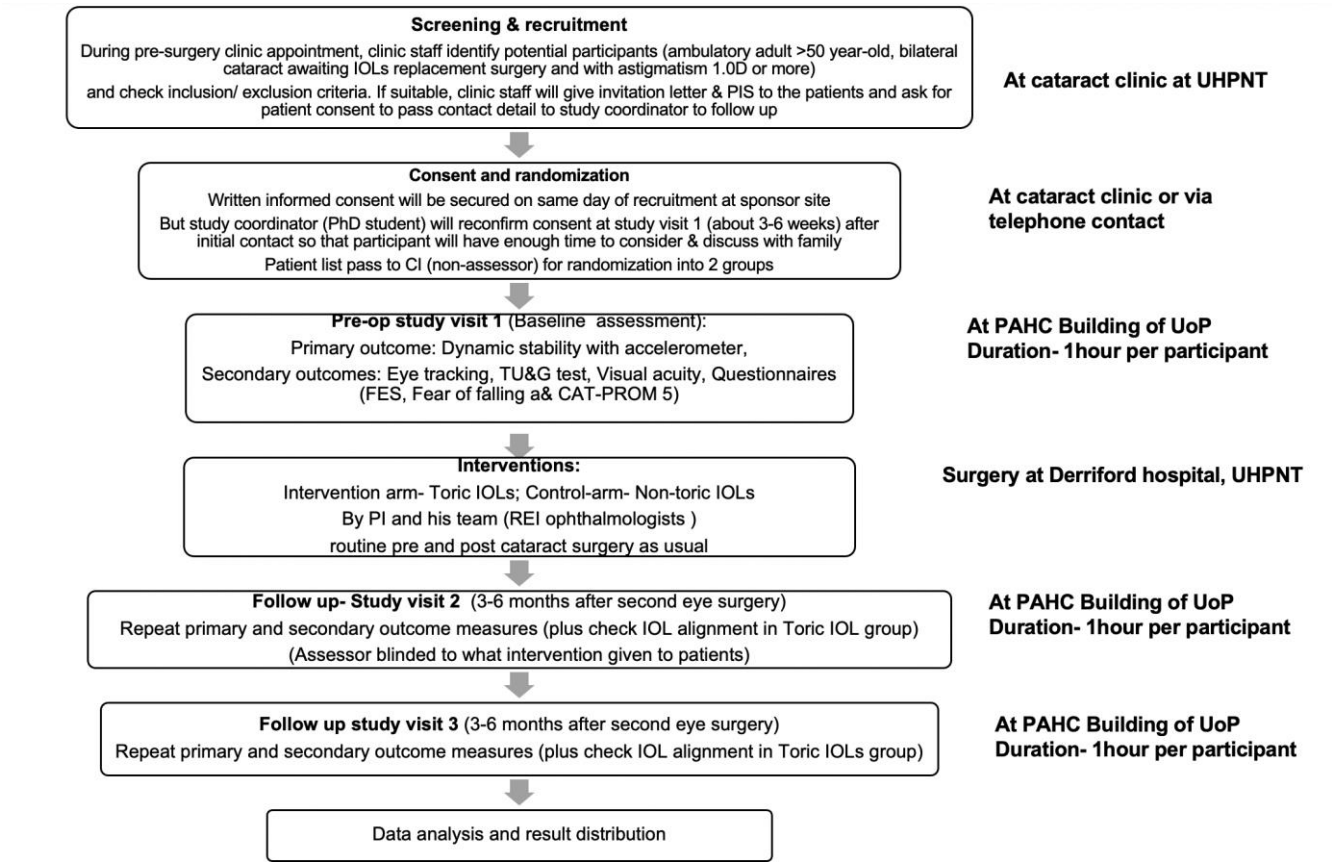
Dr Catriona MacLennan of Glasgow Caledonian University, Prof Gary Shum of Plymouth Marjon University and Dr Hetal Buckhurst of University of Plymouth, are co-investigators of this research trial. They co-supervise the PhD student; provide consultancy for the research idea and implementation including trial design, liaison with hospital and Ophthalmologists, research training provision, research implementation, data analysis, manuscript writing and dissemination of results in conference and peer reviewed journals.

This trial protocol is prepared by Ms Sherrie Choy who is a PhD student at the University of Plymouth and chief coordinator for the study. She is responsible for preparing documents to meet the required

standard for the approval ethics and the HRA. She is also responsible for patient recruitment, carrying out outcome measures, data analysis and management, writing up of major findings of results and overall study coordination.

viii. KEY WORDS:	cataracts, intraocular lens, astigmatism, Toric intraocular lens, Monofocal intraocular lens, dynamic stability, quality of life, eye tracking, visual functions, randomised controlled trial

ix. TRIAL FLOW CHART



1. BACKGROUND

Cataracts are the most common cause of low vision and blindness in the world (Brian and Taylor, 2001). Cataracts occur when the crystalline lens becomes cloudy preventing light from reaching the retina and so resulting in poor vision. Cataract is highly treatable and the surgery involves removing the cloudy crystalline lens and replacing it with a clear artificial plastic lens (made of acrylic) called an Intraocular lens (IOLs) (Foster, 2001).

Around one fifth of people attending for cataract surgery have astigmatism (Swampillai *et al*., 2020). Astigmatism refers to the imperfection in the curvature of the cornea, the clear and dome-shaped covering in front of the eye. An eye with severe astigmatism is oval (like a rugby ball) instead of round like a football. This oval shape reduces vision and make vision blurry all over, not just close-up, or far away. While most astigmatism orientated with the steep curve vertically, for some, it can be horizontal (the rugby ball on its side) or more rarely, obliquely positioned (neither horizontal nor vertical). Degree of astigmatism is measured in dioptre (D). A perfect eye has zero dioptre. Most people can have between 0.5-0.75 D and people with 1.5D or more typically need to wear contact lenses or eyeglasses for clear vision.

Conventional non-Toric monofocal IOLs is the most common implants used in cataract replacement surgery. They stay focused at one fixed distance and when chosen to correct distance vision error such as short-sightedness, reading glasses may be needed to see thing close-up. Also, these lenses do not correct astigmatism. In most NHS hospitals such as in UHP, astigmatism often is left untreated during the cataract replacement surgery.

With the advance of IOLs, a modern design of intraocular lenses called Toric IOLs, can correct the astigmatism at the time of cataract replacement surgery. They provide superior correction of astigmatism than other surgical procedures and are known to reduce the need for the patient to wear spectacles after the surgery. Although Toric IOLs may be regarded as “premium IOLs” due to higher cost than conventional Monofocal IOLs, a cost-effectiveness analysis based on hypothetical model in four European countries noted that Toric IOLs were a cost-saving alternative to conventional Monofocal lenses (Laurendeau et al., 2009). The additional vision improvement by correcting astigmatism, especially in older population not only reduce spectacle dependency, but it may also have positive

impact on balance during daily mobility, reduce fall risk and improve overall quality of life. The purpose of this study is to compare the changes in dynamic balance and vision functions during daily activities among patients with cataract replacement with Toric monofocal IOLs versus those with non-Toric monofocal IOLs.

2. RATIONALE

Cataract is one of the major causes of visual impairment and blindness in the aging population. In UK, cataract alone accounts for over a third of the cases of vision impairment in those over 75 years. The Royal College of Ophthalmologists estimated a growth in prevalent cataracts by 43-57% between 2015 and 2035, causing around 50% increase in the expected number of cataract operations over the next 20 years. During cataract correction surgery, artificial lenses, otherwise known as intraocular lenses (IOLs), are used to replace the natural crystalline lens within the eye. By selecting IOLs of appropriate lens power, the pre-existing refractive error of the eye such as short-sightedness can be corrected during the IOLs implantation (Asbell *et al*, 2005). Routine pre-operation assessment by ophthalmologists usually takes place 2-4 week before the cataract surgery. The ophthalmologist will select the appropriate IOLs by measuring of the axial length of the eye and the curvature of the cornea- the front clear covering of the eye. Implantation of the standard monofocal IOLs can only correct spherical refractive errors (near or far eyesight). Any preoperative astigmatism- imperfection of cornea curvature, can still affect the visual acuity and spectacle dependence after the operation.

Astigmatism is measured in the unit called dioptres (D). People with 1.5D or more usually need to wear contact lenses or spectacles for clear vision. Around 19-22% of the total population has over 1.50DC of corneal astigmatism at the time of cataract surgery (Swampillai *et al*., 2020). A UK study of 1230 eyes in an NHS cataract clinic even reported about 40% of the patients attending routine cataract surgery had more than 1.00D astigmatism (Khan and Muhtaseb, 2011). It is estimated that patients are 34 times more likely to use spectacles per dioptre of astigmatic error in the better eye (Wilkins *et al.*, 2009). Uncorrected astigmatism not only increases spectacle dependence, even of relatively small amount, it can also result in reduction of visual performance (Read *et al*., 2014). Reduced vision has been shown to link with poor balance or mobility (Lord, 2006) (Lord *et al*., 2010) (Black and Wood, 2005). Oblique astigmatism (where the principal meridians are not orientated vertically or horizontally) also proved to affect balance and alter foot placement on steps (Johnson *et al*., 2013). This could then

increase the risk of falls and adversely affects the overall economic costs of the cataract surgery and healthcare. Full correction of refractive error including astigmatism may have greater impact on everyday life than previously thought.

In the UK, almost all patients undergoing cataract surgery by the NHS are given monofocal intraocular lenses (IOLs) whether they have astigmatism or not. The National Institute for Health and Care Excellence (NICE) adult cataract management guideline 2017 recommended monofocal IOLs to be used for cataract surgery and only specified not to offer multifocal intraocular lenses for people having cataract surgery (in the NHS). Multifocal IOLs have areas with different focusing power which allows near and distant objects to be seen without the need for spectacles. On the evidence of effectiveness, NICE commented that multifocal IOLs "can provide good near and distance vision without the need for spectacles, but this is at the expense of a variety of potential visual disturbances." Another systematic review also noted that there was no difference in distance vision between multifocal and monofocal IOLs; but multifocal IOLs had significantly worse results for glare and halos (Khandelwal et al., 2019). Therefore, Monofocal IOLs are the standard IOLs used in NHS. However, there are no recommendations around lens design and material for further consideration.

Toric IOLs, a modern design of intraocular lenses, can provide predictable and precise correction of astigmatism with improvement in vision without spectacles for cataract patients (Kessel *et al*., 2016). However, prices for Toric IOLs are higher and buying larger volume of the same standard monofocal IOLs is often more economical for the NHS. Therefore, Toric IOLs are not often offered in routine cataract surgery. Although the latest NICE cataract pathways 2021 have added a remark "Please note: the recommendations around lens design and material have been removed to allow for further consideration," to give surgeon or local NHS Clinical Commission Group (CCG) more freedom to decide on the types of IOLS provision, but there is still insufficient evidence for consistent patient selection criteria. To date, no study has explored the additional effect of correcting astigmatism at the time of cataract surgery, on lifestyle activities and mobility. The purpose of this study is to evaluate the benefits of correcting astigmatism during cataract surgery on an individual's dynamic stability, visual functions, fear of falls and quality of life using modern design Toric IOLs when compared to conventional non-Toric IOLs. The results can provide a more holistic comparison of the two Monofocal IOLs and act as evidence to inform patient selection criteria for Toric IOLs.

2.1 Assessment and management of risk

This study has no higher risk than the risk of standard medical care. However, the study will be considered medium risk: involving an invasive interventional procedure with a low-risk patient population.

Risks

For Toric IOLs to correct astigmatism, they need to be placed specifically with reference to the steepest meridian of the eye. All IOLs can rotate, but rotation of Toric IOLs can affect its astigmatism correction effect. Small rotations do not affect the astigmatic power, but larger rotations will reduce the astigmatism correcting effect. If the IOL is rotated 30 degrees, the astigmatism correcting effect is eliminated (Visser et al., 2013). In approximately 1% of patients, the Toric lens rotates significantly reducing the level of astigmatism that is corrected by the Toric lens. If this is the case, and the participant is unhappy with their visual outcome, the surgeon will discuss the possibility of a secondary procedure to reposition the lens. The surgeon will discuss the risks of the repositioning procedure with the participant to determine if the benefits outweigh the risks. It is important to note that this repositioning (to correct any unwanted astigmatism) is only possible with Toric lenses, with standard IOLs unwanted astigmatism will not be corrected. Even with significant Toric IOLs rotation, additional surgery is generally not required as by removing the cataract, the rotated Toric IOLs still provide significant improvement in vision and the remaining astigmatism can be corrected with spectacles.

The mobility assessment involves walking over obstacles, turning, going up and down stairs. The participants will have three small portable motion sensors placed on their neck and lower back and will be asked to wear a pair of eye tracking glasses during the mobility tasks. There is a very low risk of falls, similar as during any normal activities of daily living. The risk will be minimal as all assessment will be carried out under the supervision of an experienced physiotherapist. Also, the assessment venues are part of the University campus which is regularly controlled to maintain environmental safety and has provision of first aid equipment. A patient and public involvement discussion has been conducted which covered discussion about assessments and the research design. All participants were supportive about the research idea and felt the research could raise awareness of available choice of IOLs. Participants were asked about the practicality of the research and felt it would be better to have all assessments done in one site. The assessments were to be conducted at Marjon Biomechanics Lab and

Optometry Lab at PAHC building. This is now changed to the Biomechanics Laboratory at PACH building. There was also discussion about mobility assessments and participants were asked if they felt the tasks were too difficult, risky of fall or too much. All participants felt the mobility task involved were low level and not complicated. They were told that during the mobility assessment, the participant would be required to wear eye tracking glasses and have three movement sensors placed on the body. They felt it was small and light weight and reported no concerns about the additional sensor or glasses.

To assess the eyes comprehensively and take photos, pupil dilating eye drops such as 0.5-1% Tropicamide will be used to dilate the patients' pupils for examination of the back of the eyes. These drops are routinely used in optometry and hospital clinics without need for prescription and all precautions will be taken before administration. The CI, Prof Phillip Buckhurst and co-investigator, Dr Hetal Buckhurst are registered Optometrist and will carry out this procedure during the study visit at the PAHC. Dilation eye drops may cause blurring of vision and increase sensitivity to bright light. Some people may also experience temporary stinging and dry mouth. The effects of the drops normally last between two and four hours but can be up to six hours. All patients will be reminded on the PIS and by email or telephone contact before the study visits that they must not drive for the appointment and must use alternative means of travel such as taking public transport or ask friend and family to drop them off and collect. They will be advised not to drive or operate heavy machinery until their sight returns to normal and their eyes are comfortable. They will also be advised to wear sunglasses to help reduce light sensitivity after the eyedrop.

As three additional visits are required for the study, there is an increase in number of appointments, but any travel expenses will be reimbursed, and the patients will also have additional care and screening.

As with all studies, there is a very small risk of breach in confidentiality and failure to maintain data securely. Identifiable patient information, in addition to pseudonymised data will be stored at both UHP and UoP, and will be transferred between each site. All data collected will be kept and transferred securely.

Benefits

Participating in this study may allow patients to receive specialised Toric IOLs which are not routinely given in NHS cataract surgery. As a result of the additional study visit, the participants will also have additional care and screening for both vision and mobility. The extra study visit after the surgery provides additional

follow up opportunity and if the investigators of this study find that you have a rotated lens, then they will be able to advise on whether additional treatment would be beneficial for the patients.

This is a new study to explore the benefit of full vision correction during cataract surgery on vision characteristic and dynamic balance in functional activities for fall risk management. The study can improve the understanding of visual impact on functional biomechanics and will provide evidence to inform fall risk management from vision perspective. Fall risk improvement is not currently a considering factor for IOLs selection in Cataract management, but this study may provide the needed evidence for better vision and fall management among elderly.

3. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

The objective of the study is to compare the effects of Toric intraocular lens versus Monofocal intraocular lens replacement on dynamic stability among cataract patients with astigmatism using a randomised controlled trial.

It is hypothesized that Toric intraocular lens will have additional correction of astigmatism after the cataract surgery resulting in and better outcomes in dynamic stability and higher chance of "spectacle-free".

There are two arms of the trial: Monofocal Toric intraocular lens versus Monofocal non-Toric intraocular lens

The research question is based on the PICOT criteria:

P Population	Cataract patient with astigmatism >1.0DD awaiting intraocular lens replacement surgery
I Intervention	Monofocal Toric intraocular lens
C Comparison group	Monofocal non-Toric intraocular lens
O Outcome of interest	Primary- Dynamic stability will be measured by motion sensor during functional movements (crossing obstacles, turning and stair walking) Secondary- Eye tracking characteristics, visual function, risk of fall, vision specific quality of life questionnaire and Toric IOL rotation.
T Time	Before operation (T1) and 3-6 months after each eye operation (T2, T3)

3.2 Secondary objectives

The second objective is to compare the effect of Toric versus Non-Toric monofocal intraocular lenses implantation on eye tracking characteristics, visual function, intraocular lens orientation, risk of falls and vision related quality of life.

3.3 Outcome measures/endpoints

Sample size:

140 participants will be recruited from patients undergoing cataract surgery at the Royal Eye Infirmary of the University Plymouth Hospitals NHS Trust over a three-year period.

Sample size calculation:

Sample size test calculation was carried out with the G*Power 3.1 program (Faul *et al*., 2007) for comparison of the main outcome measure of dynamic balance (between IOL design) using mixed ANOVA (repeated measures, between factor being the type of IOL).

Based on of the result of dynamic balance measurement in a previous study (Mancini *et al*., 2011), an estimated medium effect size (0.25) will be used. With a power of 85% and level of significance (p) set at 0.05 and effect size of 0.25, 55 participants will be required in each group (Standard non-Toric vs Toric IOLs). Assuming a 20% drop out rate, to secure 55 participants in each group, 70 participants will therefore be recruited in each group. For two groups of participants (Toric versus non-Toric), a total of 140 participants will be recruited.

3.4 Primary endpoint/outcome

Dynamic stability during functional activities which will be assessed by tracing centre of mass and head tilting using wireless motion sensors and eye tracker. The outcome measures of dynamic stability include the angular position, velocity and acceleration of the sensors.

3.5 Secondary endpoints/outcomes

1. The eye tracking characteristics (gaze duration, area of interest by gaze pattern and its percentage duration gaze time).

2. IOL rotation by measuring degrees of rotation from intended position and degrees rotation from steepest meridian with digital slit lamp and IOL tilt and decentration using Pentacam4. This will be part of the routine eye assessment for post cataract surgery with Toric IOL.

3. Visual acuity which is also part of routine eye assessment for all post cataract surgery patients.

4. Fear of falling and fall efficacy scale via questionnaire.

5. Cataract specific quality of life questionnaire (CAT-PROM 5)

3.6 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare dynamic stability in cataract patients with Toric versus non-Toric IOLs	**Dynamic stability:** - movement of centre of mass and head tilting using wireless motion sensors.	Three timepoints: 1. pre-operation study visit and 2. post-operation study visit (3-6 months after first eye surgery). 3. post-operation study visit (3-6 months after second eye surgery).
Second Objectives To compare eye tracking characteristics, visual functions, risk of falls and quality of life in cataract patients with Toric versus non-Toric IOLs	**Eye tracking characteristics:** -area of interest by gaze pattern -Gaze duration on area of interest **Vision function** include visual acuity, **IOL rotation** by degrees of rotation from intended position and degree rotation from the steepest meridian using special optometry equipment to look at the front of the eye (digital slit lamp and Pentacam) **Risk of fall** will be measured by fear of falling and fall efficacy scale questionnaires. **Vision related quality of life** will be measured by CAT-PROM5 questionnaire.	Three timepoints: 1. pre-operation study visit and 2. post-operation study visit of first eye at 3-6 months after the surgery 3. post-operation study visit of second eye at 3-6 months after the surgery

4. TRIAL DESIGN

The study is a randomized controlled trial comparing the change of dynamic stability, gaze characteristics, visual function, and quality of life measurements between Toric and non-Toric intraocular lens (IOL) groups.

The study is a double masked, parallel group design. 140 cataract patients with astigmatism >1.0D at the Royal Eye Infirmary (REI) of Derriford Hospital will be recruited and randomly assigned to either receive Toric IOLS or non-Toric IOLs for bilateral lens replacement surgery. The randomization will be conducted by the CI who is not involved in the surgical intervention nor the outcome measure assessments. The participants will not know which types of IOLs they are receiving and the study coordinator who assesses the outcome measures will be masked to the types of IOLs given to the participants. Study visits will be carried out before surgery, 3-6 months after first and second eye surgery.

5. TRIAL SETTING

This is a multi-centre trial. The screening and recruitment of participants will take place at the cataract clinic at the REI of Derriford Hospital, University Hospitals Plymouth NHS Trust. The intervention of Toric IOLs or non-Toric Monofocal IOLs cataract correction surgery will be carried out by the PI and his ophthalmologist team at the REI. The three study visits for outcome measurements will be carried out by masked assessors who are Allied Health Professionals (Optometrists or Physiotherapists) at the UoP (PAHC building).

6. PARTICIPANT ELIGIBILITY CRITERIA

140 cataract patients over the age of 50-year-old with astigmatism >1.0D undergoing bilateral intraocular lens replacement surgery will be recruited from the REI of the UHP over a three-year period. Three study visits will be arranged for each participant at the UoP (PAHC building) and will be followed up from before the cataract surgery to up to 12 months after the second eye cataract surgery.

6.1 Inclusion criteria

- Participants capable of giving informed consent
- Age 50 years or above
- Diagnosed with bilateral cataract with corneal astigmatism 1.00D or above
- Previously consented to routine NHS cataract surgery

6.2 Exclusion criteria

- Irregular astigmatism, Amblyopia

- Any pre-surgical corneal complications or pathology such as Fuchs dystrophy, keratoconus
- Macular pathology, glaucoma, retinal disease, abnormal iris or pupil deformation
- Irregular or malformed eyelids such as ptosis, chalazion or severe blepharitis
- Previous corneal or intraocular surgery
- Any patient who does not have traditional phacoemulsification extraction will be excluded from the reminder of the study
- Incapable of giving informed consent due to lack of mental capacity, problems with communication or language and any conditions preventing the patient from fully understanding the procedures and nature of the study
- Predicted bilateral post-op corneal astigmatism of <1.50D, dilated pupil size smaller than 5mm
- Unable to walk independently with or without walking aids for 10 meters

7. TRIAL PROCEDURES

This is a multi-centre, parallel randomized controlled trial study comparing the clinical outcomes of Monofocal Toric IOLs versus Monofocal non-Toric IOLs in cataract patients with astigmatism undergoing bilateral intraocular lens replacement surgery.

7.1 Recruitment

This study aims to recruit 140 participants over three years. The participants will be randomly assigned into Toric Monofocal IOLs group or non-Toric Monofocal IOLs group. The recruitment will take place at the cataract clinic at the REI of UHP. Adult cataract patients referred for cataract replacement surgery at REI, from community Optometrists and GPs, will enter a streamlined pathway whereby patients attend a single pre-surgical visit. During this clinic visit, the ophthalmologist surgeons will carry out medical screening and acquire relevant clinical measures, along with consent for the surgery.

The clinical team of REI will identify potential participants when they review the cataract surgery referral and medical records to arrange pre-surgery clinic appointment. A short version of PIS of this study will be sent out with the appointment letter to potential patients to give them time to read about the study before the recruitment at the clinic appointment.

The initial approach to recruit the potential participants will happen at the pre-surgery appointment at REI by the REI clinical team. One of the clinical team members will identify potential participants based

on surgery referral forms or medical records, and approach the potential participants to ask if they would like to discuss about a research project or have read the short version PIS that was sent with the appointment letter. The patients will then be introduced to a member of the research team, present at the REI, to provide further explanation of the study and if willing, the potential participant will be consented. Consent will occur on the day at the clinic. The rationale for this is that potential participants only attend a single pre-surgical visit and so there are no other opportunities to bring a participant back to the hospital for consent prior to the surgery. Should a participant wish for a longer period to think about participating in the study, then consent will be taken at the first study visit. However, most participants will be consented at their routine pre-surgical clinical visit.

7.1.1 Participant identification

Cataract surgery is a streamlined service where all cataract patients referred for cataract replacement surgery are given a single pre-surgical clinical appointment at the REI of UHP. During this pre-surgical visit appointment, the clinical team will identify potential participants for the study based on the referral form. Adult cataract patients aged 50 years or above with astigmatism and have previously consented for routine bilateral cataract correction surgery at the NHS will be identified as potential participants for the study. The initial approach to the potential participants will be conducted by a member of the routine clinical care team, who will ask if the potential participants would like to be introduced to a member of the research team to discuss about a research study. If agreeable, then the potential participant will be introduced to the member of the research team present at REI. That team member will discuss the study with the potential participant, give them a copy of the PIS and will answer any questions about the study. If willing, the potential participant will then be consented. However, if the potential participant would like more time to consider their participation in the study, then their details will be collected, and they will be contacted at a later date. If they are willing to take part, consent will be secured at the first pre-surgical study visit at the UoP.

7.1.2 Screening

For potential participants who expressed interest in taking part in the study, they will be screened against inclusion and exclusion criteria by the Ophthalmologists (PI and his ophthalmology team) during the screening appointment based on routine pre-surgery examination result and medical record. No extra equipment or examination procedures will be needed.

7.1.3 Payment

Any routine appointments for the cataract surgery procedure will not incurred reimbursement.

The three additional assessment visits at the UoP, one before eye surgery (baseline), one 3-6 months after first eye surgery and one 3-6 months after second eye surgery will be reimbursed for a reasonable nominal fee (£20) to cover any travel expenses and the additional car parking fee.

7.2 Consent

Prior to participant recruitment and any procedures for this study, ethical approval will have been obtained from both the Health Research Authority and the NHS Research Ethics Committee.

Potential participants will be asked to sign the written informed consent form on the same day as their pre-surgical routine visit at the REI (where they are consented for surgery) by a member of the research team. This is to accommodate the cataract surgery clinical pathway and to reduce the need for the patients to travel back to REI for signing the written informed consent form. Following the current cataract surgery clinical pathway, patients attend the REI for a pre-assessment cataract clinic appointment to discuss cataract surgery with their ophthalmology surgeons. If the patients would like to go ahead, consent for surgery is obtained during this appointment. The patients are then placed on a waiting list and the next time they are seen is on the day of surgery. With discussion with the sponsor, it is felt that obtaining consent at REI, where the patients will be having their surgery, is most appropriate in terms of safety and it also allow potential participants to discuss elements of cataract surgery directly with the clinic team or the surgeons. If the consent is obtained at the study site, the academic researchers, who are not ophthalmologists, would not be able to discuss the surgical aspect related to this study. There is a long period between this pre-assessment appointment and the surgery (several weeks or months). So, the patients will have considerable time to further consider about their participation. At each study visit, time will be provided for participants to ask questions or reconsider their participation.

All potential participants will be informed that participation in this research study will be entirely voluntary. No one will be coerced against their will and no undue influence will be exerted upon the patient. The participants have the right to refuse participation without giving reasons and their decision will be respected. The participants are also free to withdraw at any time from the trial without giving

reasons and without prejudicing his/her further treatment. Data collected up to the point of withdrawal from the study will be used in the analysis.

7.3 The randomisation schemes

The PI will be responsible for recruitment of potential participants from the Cataract clinic at UHP and oversee the consent and eligibility process carried out by the study coordinator. All potential participants will be allocated a unique identification number. The CI, who is independent of the outcome assessments and interventions, will randomize the participants between the intervention and control groups. He will allocate a pseudonymous participant number from 1 to 140. Using simple randomisation with 1:1 allocation ratio through random.org, the 1 to 140 number will be randomly assigned into two groups (Toric IOLs versus non-Toric IOLs). The randomization list will then be passed to the PI, who when recruiting the participants at the pre-surgery clinic can know which type of IOLs (Toric or non-Toric) to prepare for the cataract surgery. At study commencement, each number will be allocated to one of the two groups randomly. This means that subjects are allocated to either arm of the study at the point of recruitment. The randomized list will be held by the PI, who delivers the intervention surgeries. The PI needs to know which lenses are allocated to the patients for surgery purposes but will not participate in the outcome assessment. The study coordinator who is the assessor of the outcome measures will be masked to the allocation of lenses.

7.3.1 Method of implementing the randomisation/allocation sequence

The study randomization scheme will use simple randomization with a 1:1 allocation ratio using Microsoft Excel with same number of participants in each of Toric IOLs group and non-Toric IOLs group. The consenting patients will be randomly assigned to one of two groups: Toric IOLs with open loop haptic design and standard non-Toric IOLs of similar haptic design.

7.4 Blinding

The participants will be masked to the interventions prior to the surgery. They will be told which IOLs they received at the end of their final visit. The CI will conduct the simple randomization for the participants through the random.org and he will be masked to the outcome assessment. The randomized list of participants will be passed to the PI and his ophthalmologist team to prepare the IOLs and deliver the

cataract correction surgery. So, the PI cannot be masked to the intervention, but he is masked to the outcome assessment.

The outcome assessors for study visits will be masked to the interventions given to the participants. In the post-surgery study visit, the outcome assessors will carry out the dynamic stability reassessment before any visual assessment to ensure they are still masked to the primary outcome measures as the visual assessment will reveal which types of the IOLs the participants received.

7.5 Emergency Unmasking

During the follow up study visit, if the outcome assessors discover any medical conditions or complications that require further attention, the participants will be referred back to the cataract clinic (for eye complications) or to their GP for any other medical concerns such as acute osteoarthritis needing review of medication. As the study visit takes place at three to six months after the surgery, post-operative complication regarding the IOL implantation or cataract surgery procedure is unlikely. In case it happens, the outcome assessors will be unmasked to the type of interventions received by the patients for further care by asking the patients directly, reviewing discharge summary or contacting CI who holds the randomization list.

7.6 Baseline data

At each study visit based at the UoP, the participant's full name, DOB, address and contact details will be checked for identification purposes. These details will remain separate from the study data which will be identified using the unique study number allocated to the participants.

The outcome measures will include the following:

- General demographic information such as age, gender, ethnicity, relevant medical history, cataract diagnosis and vision assessment results. This will last about 10 minutes.

- Dynamic stability assessment lasts about 30 minutes. Three motion sensors will be put on the participants' body (neck, lower back and upper leg) and they will be asked to wear a special eye tracking glass (figure 1). After that, the participants will be asked to perform a Timed Up and Go (TUG) test which involves getting up from a chair, walking 3m-distance and return to sit back on the chair. They will also be asked to walk over obstacles on level ground and the last mobility task is walking up and down a standardized staircase. Movement outcomes will be measured using three-dimensional motion analysis

(ProMove 3D, Inertia Technology, The Netherlands) and eye tracking data will be collected *via* Tobii-pro glasses 2 (Tobii AB, Sweden) (figure 2 and 3). Three trials will be taken to estimate the average and the best recorded time will be taken for the TUG test. As all the participants are active community dwelling elderly without mobility problem, the dynamic stability tasks are no more demanding than their usual daily activities. The PPI also include discussion about the demand of the assessment and all participants agreed the dynamic stability tests only required low level mobility and no concerns were raised.

- Some qualitative data will be collected *via* self-administered questionnaires which takes about 15 minutes. Risk of fall will be assessed with the short Fall Efficacy Scale (FES-short) and Fear of Falling questionnaire. Vision specific quality of life will be assessed with CAT-PROM 5 questionnaire.

- Standard visual function assessment will also be carried out to assess visual acuity and degree of astigmatism and this takes about 20 minutes.

A paper CRF has been prepared for this study to collect data directly relevant to the objectives and outcomes measures detailed in the protocol.


(a)

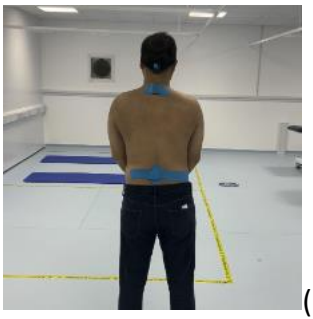

(b)

Figure 1. Set up with movement sensor and eye tracking device (a) and movement sensors placement reinforced with tape (b)

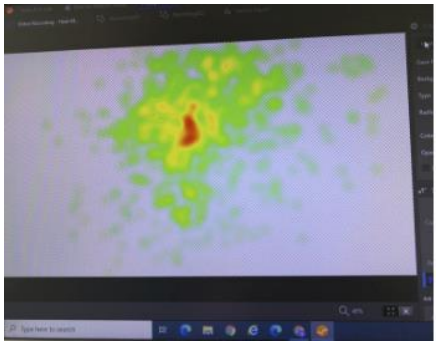


Figure 2. Example of eyetracking analysis using Tobii pro lab software: a) study of gaze on defined area of interest (stool in this example) and b) heat map analysis

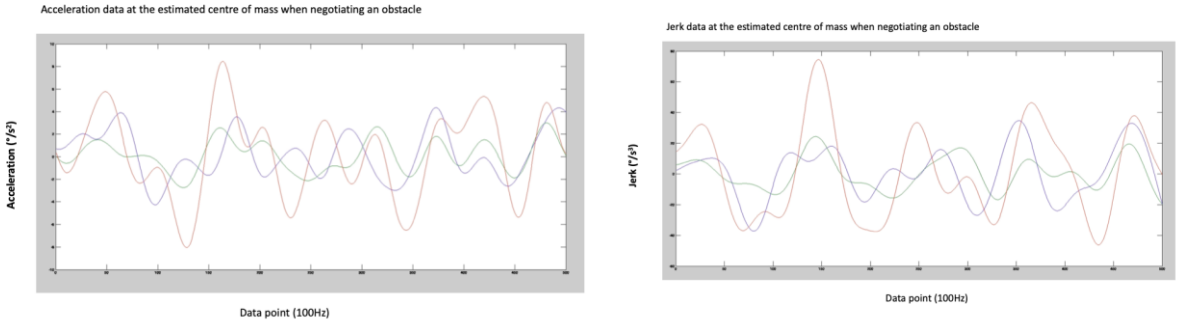


Figure 3. Example of movement sensor output data using Promove 3D software

7.7 Trial assessments

Three study visits will be arranged for each participant who have given written informed consent to take part in the study.

Study visit 1: Pre-surgery baseline assessment will take place at the PAHC building of UoP, at least one week before the cataract surgery. After the participants have the cataract screening appointment at REI, they usually wait 3 to 6 weeks before the cataract surgery. The first study visit for the pre-operation baseline assessment will be arranged during this period. This also gives participants extra time to reconsider taking part in the study from when they signed the informed consent form at the REI. The study coordinator will reconfirm informed consent over the phone or by email (whichever is the preferred contact method) with the participant before arranging the first study visit and at the start of each study visit. If a participant needs to delay or cancel the cataract surgery due to a medical reason, the study coordinator will liaise with the PI who is the Ophthalmologist to confirm the participant is still suitable to take part in the study.

Intervention: participants will be randomized into two groups. One group will receive Toric Monofocal IOLs and the other group will receive standard non-Toric Monofocal IOLs.

Study visit 2: Reassessment of outcome measures will take place three to six months after first eye surgery at the PAHC building of UoP.

Study visit 3: Reassessment of outcome measures will take place three to six months after second eye surgery at the PAHC building of UoP.

7.8 Long term follow-up assessments/ lost to follow-up

There is no long term follow up assessments. If the participants miss their scheduled study visit, they will be contacted by telephone or email (depending on their indicated preference). If no response, two more attempts within 2 months will be made. Participants who are not contactable will be marked as lost to follow-up and notification sent to their GP and the PI for their medical records. A notification letter will be sent to the participants' address or email account.

7.9 Withdrawal criteria

The participants can withdraw from the study at any time without giving any reason. Should there be a requirement to reassess eligibility, the PI or study coordinator may withdraw the participant if they do not meet the inclusion/exclusion criteria.

7.10 End of trial

The third study visit (3 to 6 months after the second eye cataract surgery) is the last contact with the participant. Upon completion of the last study visit for all 140 recruited participants (unless they have withdrawn) will be the end of the trial.

8. TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

Arms	Product name	Further information
Intervention arm	**Monofocal Toric IOLs: Zeiss AT TORBI**	This is a CE marked medical device which has market approval and is being used according to its intended use
Control arm	**Standard Monofocal non-Toric IOLs: Zeiss CT ASPHINA**	This is a CE marked medical device which has market approval and is being used according to its intended use

8.2 Regulatory status of the device

Control arm: Zeiss monofocal intraocular lens. This has a marketing authorisation (MA) in the UK and is being used in its marketed presentation and packaging bearing the MA number.

Intervention arm: Zeiss Toric intraocular lens. This has a marketing authorisation (MA) in the UK and is being used in its marketed presentation and packaging bearing the MA number.

Both IOLs are regulated by the Medicines and Healthcare products Regulatory Agency UK (MHRA) and compliant with both the Medical Devices Regulations 2002 (SI 2002 No 618, as amended) and the General Product Safety Regulations 2005 (SI 2005 No 1803). Although Toric IOLs are not used in UHP but the PI has used both IOLs for cataract surgeries in other hospital in UK.

8.3 Product Characteristics

Products	Characteristics
Monofocal Toric IOLs: Zeiss AT TORBI	Monofocal Toric IOLs with bitoric and aberration-neutral design offering precise correction of astigmatism and achieving spectacle-free distance vision. It is made of hydrophilic acrylic material with hydrophobic surface properties. It is a one-piece plate-haptic construction with four-point fixation for exceptional rotational stability. It is implanted into the capsular bag of the eye through a small incision.
Standard Monofocal non-Toric IOLs: Zeiss CT ASPHINA	Standard monofocal IOLs used in most of the cataract correction surgery. Similar to the Toric, it is made of hydrophilic acrylic material with hydrophobic surface properties. It is also a one-piece plate-haptic construction with four-point fixation and is implanted into the capsular bag of the eye through a small incision.

*Link to technical specifications of all model of Zeiss IOLs https://www.zeiss.com/content/dam/med/ref_international/products/iols-injectors-bss-ovd/ovd/pdf/iol-ovd-portfolio.pdf

8.4 Device storage and supply

The funder Carl Zeiss will supply both Monofocal non-Toric IOLs and Toric IOLs required for this study free of charge to the REI of the UHP. The PI will have a specific order portal from Carl Zeiss to order IOLS according to pre-surgery assessment data. The IOLs will then be sent to REI directly and handled in similar way as other IOLs used in cataract surgery. The IOLS will be stored as recommended on the packaging and requires nothing different than any other brand of IOLs used at the REI.

All individual IOLs are supplied sterile, non-pyrogenic in its own sterilization pouch. Sterility is assured provided the sterilization pouch seal has not been compromised or the pouch has not been punctured.

8.5 Preparation and labelling of device

The PI and his ophthalmologist team are responsible for calculating the IOL power and select the specific IOL as indicated on the individual IOL packaging. The preparation of the IOLs used in this study will be the same as other IOLs used in routine cataract lens replacement surgery.

The surgeons (PI and his team) need to check the label on the lens box for proper lens model, dioptric power and expiration date. After verification of the dioptric power of the lens after opening, the lens will be removed from the pouch and transfer in a case to a sterile environment. Prior to the actual folding process, the lens should be handled by the haptic portion only. The lens needs to be rinsed thoroughly using sterile intraocular irrigating solution. Then, the lens can be oriented for insertion.

8.6 Cataract schedules

Each eye will be implanted with one IOL in the capsular bag and two separate occasions. PI reported at the time of writing this protocol, the second eye cataract surgery would be scheduled at around four months after the first eye surgery.

Orientation of the IOLs will be checked before and after implantation of IOLs by the ophthalmologists as part of routine care. The PI has extensive experience using Toric IOLs for cataract surgery, they communicated that the cataract surgery using Toric IOLs usually took five to eight more minutes because it took longer time to put in and to ensure the axis of the lenses were in a precise position for correction of astigmatism.

9. SAFTEY REPORTING

9.1 Definitions

Term	Definition
Adverse Event (AE)	Any unfavourable sign, symptom, or disease in a participant, regardless of severity and regardless of cause.
Adverse Device Effect (ADE)	All untoward and unintended responses to a medical device. The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect. This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.
Serious Adverse Event (SAE)	A Serious Adverse Event (SAE): • results in death • is life-threatening* • requires inpatient hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability/incapacity • is a significant or important medical event *The term "life-threatening" in this context refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. **Hospital admissions for elective procedures will not be reported as SAEs. All unplanned hospital admissions will be reported as SAEs, regardless of duration of hospital stay. This includes visits to ED departments. **NOTE** Device deficiencies that might have led to a serious adverse event where a suitable action had not been taken or an intervention had not been made or if circumstances had been less fortunate are handled under the serious adverse event reporting system.
Suspected Serious Adverse Device Effect (SADE) / Serious Adverse Reaction (SAR)	An Suspected Serious Adverse Device Effect (SADE)/ Serious Adverse Reaction (SAR) which has previously been identified in the study protocol that results in: • Death • Life threatening illness or injury • Hospitalisation or prolongation of existing hospitalisation.

	• Persistent or significant disability or incapacity. • Foetal distress, foetal death or congenital anomaly or birth defect. • Is otherwise considered medically significant by the Investigator All cases judged by either the reporting medically qualified professional or the sponsor. Any hospitalisation planned prior to enrolment is not a SADE.
Unanticipated Serious Adverse Device Effect (USADE)	Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

9.2 Responsibilities

A sponsor or investigator may take appropriate urgent safety measures in order to protect research participants against any immediate hazard to their health or safety, without prior authorisation from a regulatory body.

The CI takes primary responsibility for the conduct of this study. They will also lead and manage all investigators of this study and coordinate with the sponsor. They are responsible for the adherence and implementation of safety reporting relating to the study visits at the UoP (PAHC building).

The PI is responsible for management of the participant recruitment and clinical interventions at the UHP site. The PI is also responsible for the adherence and implementation of safety reporting relating to the cataract surgery, clinical care or at the site of REI of Derriford Hospital and for coordination with CI.

9.3 Reporting of AEs and ADEs

Only the following AE's occurring during the study, observed by the investigator or reported by the participant will be recorded on the CRF.

- AE's related to the treatment, but not including well known side effects due to eye drops such as blurriness.
- AE's associated with falls.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device will be assessed by a medically qualified investigator and will be followed up until resolution, or the event is considered stable. Any events continuing at the end of the study will be followed up by the participants GP and/ or the routine clinical care team until discharge. This will apply to participants who withdraw from the study.

9.4 Recording and reporting of SAEs, SADEs and USADEs

This study uses CE marked devices and is not regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). All SAE/SADE/UADEs need to be reported to the sponsor R&D **within one working day** of the investigator team becoming aware of them. The Chief Investigator will assess the event for expectedness using the current study protocol, see section 9.5 Known (expected) complications associated with Toric IOL surgery.

Reports of related and unexpected SAEs/ SADE's should be submitted by the Sponsor to ethics within 15 days of the Chief Investigator or Principal becoming aware of the event, using the SAE report form for non-CTIMPs published on the HRA website.

All reporting to R&D should be by e-mail the Research Governance Manager (RGM) or their Deputy giving as much information about the incident as possible.

The RGM will undertake an initial review of the information. Events will be followed up until resolution, any appropriate further information will be sent by the research team in a timely manner. Any events continuing at the end of the study will be followed up by the participants GP and/ or the routine clinical care team until discharge. This will apply to participants who withdraw from the study.

Reporting to the Manufacturer will be done in liaison with the Chief Investigator.

The Manufacturer has a legal obligation to report all events that need to be reported to the Nominated Competent Authority immediately (without any unjustifiable delay) if a link is established between the event and the device, but no more than:

- 2 days following the awareness of the event for Serious Public Health Threat.
- 10 days following awareness of the event for Death or unanticipated serious deterioration in health.
- 30 days following the awareness of the event for all other event meeting the SAE criteria.

In the event of an accident, incident or near miss relating to cataract surgery or clinical care or happens at the Derriford Hospital, in addition to previous reporting requirements, the recording and reporting should follow the Incident Management Policy of the University Hospitals of Plymouth NHS Trust. The PI or need to report *via* UHP Datix and notify the CI and Sponsor.

In addition, all accidents, incidents, near misses during study visit at PAHC building of UoP must be reported following the Universities internal procedures. The CI will assess the seriousness of the event for reporting to the Health and Safety Department according to the Health and Safety Policy of the University and notify the sponsor and PI.

9.5 Known (expected) complications associated with Toric IOL surgery

Intraoperative risks

- Anterior segment bleeding
- Posterior capsular rupture
- Zonular dehiscence
- Incomplete continuous curvilinear capsularhexis
- Severe iris/corneal Trauma
- Anterior vitrectomy

Post-operative complications:

- endophthalmitis (inflammation of the internal eye tissues, most commonly caused by an infection) and bleeding.
- irregular astigmatism
- dry eye
- keratectasia (progressive myopia, irregular astigmatism, ghosting, fluctuating vision and problems with scotopic vision. The progression leads to severe loss of corrected visual acuity)
- Patient reported subjective complaints of halos, glare, and ghost images.
- Wound leak
- Flat anterior chamber
- Hyphema
- Vitreous in anterior chamber
- Vitreous in wound

- Raised IOP
- Pupillary block
- Anterior synechiae
- Posterior synechiae
- Deposits on IOL
- Fibrin in Pupil
- Nuclear remnants
- Cortical Remnants
- Retinal detachment
- Cystoid macular oedema
- Anterior capsular Opacification
- Posterior capsular opacification
- Intraocular lens tilt and decentration
- Cells/flare in the anterior chamber

Toric IOLs have a few other potential complications. Astigmatism may be overcorrected or under-corrected.

As mentioned previously, the Toric IOL may rotate off-axis. There will be some partial effect if it rotates off-axis. For example, the correction effect of the Toric IOLs is reduced by 10% for every 3^{o} rotation off-axis. For the lens to lose its full effect, it would have to be off axis by 30^{o}. Prevention of IOL rotation includes complete removal of Ophthalmic Viscosurgical Devices (OVDs), especially posterior to the IOL.

Most patients do extremely well following this surgical technique. The technical surgical learning curve for the surgeon is minimal for an outcome that is reliably predictable. Toric IOLs, exclusively or in conjunction with astigmatic keratotomy and/or strategic cataract incision placement, can result in excellent management of astigmatism.

9.6 Notification of deaths

Any study death in relation to the cataract surgery should be reported by the corresponding surgeon and CI, following the *Care of Deceased Patient Policy* of the UHP. The study sponsor must also be notified as per the reporting of SAEs, SADEs and USADEs in 9.3.

9.7 The type and duration of the follow-up of participants after adverse reactions.

All adverse events must be followed-up until resolution or death of the participant. Any events continuing at the end of the study will be followed up by the participants' GP and/ or the routine clinical care team until discharge.

9.8 Reporting urgent safety measures

The investigator and sponsor have the authority to deviate from the protocol if doing so relates to the immediate safety of a participant, where continuing to follow protocol would put that participant at risk. This is classed as an urgent safety measure and must be reported to REC immediately and in any event within three days, in the form of a substantial amendment, that such measures have been taken and the reasons why.

10. STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

Sample size test calculation was carried out with the G*Power 3.1 program (Faul *et al*., 2007) for comparison of the main outcome measure of dynamic balance (between IOL design) using mixed ANOVA (repeated measures, between factor being the type of IOL).

Based on of the dynamic balance measurement (JERK score) in a previous study (Mancini *et al*., 2011) an estimated medium effect size (0.25) will be used. With a power of 85% and level of significance (p) set at 0.05 and effect size of 0.25, 55 participants will be required in each group (Monofocal *vs* Toric IOL). Accounting for a 20% drop out rate, 70 participants will therefore be recruited in each group (A total of 140 participants).

10.2 Planned recruitment rate

140 participants will be recruited over three-year period (minimal sample size of 110 plus 20% drop out rate estimation)

According to latest data from the National Ophthalmology audit database by the Royal College of Ophthalmologists, the REI of UHP performed 2525 cataract between 1st of September 2018 to 31st August 2019. The PI who performed cataract surgery at the REI reported around 3000 cataracts surgery were performed last year and the number is estimated to be similar this year. Due to COVID, there were longer waiting list and the waiting time between first and second cataract surgery at UHP has increased to about 4 months.

Approximately 40% patients undergo cataract surgery on both eyes (Jaycock, 2009 #281) (Day, 2015 #282). Among patients eligible for cataract surgery in NHS, 42% were reported to have mild to moderate astigmatism (>1.0 D) (Day, 2019 #283). Therefore, it is estimated about 500 patients at REI annually will meet the inclusion criteria (needing cataract surgery in both eye with mild-moderate astigmatism) and our target for 140 participants out of the potential 1500 patients over three year

should be a feasible number (10% of potential eligible patients), especially with the increasing number of cataract surgeries done every year.

10.3 Statistical analysis plan

All data will be assessed for normality using a combination of assessing histogram plots and the Shapiro-Wilks Normality Test. Descriptive summary statistics for outcome measures relating to vision (acuity and refraction) will be recorded as mean +/- standard deviation.

Mixed ANOVA and post-hoc Bonferroni tests will be used to determine the statistical differences in the baseline characteristics and outcome measures between the Toric monofocal IOLs group and the non-Toric monofocal IOLs group. The between-subjects factor would be type of IOL lens and the within-subjects factor would be time (pre-surgery *vs* post-surgery). Level of significance will be set at 0.05.

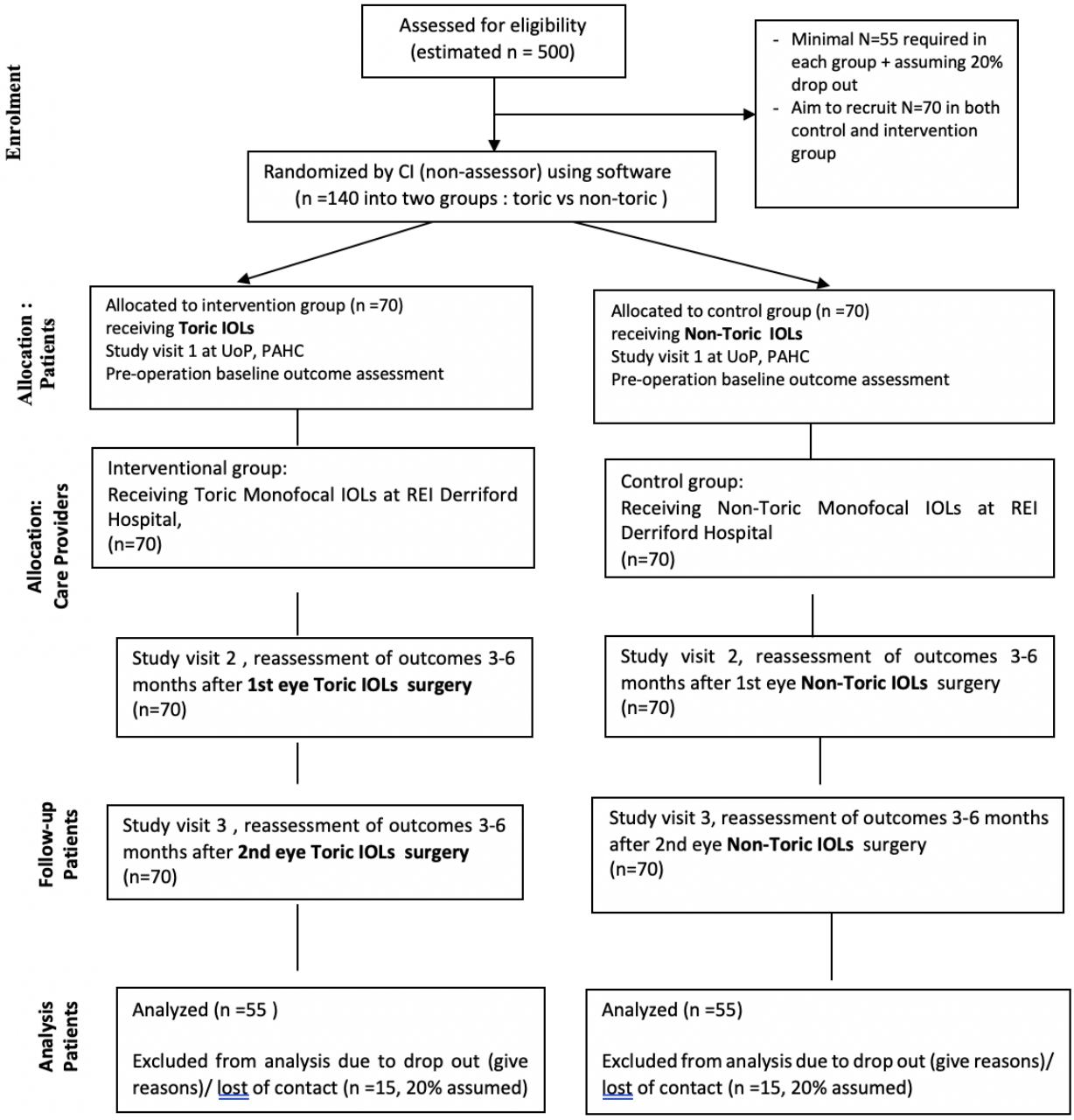
10.3.1 Summary of baseline data and flow of patients

Randomization	Sample size calculation with the G* Power 3 program N=140	Randomization list generated in MS Excel at the commencement of the study by the Chief investigator: independent of assessment and intervention	Execution- randomization list will be held by the PI (ophthalmologist at REI) so that they know who is allocated into either the intervention or control groups according to the list.
Outcome measures		**Trial description**	**Outcome recorded**
Primary outcomes Dynamic stability	**1.Eye gazing characteristics**	Gazing duration on obstacles during the obstacle negotiation. Area of interest and corresponding glazing duration during stair walking	1. Gazing duration and frequency on obstacles and area of interest. 2. Heat map on area of interest from eye tacking device all data will be recorded and saved in file name in the format: participant number-obstacle-trial1/2/3-date.
	2.Movement biomechanics	-participants perform Timed up and go (TU&G) test involving getting up from chair ,then walking over 3m level ground, turning and walking back to sit down on the chair - participants walk over a 3m level ground with obstacles of different contrast colour to background. - accelerometers of head tilting and change in movement of centre of gravity will be recorded during TU&G test and during crossing over obstacles.	1. accelerometers data of change in head tilting and centre of gravity will be recorded 2. Duration in seconds of TU&G test all data will be recorded and saved in file name in the format: participant number-obstacle-trial1/2/3-date.
Secondary outcomes	**1.Refraction and visual acuity**	-standardized protocol for routine visual function test	-vision 20/20, sphere cylinder, axis -DVA, NVA -IOL rotation (for Toric IOL group only)
	2.Questionnaire	Short Fall Efficacy Scale International Fear of Falling Questionnaire CAT-PROM 5 Quality of life Questionnaire	

- *A CRF form has been prepared for this study*

Modified CONSORT flow diagram
for

Vision and balance changes using after bilateral implantation of Toric versus non-Toric intraocular lenses in Cataract patients with astigmatism



Cite as: Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017 Jul 4;167(1):40–7.

10.3.2 Primary outcome analysis- Dynamic stability in three functional activities

The following outcomes will be collected at three time points: before surgery, 3 to 6 months after first and second eye surgery.

Outcome measures	Data collected	Data type/ details	Quantitative Statistical Analysis
Dynamic stability during turning, obstacle crossing and stair walking	Accelerometers data (angular position and acceleration) of change in head tilting and centre of mass will be recorded Performance of TU&G test	Interval Centre of mass and head movement will be calculated using ProMove 3D (Inertia Technology, The Netherlands) and MATLAB. The angular position, velocity and acceleration of the sensors will be tracked on each participant Duration in seconds of TU&G test	The average reading of the 3 trials in each functional activity will be calculated. Mixed ANOVA and post-hoc Bonferroni tests will be used to determine the differences between the Toric IOLs group and Monofocal IOLs group before surgery and 6 months after second eye surgery.

10.3.3 Secondary outcome analysis

Outcomes	Data collected	Data type	Quantitative statistical Analysis
Eye glazing characteristics during obstacle crossing and stair walking	Gazing duration on obstacles and area of interest on environment during stair walking Area of interest determined by heat map (area with highest frequency of gazing)	Interval Gaze pattern of location of hotspots and duration of gaze will be collected using Tobii pro eye tracker. % time spent on fixation of highlighted object or area of interest Best performance among 3 trials will be used.	Mixed ANOVA and post-hoc Bonferroni tests will be used to determine the differences between the Toric IOLs group and Monofocal IOLs group before surgery and 6 months after second eye surgery.
Refraction and visual acuity	-Visual acuity (vision, sphere, Cylinder, Axis, DVA, Add NVA) -IOL tilt and decentration -IOL rotation (for Toric IOL group only)	Interval Average tilt, decentration and rotation of lens will be analysed by calculating average value in Toric and monofocal groups. Bland Altman will be used to study the agreement of position-level of error for IOLs tilt, decentration and rotation.	Mixed ANOVA and post-hoc Bonferroni tests will be used to determine the differences between the Toric IOLs group and Monofocal IOLs group before surgery and 6 months after second eye surgery. Unaided and aided distance visual acuity will be recorded in Log MAR and comparisons between the two lenses pre and post cataract surgery will be conducted using a two-way ANOVA. Post-operative refractive astigmatism will be analysed using the Alpins method*. Correlation between SIA and TIA will be assessed, and dependent t-tests will be used to analyse the remaining metrics in the two groups
Questionnaire	Short Fall Efficacy Scale International	Ordinal (non-parametric)	Mixed ANOVA and post-hoc Bonferroni tests will be used to determine the differences between the Toric IOLs group

	Fear of Falling Questionnaire CAT-PROM 5 Quality of life Questionnaire		and Monofocal IOLs group before surgery and 6 months after second eye surgery.

*Post-operative refractive astigmatism will be analysed using the Alpins method. Cylindrical power and axis will be converted to vectors (J0 and J45; Equations 1 &2).

Equation 1: Calculation of J0	$J0 = J\cos 2\alpha$ J0 = cylindrical effect at 180° J = cylindrical power a = axis in radians
Equation 2: Calculation of J45	$J45 = J\sin 2\alpha$ J45 = cylindrical effect at 45° J = cylindrical power a = axis in radians

Target induced astigmatism (TIA) is the astigmatic correction predicted to occur and will be calculated with Equation 3.

Surgically induced astigmatism (SIA) is the astigmatic correction achieved post-operatively and calculated as Equation 4.

Equation 3: Target induced astigmatism	$TIA = \sqrt{((PreOp\ J0 - Predicted\ residual\ J0)2 + (PreOp\ J45 - Predicted\ residual\ J45)2)}$
Equation 4: Surgically induced astigmatism	$SIA = \sqrt{((PreOp\ J0 - PostOp\ J0)2 + (PreOp\ J45 - PostOp\ J45)2)}$

The Correction index (CI) is the ratio of SIA to TIA (Equation 5) and difference vector is the difference between TIA and SIA (Equation 6).

Equation 5: Correction Index	$CI = \frac{SIA}{TIA}$
Equation 6: Difference Vector	$Difference\ Vector = TIA - SIA$

10.4 Subgroup analyses

Within the Toric IOLs group, a subgroup of participants presented with post-surgery IOL rotation > 5 degree will be isolated to compare the outcomes. This subgroup of participants is very likely to need

another adjustment surgery. Their data will inform the impact of IOLs rotation on surgery complications and whether such rotation may be related to degree of astigmatism.

In both the Toric IOLs and non-Toric IOLs group, subgroups of different degree of astigmatism: mild (<1.50), moderate (1.5-3.0) and severe (3.0+) will be differentiated to compare the outcomes to help inform if Toric IOLs offer similar beneficial effect across cataract patients with wide range of astigmatism. This will help to identify which patients should be referred for Toric IOLs and support evidence-based practice.

10.5 Participant population

Participants will be adult cataract patients of any sex, aged 50 years or above with astigmatism >1.0D who have already consented for bilateral cataract correction surgery at the REI of Derriford Hospital.

10.6 Procedure(s) to account for missing or spurious data

If the participants miss the study visit appointment without notification, they will be contacted for two more attempts within two months of the planned visit date. A letter of notification will be sent to their home address and if they have not replied within four weeks, they will be withdrawn from the study and any related data will be discarded.

11. DATA MANAGEMENT

11.1 Data collection tools and source document identification

A case report form (CRF) has been prepared for this study to record the participants' data collected during the three study visits. The CRF data will be used to perform statistical analysis and aid audit of data during and after the trial.

Printed copies of CRF will be used in the three study visits for data collection. An electronic copy will be made and stored in a designated folder of the MS OneDrive provided and maintained by the UoP. All study data will be recorded in pseudonymised form using designated participant identification code. Access to the drive is password protected and limited to the research team. All original singed pseudonymised CRF will be stored in a designated and lockable cabinet at the Optometry department of the UoP and the informed consent forms will be stored separately in another designated lockable cabinet to minimize risk of exposing participant identity.

Guidance can be found here:

http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/08/WC500095754.pdf

11.2 Data handling and record keeping

All research team members of this study are registered medical or Allied Health Professionals who have completed update training on the Data Protection legislation including the General Data Protection Regulation (GDPR) and bounded by a code of conduct. The UHPNT and UoP both have their own policy to ensure compliance of data protection and their own IT team to support electronic system for data storage. Password protected laptop and MS OneDrive will be provided by the UoP and maintained by their IT team. A lockable filing cabinet in a locked room at the Optometry department of the UoP will be provided to store any paper records containing participant data.

11.3 Access to Data

Direct access will be limited to the research team members (CI, PI and co-investigators). Further access will be granted to authorised representatives from the UoP, UHP and the regulatory authorities to permit study related monitoring, audits, and inspection in line with participant consent.

11.4 Archiving

At the end of the study, electronic data files will be share with UHPNT for archiving using MS OneDrive. All original documents and data files will be detained and archived for 10 years in line with Trust policy.

12. MONITORING, AUDIT & INSPECTION

The study will be subject to monitoring by UHP under their remit as sponsor to ensure adherence to the UK Policy Framework for Health and Social Care Research (2017). First routine monitoring visit will occur within approximately 30 days of local R&D Confirmation of Capacity and Capability. The subsequent level of monitoring will be determined by a risk assessment, or on a for cause basis. The study may also be audited/ inspected by regulatory bodies to ensure compliance with national regulations.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review& reports

- Before the start of the trial, sponsorship approval will be sought from and the UHP and HRA approval will be obtained through the Integrated Research Application System (IRAS) system.
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial.
- All correspondence with the REC will be retained in the Trial Master File/ Investigator Site File
- an Annual Progress Report (APR) will be submitted by the CI to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended
- the CI will notify the REC of the end of the study
- if the trial is ended prematurely, the CI will notify the REC, including the reasons for the premature termination
- within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC

13.2 Peer review

The research protocol has been reviewed by the funder, Carl Zeiss Meditec AG. The study is also part of PhD project of Ms Sherrie Choy under the UoP and the research protocol has been reviewed by independent reviewer Dr Antonio Del Aguila-Carrasco who is a lecturer in Optometry and have expertise in IOLs research methodology and statistics. The research methodology and statistics have been reviewed by Prof Victoria Allgar, Director of the Peninsula Clinical Trials Unit (PenCTU) of the UoP.

13.3 Public and Patient Involvement

A Public and Patient Involvement (PPI) has been included at the protocol development stage. A total of seven participants were involved in the PPI to comment on the proposed study. A summary report can be found in appendix 16.4

This study follows on directly from previous research and is similar in structure to the clinical trials on IOLs conducted by the research team. We have evaluated the use of these lenses at UHP which demonstrated excellent visual outcomes following Toric implantation:

Swampillai AJ, Khanan Kaabneh A, Habib NE, Hamer C, Buckhurst PJ. (2020) Efficacy of toric intraocular lens implantation with high corneal astigmatism within the United Kingdom's National Health Service. Eye 34 (6) 1142-1148.

With regards to similar randomised clinical trials, our experience comes from a very similar RCT with the same recruitment strategy and number of follow ups. The study has been published last year as shown in the reference below.

Law EM, Aggarwal RK, Buckhurst H, Kasaby HE, Marsden J, Shum G, Buckhurst PJ. (2020) Visual function and subjective perception of vision after bilateral implantation of monofocal and multifocal IOLs: a randomized controlled trial. Cataract Refract Surg. 2020 Jul;46(7).

Cataract surgery is a positive experience. Regardless of the arm that the participant is randomised to, they will have good visual outcomes following removal of the cataract. Our previous experience of IOL RCTs have been that participants have a positive experience and that we have few dropouts.

13.4 Regulatory Compliance

- The study will not commence until a HRA research ethics have been granted
- All the data will be handled in line with GDPR
- This research project will follow the standard operating procedure of the sponsor and be regulated by their R&D team throughout the study period.
- This research project will also need to comply with the research governance and ethics standard of the UHP.

13.5 Protocol compliance

- Participants not meeting the eligibility criteria specified in the trial protocol will not be recruited to the study.
- Should any accidents happen at any time during the study visits, they will be adequately documented on the accident report forms and reported to the CI and the sponsor UHP, in compliance to the Incident Management Policy of the UHP.
- Deviations from the protocol which are found to frequently recur are not acceptable and will require immediate action and could potentially be classified as a Serious Breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "Serious Breach" is a breach which is likely to effect to a significant degree –

a) on the safety or physical or mental integrity of the participants of the trial; or
b) on the scientific value of the trial or
c) on the rights of trial participants

- the sponsor and research committee of the UoP will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor will notify the licensing authority in writing of any serious breach of
  a) the conditions and principles of GCP in connection with that trial; or
  b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

13.7 Data protection and patient confidentiality

The CI, PI and all co-investigators have completed update training in Good Clinical Practice (GCP) by NIHR and must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing, and disclosure of personal data.

The study data collected for each participant will be pseudonymised, each participant will be assigned a unique study number upon being recruited for the study. The participants identifiable information i.e. name, DOB, address and contact details will be separately kept from the study data, on a UoP computer, only accessible by the researchers of this research project (a copy will be held by the PI at UHP). The password protected encrypted laptop and MS OneDrive will be provided by the UoP and maintained by their IT team. A lockable filing cabinet in a locked room at the Optometry department of the UoP will be provided to store any paper records containing participant data.

At the end of the study, all data will be transferred to the sponsor, UHP, and stored for 10 years in line with Trust policy.

UHP will be the Data Controller for this study, responsible for the management and oversight of the data. The UoP will be the Data Processor. The CI, Professor Phillip Buckhurst of the UoP will be, responsible for ensuring that identifiable and pseudonymised information are handled and managed

appropriately. The study coordinator is delegated the task of day-to-day management of data within the study.

All members of the research team have a shared responsibility for ensuring the confidentiality of the data and that it is handled appropriately in accordance to Data Protection legislation.

13.8 Financial and other competing interests for the CI, PIs at each site and committee members for the overall trial management

The funder, Carl Zeiss Meditec AG, is a commercial company. They are one of the NHS approved IOLs supplier but do not supply the cataract clinic of UHP at the time of writing this protocol. The funder supplied IOLS for this research project, a full-time PhD studentship, travel subsidy for patients' study visit and expenses for research presentation in conferences. The CI, PI and other co-investigators have no other financial interest for the research activities.

13.9 Indemnity

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

The PI is an ophthalmologist, and all co-investigators are allied health professional, they all have their additional professional liability insurance with their professional governing body for clinical negligence and public liability insurance.

If a SAE happens during any of the three study visits (on the University site), it has to be reported formally to the study CI, Professor Phillip Buckhurst, to assess the seriousness and causality, if deemed to be serious it must be reported to the Study Sponsor within 24 hours and would trigger a Serious Incident Requiring Investigation (SIRI) by the University. Additionally, the Optometry department of the UoP is responsible for any insurance claim regarding loss or damage to equipment used in the three study visits at their campus.

UoP has in force an insurance for Professional Negligence indemnity for research and consultancy service. It also has in force an employer's and public liability insurance to cover activities on campus.

https://www.plymouth.ac.uk/about-us/university-structure/service-areas/procurement/insurance-certificates

13.10 Post-study care

No further follow up will be required from the researcher after the third study visit. The participants will be continued their usual care.

Information about the intervention, benefits, risk and right of the participants will be outlined in the PIS with contact details to the chief investigator or study coordinator. A copy of PIS will be retained by the participants.

13.11 Access to the final study dataset

Direct access will be limited to research team members (CI, PI and co-investigators). Further access will be granted to authorised representatives from the UoP, the R&D offices of UHPNT and the regulatory authorities to permit study-related monitoring, audits, and inspections in line with participant consent.

14. DISSEMINIATION POLICY

14.1 Dissemination policy

The UHP owns the data arising from the study.

The research data will be recorded pseudonymously. The data collected will then be stored in password protected University MS OneDrive for data analysis.

The data will then be analysed by the CI and co-investigators in its pseudonymous form. No identifiable details will be used in any stage of the analysis.

This project is part of a PhD thesis of the study coordinator. The results in anonymous form will be placed in the thesis for publication on the University's library system (PEARL).

A lay summary of study results will be sent to participants.

14.2 Authorship eligibility guidelines and any intended use of professional writers.

Authorship of the content generated by the result will be credited to the research team members: Prof Nabil Habib, Prof Phillip Buckhurst, Ms. Sherrie Choy, Dr Catriona MacLennan, Prof Gary Shum, Dr Hetal Buckhurst and Prof Victoria Allgar, who have shown substantial contributions to the conception and design of this study, analysis and interpretation of data, revising intellectual content critically, writing up for publication and being accountable for all research enquiry and integrity.

The first author will be Ms. Sherrie Choy. She is the PhD student of this study. She acts as trial coordinator and data manager, as well as conducting outcome measure assessments in the study visits.

Corresponding authors will be Dr Catriona MacLennan, who take primary responsibility for communication with the journal during any manuscript submission, peer review and publication process to meet the journal's administrative requirements.

No professional writers will be used in the publication of the study and UHP will be acknowledged in all publications.

15. REFERENCES

ASBELL, PA, DUALAN I, MINDEL J, BROCKS D, AHMAD M, EPSTEIN S. Age-related cataract. Lancet. 2005 Feb 12-18;365(9459):599-609. doi: 10.1016/S0140-6736(05)17911-2. PMID: 15708105.

BLACK, A. & WOOD, J. 2005. Vision and falls. *Clinical and Experimental Optometry,* 88**,** 212-222.

BRIAN, G. & TAYLOR, H. 2001. Cataract blindness: challenges for the 21st century. *Bulletin of the World Health Organization,* 79**,** 249-256.

FAUL, F., ERDFELDER, E., LANG, A. G. & BUCHNER, A. 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods,* 39**,** 175-91.

FOSTER, A. 2001. Cataract and "Vision 2020—the right to sight" initiative. *British Journal of Ophthalmology,* 85**,** 635.

JOHNSON, L., SUPUK, E., BUCKLEY, J. G. & ELLIOTT, D. B. 2013. Effects of induced astigmatism on foot placement strategies when stepping onto a raised surface. *PLoS One,* 8**,** e63351.

KESSEL, L., ANDRESEN, J., TENDAL, B., ERNGAARD, D., FLESNER, P. & HJORTDAL, J. 2016. Toric Intraocular Lenses in the Correction of Astigmatism During Cataract Surgery: A Systematic Review and Meta-analysis. *Ophthalmology,* 123**,** 275-286.

KHAN, M. I. & MUHTASEB, M. 2011. Prevalence of corneal astigmatism in patients having routine cataract surgery at a teaching hospital in the United Kingdom. *J Cataract Refract Surg,* 37**,** 1751-5.

LORD, S. R. 2006. Visual risk factors for falls in older people. *Age Ageing,* 35 Suppl 2**,** ii42-ii45.

LORD, S. R., SMITH, S. T. & MENANT, J. C. 2010. Vision and falls in older people: risk factors and intervention strategies. *Clin Geriatr Med,* 26**,** 569-81.

MANCINI, M., HORAK, F. B., ZAMPIERI, C., CARLSON-KUHTA, P., NUTT, J. G. & CHIARI, L. 2011. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinsonism Relat Disord,* 17**,** 557-62.

MONACO, G. & SCIALDONE, A. 2015. Long-term outcomes of limbal relaxing incisions during cataract surgery: aberrometric analysis. *Clin Ophthalmol,* 9**,** 1581-7.

READ, S. A., VINCENT, S. J. & COLLINS, M. J. 2014. The visual and functional impacts of astigmatism and its clinical management. *Ophthalmic and Physiological Optics,* 34**,** 267-294.

SIDEROV, J., MEHTA, D. & VIRK, R. 2005. The legal requirement for driving in the United Kingdom is met following pupil dilatation. *Br J Ophthalmol,* 89**,** 1379-80.

SWAMPILLAI, A. J., KAABNEH, A. K., HABIB, N. E., HAMER, C. & BUCKHURST, P. J. 2020. Efficacy of toric intraocular lens implantation with high corneal astigmatism within the United Kingdom's National Health Service. *Eye,* 34**,** 1142-1148.

WILKINS, M. R., ALLAN, B. & RUBIN, G. 2009. Spectacle use after routine cataract surgery. *Br J Ophthalmol,* 93**,** 1307-12.

16. APPENDICIES

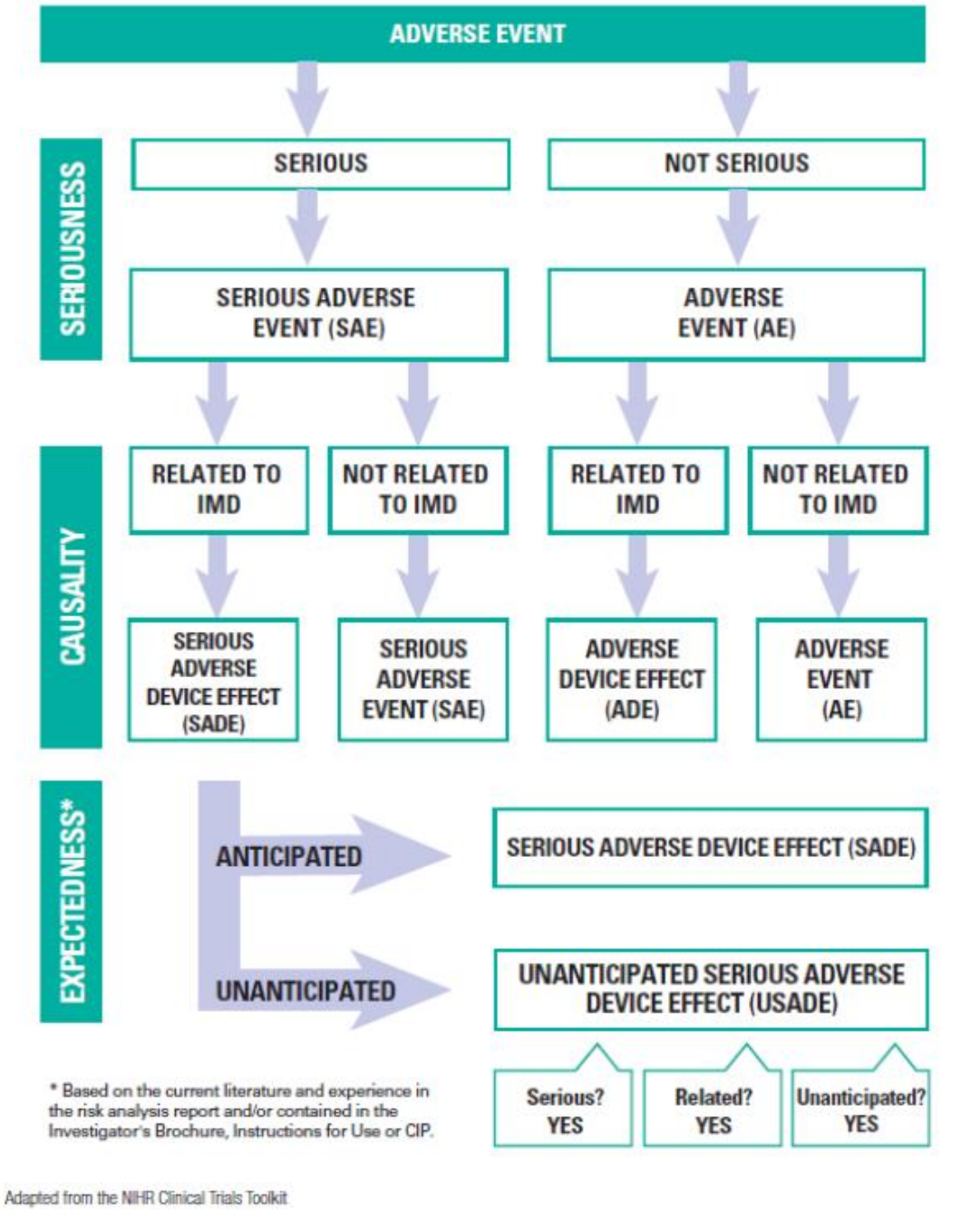
16.1 Appendix 1-Risk

Risks associated with trial interventions A ≡ Comparable to the risk of standard medical care				
Justification: The participants recruited in the study are on the list to receive cataract correction surgery. There is no difference in risk of surgery between Toric and standard intraocular lens. The two additional study visits may cause additional risk due to movement tasks but the additional fall risk would be the same as in any other daily activities as this group of participants are active community dwelling elderly. Briefly justify the risk category selected :				
What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Surgery complication	Eye infection	Usual pre-surgery screening and post-surgery care	1 pre-surgery clinic appointment and at least 2 post- surgery follow up	Risk level: A
Reaction to eyedrops during eye examination	Eye	Eye drops will only be administrated by chartered optometrists. Allergy history will checked again before administering.	Once in each study visits. Two visits in total	Risk level: A
Dynamic stability test	Fall	Mobility assessment will be conducted by experienced physiotherapists. Equipment and environment check will take place prior to start of each testing.	Two study visits.	Risk level: A All participants are ambulatory community dwelling individuals so the risk will be similar to normal mobility activities.

16.2 Appendix 2 - Schedule of Procedures

Procedures	**Visits x3**					
	Screening	**Baseline (study visit 1)**	**Treatment Phase (routine cataract surgery schedule and care)**		**Follow Up after 1st eye surgery (study visit 2)**	**Follow Up after 2nd eye surgery (study visit 3)**
Informed consent	x	x				
Demographics		x				
Medical history	x	x				
General eye examination		x			x	x
Visual function -visual acuity -astigmatism power	x	x			x	x
Eligibility assessment	x					
Randomisation	x	x				
Dispensing of Toric and Monofocal IOLs		x	x	x		
Compliance (IOLs post-op care)			x	x		
Dynamic stability assessment 1. Motion sensor and eye tracking during Timed up & go test (TUG)		x			x	x
Dynamic stability assessment 2. Motion sensor and eye tracking during walking over obstacles		x			x	x
Dynamic stability assessment 3. Motion sensor and eye tracking during stair walking		x			x	x
Risk of fall Questionnaires -Short Fall Efficacy Scale -Fear of falling		x			x	x
Quality of life questionnaire -CAT-PROM5		x			x	x
IOL orientation (Toric IOL only)		x			x	x

16.3 Appendix 3- Safety Reporting Flow Chart



Adapted from the NIHR Clinical Trials Toolkit

16.4 Appendix 4-Summary of Patient and Public Involvement

Patient and public involvement on research project "Vision and balance changes after bilateral implantation of Toric versus non-Toric intraocular lenses in Cataract patients with astigmatism".

Project title: Pseudophakic vision and lifestyle changes after bilateral implantation of Toric versus non-Toric intraocular lenses in Cataract patients with astigmatism

IRAS ID: 286913

Chief Investigator: Prof. Phillip Buckhurst

Principal Investigator: *Prof Nabil Habib*

Collaborators: *Dr Catriona MacLennan, Prof Gary Shum, Dr Hetal Buckhurst, Ms Sherrie Choy*

Date: 28th June-2nd July 2021

Background of study project

Cataract is one of the major causes of visual impairment and blindness in the aging population. In UK, cataract alone accounts for over a third of the cases of vision impairment in those over 75 years. The Royal College of Ophthalmologists estimated around 50% increase in the expected number of cataract operations over the next 20 years. During cataract surgery the natural lens within the eye is removed and is replaced with an artificial lens called an intraocular lens (IOLs). Cataract surgery using standard monofocal IOLs can correct visual error such as short sightedness or long sightedness.

However, these IOLs do not correct astigmatism which refers to the imperfection in the curvature of the cornea- the clear and dome-shaped covering in front of the eye. An eye with severe astigmatism is oval in shape (like a rugby ball) instead of spherical (like a football). This oval shape reduces vision and causes some distortion. Degree of astigmatism is measured in dioptre (D). A perfect eye has zero dioptre. Most people can have between 0.5-0.75 D and people with 1.5D or more typically need to wear contact lenses or eyeglasses for clear vision. Astigmatism can cause impaired vision, which has been shown to reduce quality of life and increase fall risk. It has been reported that around one fifth of people attending for cataract surgery have astigmatism (Swampillai *et al*., 2020). A modern type of IOLs called

Toric IOLs provides an alternative design with correction of astigmatism. The Toric IOLs offers better vision correction and may reduce the need for spectacles for cataract patients with astigmatism. Therefore, full correction of refractive error for cataract patients of any degree of astigmatism using specialized Toric IOL could be a more cost-effective and patient-centred approach.

This study aims to determine if Toric intraocular IOLs, when compared to standard IOLs, provide better visual function, dynamic stability and quality of life. This information has the potential to influence the availability of types of IOLs offered to cataract patients in NHS.

Table 1. PPI for Toric IOLs study using GRIPP 2-SF*

Section and Topic	Item description
1. Aim of the PPI	The project "Pseudophakic vision and lifestyle changes after bilateral implantation of Toric versus non-Toric intraocular lenses in Cataract patients with astigmatism" is a RCT comparing the effect on dynamic balance, vision function and quality of life changes between Toric intraocular lens versus (IOLs) conventional monofocal non-Toric IOLs used in cataract surgery. The aim of the PPI is to obtain comment from cataract patients and general public about the research proposals, intended outcome measures and any other potential practicality of the research implementation before the start of the research and to support research ethics application.
2. Methods	***Public and Patient recruitment:*** 1. <u>Cataract patients awaiting surgery</u> The optometry clinic of University of Plymouth -Centre of Eyecare Excellence (CEE) has been contacted to help recruiting cataract patients who has been referred for cataract surgery. A list of 20 patients referred for cataract surgery in the last six months was obtained. Ten of them had previous consent for further contact for research related activities. Five out of them were successfully recruited for this PPI. They were given a choice for an online group meeting or individual telephone interview and all of them preferred telephone interview.

	2. Post-surgery cataract patient and care One cataract patient who recently had received multifocal IOLS for his cataract surgery seven weeks ago. He and his carer who worked at UOP, attended PPI online zoom meeting with the researcher. 3. Community optometrist One community optometrist from CEE was recruited for face-to-face interview about the research project. 4. Physiotherapist researcher One Physiotherapist researcher who had health research and PPI experience with Multiple Sclerosis patients was interviewed via online Zoom meeting. ***Contents of PPI*** During the interview, all participants were given a short description about the background of the project and the study design including the description of interventions (Toric IOLs) and control (conventional non-Toric IOLs), the randomization of two groups of participants, number and duration of study visits, what happened during the study visits, what data would be collected, any potential risks of intervention and assessments and who were the researchers. They were all offered a copy of the participant information sheets and consent forms to be sent via email. Discussion with participants were focus on the following areas: 1. Views on the design and importance of the study 2. Views on patients being randomly assigned to either one type of intraocular lens in Cataract surgery 3. Views on assessments used study visits 4. Views on the number, length, timing and location of study visits 5. Views on information (PIS and consent form) for potential research participants 6. Views on any other practicality of the research implementation 7. Views on the plan of data collection and analysis

	8. Views on the plan of dissemination of results
3. Results	The PPI for this project included a range of participants: five cataract patients who were awaiting surgery, one recent post-cataract surgery patient, one carer, one local community optometrist and one experienced researcher who has PPI and health research experience. PPI contributed to the study in several areas, including: **1. *Patient information:*** - almost all patients had not heard of Toric IOLs before. In fact, they reported there were not aware of different types of design of IOLs and had not been offered any discussions during their medical follow up. Only one patient who had private ophthalmologist consultation before was aware of Toric IOLs but chose to have non-Toric IOLs at NHS for financial reason. All of them felt the PIS should include details about what was Toric IOLs and how was it different than the conventional one. A few of the patients reported they were particularly interested in the risk and complications. ***2. Research Design and Importance.*** - All participants were supportive of this research project and felt it could provide more evidence about what Toric IOLs could offer and who might benefit from this type of IOLs. One participant who worked in visual arts said she needed perfect eyesight for work, but she was not given any choice about IOLS for her cataract surgery in NHS. She felt our research project was important as it could provide information for patients to make choice whether to go private for the best types of IOLs or to provide evidence so that NHS in the future can provide Toric IOLs to cataract patients. ***3. Practical consideration of the research implementation.***

	- All participants felt one pre-surgery study visit and one post-surgery study visit after cataract surgery were appropriate amount and the duration of 60 minutes was within their expectation. - The planned post-surgery visit was within 6 months after the surgery. The patient who had recent cataract surgery reported he was able to resume his normal daily activities about a week after the surgery and felt it was safe for the post-surgery study visits to take at 3-6 months after the surgery. The community optometrist also reported most complications such as eye infection or wound complication happened in the first month after the surgery and agreed it was appropriate to arrange post-surgery study visit for 3-6 months afterwards. - All participants in this PPI were local and they all know where the Plymouth Marjon University are and had no concerns about taking transport (bus or taxi) or having friends or family to drop off/pick up from there. They all reported this study site was much preferable than hospital site especially due to current COVID situation. - All participants said they would participate in such research project. Although they would not expect any monetary support but felt there were other patients who would be put off due to extra cost and time needed for participation. When mentioned there would be about £20 travel subsidy and they all felt it was enough amount to support commuting or parking. - The health researcher suggested to simplify the subsidy process especially the administrative procedures. She had previous experience with Multiple Sclerosis patients and most of them ended up not claiming due to too many forms to fill. - The initial plan for the study involving potential participants having their vision assessment at the Optometry department at PAHC building and movement assessment at Biomechanics lab. Although both labs are at Marjon Campus, but it involves two sites as the PAHC belongs to

	the University of Plymouth and the Biomechanics lab belongs to the Plymouth Marjon University. The Physiotherapist researcher who are academic staff of the University of Plymouth suggested it was possible to share the biomechanics practical room (FF22) to conduct the movement assessment to reduce the number of sites and travelling for patients. - Eyedrop use of eyedrops is not a worry for all PPI patients but will be helpful to have a consistent advice with local optometry and REI. A copy of post eyedrop care was obtained from the CEE. ***4. Review and communicate the research*** - All participants welcomed the idea of a separate WhatsApp group or email newsletter to maintain contact and keep update about the research progress. - The physiotherapist researcher shared her experience of reducing dropout rate especially when the study duration is long. She said simple update information such as update of number of participants, upcoming events or care advice could really help with group retention and future PPI.
4. Discussion	Following the PPI, the search team had two follow up meetings to discuss the feedback from the participants and any modification needed for the research protocol and patient information. A draft of PPI summary was produced and reviewed during the meeting.
5. Reflection	Actions to be taken following the PPI are summarized as below: 1. Update on the participant information sheet to expand on explanation of what Toric IOLs are and their potential risk. 2. Update the advice about post eyedrop care to be consistent with the Royal Eye Infirmary of UNPNT and CEE of University of Plymouth. No driving and operation of heavy machine after the pupil dilating

	eyedrop and patients should either take public transport or have someone to drive them to and from the study visit appointments. 3. To arrange the dynamic balance assessment at the same building (PAHC) as the visual assessment instead of using Marjon Biomechanics lab to reduce number of study sites and to reduce the amount of walking required by patients during study visits. 4. Post-surgery study visit to be arranged at ***3 to 6 months*** instead of ***after 6 months*** after second eye surgery

*GRIPP2 short form (Staniszewska *et al*., 2017)

The GRIPPS-SF is an international, evidence based, community consensus informed guidelines for the reporting of patient and public involvement (PPI) in research. It aims to provide a consistent and high quality of reporting in PPI. GRIPP2 is available in long form and short form. The short form (GRIPPP2-SF) has been used for this project as the PPI is not the focus of this research project.

References:

BLACK, A. & WOOD, J. 2005. Vision and falls. *Clinical and Experimental Optometry,* 88**,** 212-222.
BRIAN, G. & TAYLOR, H. 2001. Cataract blindness: challenges for the 21st century. *Bulletin of the World Health Organization,* 79**,** 249-256.
FAUL, F., ERDFELDER, E., LANG, A. G. & BUCHNER, A. 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods,* 39**,** 175-91.
FOSTER, A. 2001. Cataract and "Vision 2020—the right to sight" initiative. *British Journal of Ophthalmology,* 85**,** 635.
JOHNSON, L., SUPUK, E., BUCKLEY, J. G. & ELLIOTT, D. B. 2013. Effects of induced astigmatism on foot placement strategies when stepping onto a raised surface. *PLoS One,* 8**,** e63351.
KESSEL, L., ANDRESEN, J., TENDAL, B., ERNGAARD, D., FLESNER, P. & HJORTDAL, J. 2016. Toric Intraocular Lenses in the Correction of Astigmatism During Cataract Surgery: A Systematic Review and Meta-analysis. *Ophthalmology,* 123**,** 275-286.
KHAN, M. I. & MUHTASEB, M. 2011. Prevalence of corneal astigmatism in patients having routine cataract surgery at a teaching hospital in the United Kingdom. *J Cataract Refract Surg,* 37**,** 1751-5.
KHANDELWAL, S. S., JUN, J. J., MAK, S., BOOTH, M. S. & SHEKELLE, P. G. 2019. Effectiveness of multifocal and monofocal intraocular lenses for cataract surgery and lens replacement: a systematic review and meta-analysis. *Graefe's Archive for Clinical and Experimental Ophthalmology,* 257**,** 863-875.
LAURENDEAU, C., LAFUMA, A. & BERDEAUX, G. 2009. Modelling lifetime cost consequences of toric compared with standard IOLs in cataract surgery of astigmatic patients in four European countries. *J Med Econ,* 12**,** 230-7.
LORD, S. R. 2006. Visual risk factors for falls in older people. *Age Ageing,* 35 Suppl 2**,** ii42-ii45.

LORD, S. R., SMITH, S. T. & MENANT, J. C. 2010. Vision and falls in older people: risk factors and intervention strategies. *Clin Geriatr Med,* 26**,** 569-81.
MANCINI, M., HORAK, F. B., ZAMPIERI, C., CARLSON-KUHTA, P., NUTT, J. G. & CHIARI, L. 2011. Trunk accelerometry reveals postural instability in untreated Parkinson's disease. *Parkinsonism Relat Disord,* 17**,** 557-62.
MONACO, G. & SCIALDONE, A. 2015. Long-term outcomes of limbal relaxing incisions during cataract surgery: aberrometric analysis. *Clin Ophthalmol,* 9**,** 1581-7.
READ, S. A., VINCENT, S. J. & COLLINS, M. J. 2014. The visual and functional impacts of astigmatism and its clinical management. *Ophthalmic and Physiological Optics,* 34**,** 267-294.
STANISZEWSKA, S., BRETT, J., SIMERA, I., SEERS, K., MOCKFORD, C., GOODLAD, S., ALTMAN, D. G., MOHER, D., BARBER, R., DENEGRI, S., ENTWISTLE, A., LITTLEJOHNS, P., MORRIS, C., SULEMAN, R., THOMAS, V. & TYSALL, C. 2017. GRIPP2 reporting checklists: tools to improve reporting of patient and public involvement in research. *BMJ,* 358**,** j3453.
SWAMPILLAI, A. J., KAABNEH, A. K., HABIB, N. E., HAMER, C. & BUCKHURST, P. J. 2020. Efficacy of toric intraocular lens implantation with high corneal astigmatism within the United Kingdom's National Health Service. *Eye,* 34**,** 1142-1148.
VISSER, N., BAUER, N. J. & NUIJTS, R. M. 2013. Toric intraocular lenses: historical overview, patient selection, IOL calculation, surgical techniques, clinical outcomes, and complications. *Journal of Cataract & Refractive Surgery,* 39**,** 624-637.
WILKINS, M. R., ALLAN, B. & RUBIN, G. 2009. Spectacle use after routine cataract surgery. *Br J Ophthalmol,* 93**,** 1307-12.

16.6 Appendix 5 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
	V1.0. April 2022	11th April 2022		