NATIONAL STUDY OF PRIMARY INTRAOCULAR LENS IMPLANTATION IN CHILDREN ≤2 YEARS OLD WITH CONGENITAL AND INFANTILE CATARACT

AMEENAT OLUFUNMILOLA SOLEBO

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I, Ameenat Olufunmilola Solebo, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

ABSTRACT

Cataract is a potentially reversible cause of childhood blindness which is responsible for at least 15% of the world's blind children. Primary intraocular lens (IOL) implantation is the most important recent innovation in the management of childhood cataract, and has been widely adopted despite unanswered questions regarding best practice, visual benefits and adverse outcomes.

In order to answer these questions, an epidemiological study was undertaken through systematic, standardised data collection through a national clinical network, the British Isles Congenital Cataract Interest Group.

At the time of submitting this thesis, data are available for 236 children. IOL implantation was undertaken in the majority of children over 6 months old, but aphakia was the preferred option for younger children, due in part to the higher than anticipated frequency of other ocular anomalies.

Overall primary IOL implantation conferred no visual benefit for children with unilateral cataract, but may be associated with better visual outcome following bilateral cataract surgery, whilst increasing the risk of the need for further surgical procedures under general anaesthetic, which may adversely impact on future cognitive development.

16% of all children developed glaucoma during the first postoperative year with age at surgery being the most significant factor. The potential eventual burden of aphakic and pseudophakic glaucoma is considerable, and these findings should encourage debate about the balance between the risk of amblyopia and the risk of glaucoma, as well as future research on this blinding complication

Refractive planning and outcome in early life pseudophakia is highly variable. There is a pressing need for standardisation of refractive planning and continuous national monitoring of refractive outcomes, similar to that which exists in adult cataract surgical practice.

Follow up studies of this unique inception cohort will provide further information on longer term outcomes and their impact on educational and personal development.

ACKNOWLEDGEMENTS

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I am grateful for the support and work of the members of the British Isles Congenital Interest Group, particularly those who piloted the draft study documentation, helped us to recruit children, and who collected data. As my supervisor's supervisor said, if you want something done, ask a busy person.

And I have been incredibly wise in my choice of supervisors. Professor Rahi is all that one could wish for as a manager, a colleague, and a role model – insightful (laser beam gaze!), an effective communicator (able to synthesise complex research themes with a single bound!) and approachable. Ms Russell-Eggitt has been consistently generous with her time, her knowledge and her supportive spirit, and has helped me to maintain the link between this study and the study participants – the children and their families.

I would like to thank the clinical and research staff at the recruiting hospitals, particularly the clinical staff at the Manchester Royal Eye Hospital, Birmingham Children's Hospital, Leicester Royal Infirmary and of course Great Ormond Street Hospital.

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I'll finish off by thanking my friends and family for their support (thank you for the story about the mother turtle and her slow, determined and eventually successful attempts to bury her eggs on a beach in Cyprus, Senay) and their understanding of my necessary neglect of them. Sorry Mark – but it was worth it, no?

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1. INTRODUCTION

Cataract, or clouding of the eye's natural crystalline lens, is a significant and potentially reversible cause of childhood blindness. Early intervention affords children with congenital or infantile cataract the best opportunity of good visual outcome. Following surgical extraction of the lens, the impact of the loss of focusing power on early childhood visual development also necessitates visual rehabilitation through optical correction, which has traditionally been achieved with glasses and / or contact lenses.

Replacement of the lost focusing power using primary implantation of an artificial intraocular lens (IOL) is the most important recent innovation in the management of congenital and infantile cataract. This intervention, originally developed for adults in the seventh and eighth decades of life, is being increasingly adopted for young children despite a paucity of systematic investigations of outcomes. There are unanswered questions regarding the benefits and risks of IOLs in early childhood (children aged 2 years and under), and the safety and efficacy of different surgical techniques.

The aim of the study reported in this thesis is to address these questions through an investigation of the outcomes in a nationally representative inception cohort of children undergoing cataract extraction with or without intraocular lens implantation aged ≤2 years old in the United Kingdom and Ireland.

2. BACKGROUND

Whilst removal of the cloudy lens is essential for the restoration of functional vision in children with visually significant congenital and infantile cataract, intraocular surgery during the first two years of life results in an ‘insult’ to the eye during a critical stage of development of the structure and function of the visual system.

2.1. The anatomy and development of the eye and visual system

The eye can be divided into anterior and posterior segments, with the naturally clear crystalline lens forming the dividing plane (Figure 1).

2.1.a. **The anatomy and pre-natal development of the lens**

The lens consists of an optically optimal arrangement of fibres (Figure 2) within a supportive capsular bag, held in place by equatorial suspension cables, the *ciliary zonules*. Tension on the *capsule*, created by the *ciliary body* muscles and transmitted through the zonules, can change the shape and focusing power of the lens (a process termed *accommodation*).

Figure 1. Anatomy of the eye, shown in sagittal (vertical) section
The lens sits between the anterior and posterior segments of the eye, supported by the zonules (z*).
Modified from image from National Eye Institute library, National Institute of Health

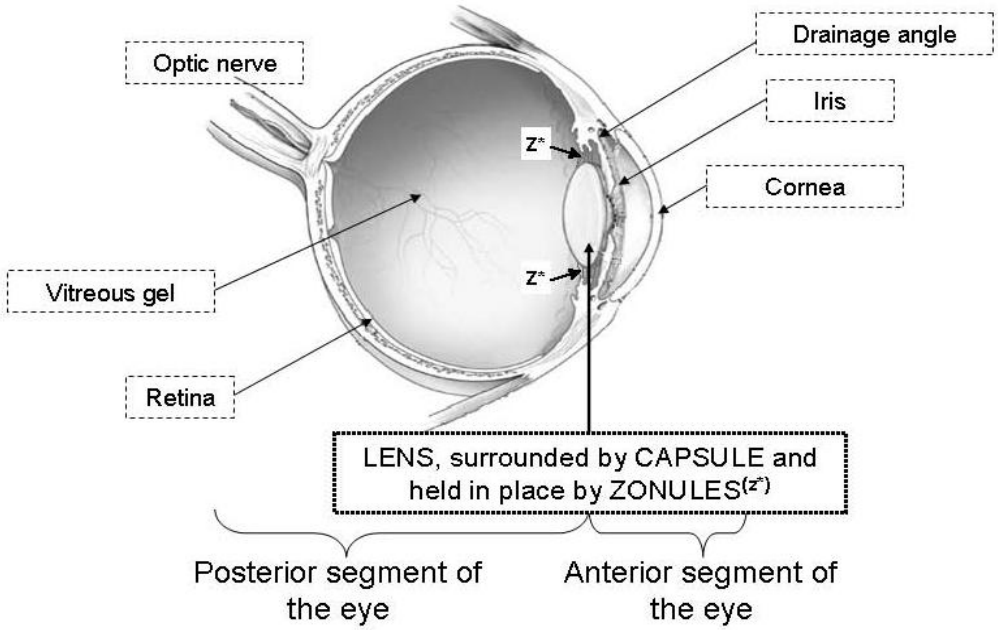
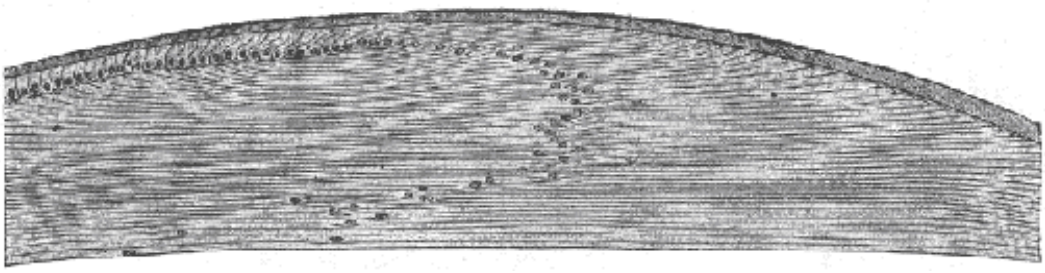
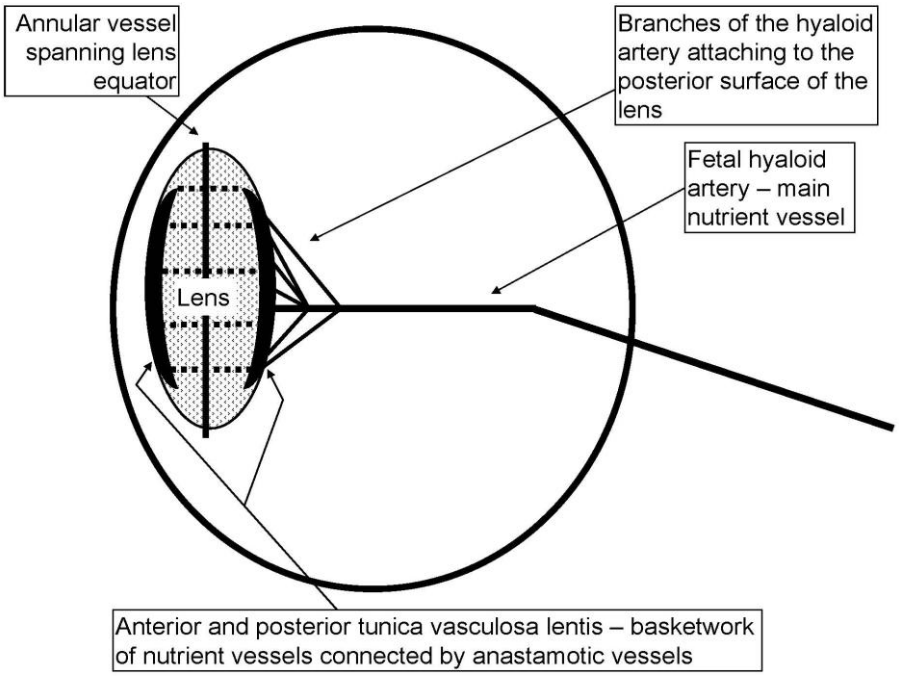


Figure 2. Cross section through the lens
showing migration and lengthening of lens fibres, image courtesy of Apple et al[1]



In humans, the lenses first appear on day 33 of gestation, as vesicles which fill with fibres to become the central lens fetal *nucleus*.[2;3] More lens fibres form beneath the capsule, lengthen and migrate to form the outer lens *cortex.* Fetal nutrient vasculature nourishes the developing lens (Figure 3). These vessels regress in the second trimester, disappearing altogether by birth at term. At term, although the lens is functionally transparent the different lamellae are visible through an examining microscope.

Figure 3. The fetal intraocular vasculature
This anastamotic nutrient network disappears by full term birth.



2.1.b. **The anatomy and development of the anterior and posterior segments**

2.1.b.i. Anterior segment

The most easily visible part of the anterior segment, the iris, is itself the anterior section of the pigmented layer of the eye, the *uvea*, which continues posteriorly as the ciliary body. Whilst the adult iris, seen under magnification, resembles a hilly landscape with deep crypts and flattened peaks, the neonatal iris is flatter and more vascular, and the optically empty centre, the pupil, is smaller.[2;4] Over the first six months of life, the iris muscles mature, and may, as a result, change colour.

The ciliary body is a thick doughnut of tissue lying behind the iris. The ciliary body is not only the effector of accommodation, but also creates and secretes *aqueous fluid*. Aqueous flows into the anterior chamber through the pupil, providing optically clear hydrostatic support as well as nutrition and immunological support.

A transparent dome, the *cornea*, sits atop the anterior segment. The cornea's transparency is again due to optically optimal cellular organisation, supported by the active continuous removal of water and electrolytes undertaken by the innermost layer of cells, the corneal endothelium. The normal adult horizontal corneal diameter is approximately 11.5mm, and this adult size is usually reached within the first year of life.[5]

Internally, the iris and cornea meet at the *iridocorneal angle*. Drainage of aqueous occurs at the angle, through a series of sieves, the *trabecular meshwork*. The internal pressure of the eye, or intraocular pressure, depends on the egress of fluid from the eye. Thus abnormalities of the angle may result in high intraocular pressures, which may then result in destructive changes, negatively impacting on vision. Although studies of fetal ocular development consistently report on the posterior movement of the ciliary body (moving the iris root away from the cornea, thus widening the angle)

and on the differentiation of the trabecular meshwork membranes and development of the post-meshwork vascular drainage channels during the third trimester,[3;6-8] less is known regarding the normal post-natal development of the angle. In neonates, in comparison to children aged over 1 year old, the iridocorneal angle opening is narrower and the trabecular meshwork less differentiated and the angle and the iris are less pigmented. Thus, crucial development of the angle occurs at some point during the first year, but the window of time within which they occur during this period is unclear.[3;9]

2.1.b.ii. Posterior segment

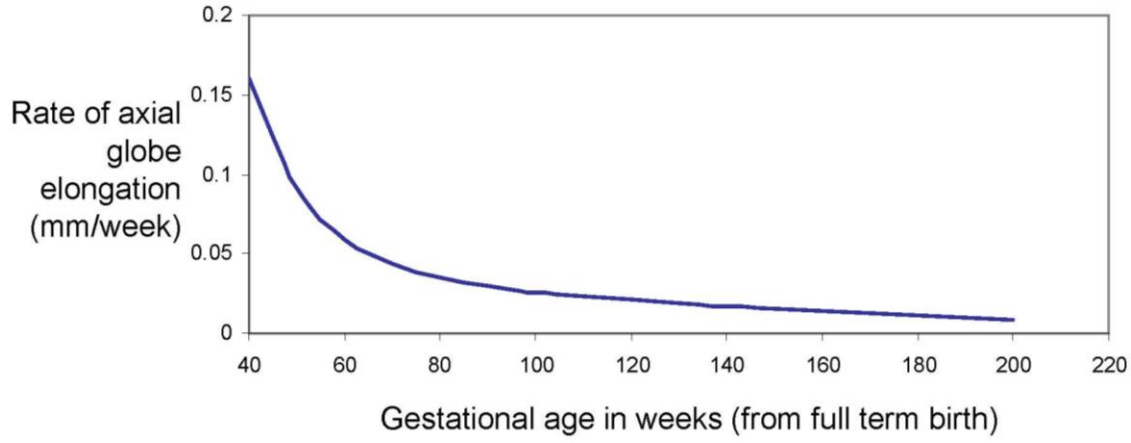
Behind the lens sits the gelatinous *vitreous* hyaloid body. Within the otherwise transparent vitreous gel runs a potential track, the footprint of the main embryological nutrient vessel, the fetal posterior hyaloid artery. The anterior face of the gel lies almost in contact with the posterior face of the lens.[3]

In the frequently used analogy of the eye as a camera, the *neural-retina*, a layer of photosensitive cells at the back of the eye, is the film. At the centre is the fovea, which is responsible for detailed vision. A hierarchical system of cells passes information from the outer to inner retina. The innermost retinal cells, the ganglion nerves, then leave the eye as a cable of fibres. This *optic nerve*, which passes through the apex of the bony orbital socket of the skull, then travels on to the cerebrum.

2.1.c. **The growth and development of the globe in childhood**

The mean axial length of the neonatal eye is 16.8mm, whilst mean adult length is 23mm[10;11] (Figure 4). The majority of this postnatal growth takes place in the first two years of life, with most growth occurring in the first 6 months. Corneal curvature also changes: the cornea becomes flatter with time, with most change occurring over the first 36 months of life.[11] These changing parameters contribute to the early childhood changes in the focusing (refractive) state of the eye

Figure 4. Postnatal growth of the globe
modified from Fledelius.[10].
The majority of postnatal growth takes place in the first two years of life, with most growth occurring in the first 6 months.



2.1.d. **Emmetropisation**

The focusing power of the eye is determined not only by how light rays are bent or refracted by the ocular surfaces (steeper more curved ocular structures bend light more), but also the distance light rays travel between the ocular refracting surfaces and the final focal point at the retina. The essential ocular focal determinants, which all change significantly in the first two years of life, are therefore:

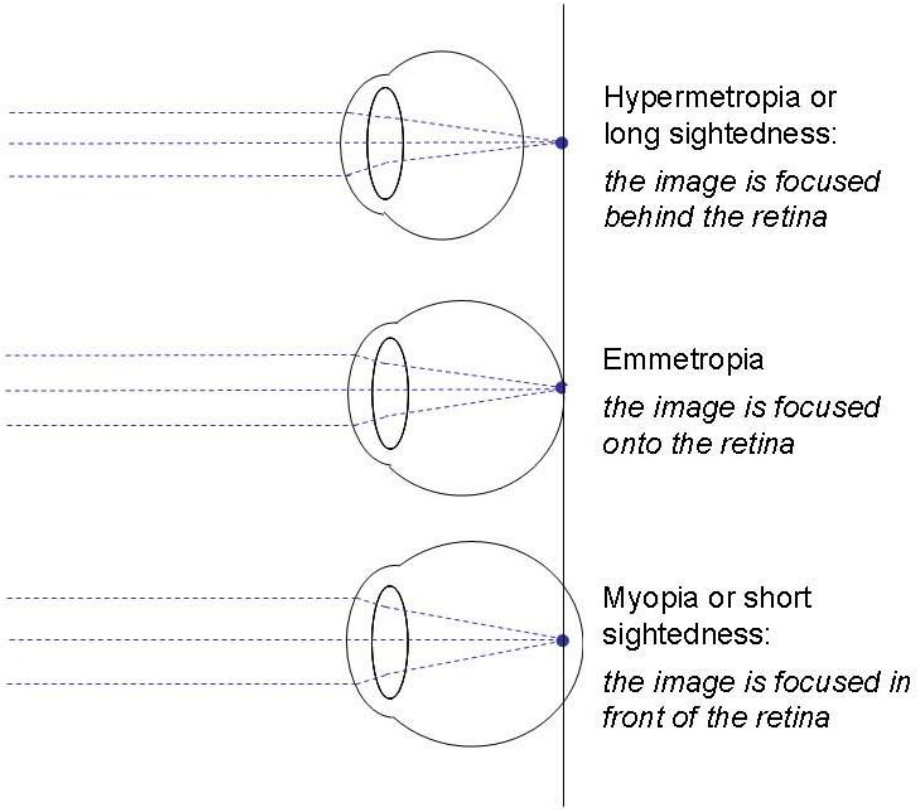
- the curvature of the cornea
- the curvature of the lens
- the axial length of the eye, and within this the distance between the cornea and lens (anterior chamber length or depth) and distance between the lens and the retina.

The ocular focusing power or refractive state of the two eyes of any one individual is usually broadly similar. A significant inter-ocular refractive difference is called anisometropia.

The focusing power of the normal neonatal eye results in a long sighted state of refraction or *hypermetropia*. Over the first 2 years of life, globe elongation and flattening corneal curvature move the focusing system away from *hypermetropia* and towards *myopia*, or short sightedness, with axial elongation playing the primary role. [10-12] Ideally, this 'myopic shift' ends with the eye at emmetropia, a neutral midpoint refractive state (Figure 5). The process is thus termed *emmetropisation.*

Figure 5. Changing refractive (focusing) state with globe elongation

As the eye lengthens axially, the infant eye undergoes emmetropisation, or a 'myopic shift' from an initially hypermetropic state



The factors influencing emmetropisation are not yet fully understood, but animal and human models have shown that whilst it is sensitive to genetic factors,[13] emmetropisation is an active bio-feedback process, with retinal stimulation acting as the sensory component driving the structural changes which result in altered refraction states. Vertebrates reared in complete darkness fail to emmetropise normally.[14] Deprivation of visual form in vertebrates reared with high power lenses (creating unfocused, blurred images)[15;16] and in human infants with form deprivation due to ophthalmic disease also results in abnormal emmetropisation, usually in the form of myopia due to abnormal axial elongation.[17-19] Infants with impaired accommodative responses have been found to be more likely to develop myopia due to axial elongation,[20] and an association exists between childhood refractive error and ciliary

body thickness.[21] Thus there may also be a role for the ciliary muscle in the sensory arc of the emmetropisation process, with poor accommodation inducing blur which drives ocular remodelling.

The effector arms of the emmetropisation process are also unknown. Structural changes may be due to scleral remodelling orchestrated by metalloproteinases[22;23] with primary sites at the posterior pole of the eye[24] and / or the area behind the ciliary body,[25] but as ciliary body thickness is associated with emmetropisation, ocular remodelling may also be effected by structural changes in the middle, uveal lining of the eye.

2.1.e. **The visual pathways**

The optic nerves travel posteriorly from the eyes to meet centrally within the cranium at the optic chiasm, where there is a re-organisation of fibres which delivers to each hemisphere visual information from each eye's ipsilateral vertical hemi-field of vision, rather than information only gathered from the ipsilateral eye. The fibres travel within the hemispheres as the optic tract with the final destination being the occipital visual cortex (although further, complex higher level processing occurs upstream of the visual cortex). As visual information traverses across the length of the cerebrum to synapse within an area at the back of the brain, a wide range of cerebral disease and disorders can have a profound effect on vision.[26]

2.1.f. **Summary**

The eye is a complex structure within the visual system which focuses and processes light. The first two years of life is a time of rapid development of the anatomy and physiology of the ocular structures.

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2.2. Vision and visual impairment

The primary aim of intervention for congenital and infantile cataract is the restoration of functional vision. Vision is an age related function, which rapidly matures during the first few years of life as the anatomy and circuitry of the visual pathways develop. Normal visual function is an important aspect of child health, and visual impairment has a significant impact on the affected child's developmental, educational and socioeconomic experiences, during childhood and beyond.

2.2.a. **Normal visual function**

2.2.a.i. Acuity

Acuity is the ability to resolve visuo-spatial cues – that is, to visually discriminate the edges of objects in space. The closer together the edges or the finer the detail, the better the resolution and acuity needed to discriminate them.

2.2.a.ii. Visual acuity metrics

In early childhood (the first few years of life) acuity can be quantified using gratings or optotypes (symbols such as shapes, numbers and letters) as described in detail in section 2.2.c, page 38.

Grating acuity

Black and white gratings of differing width, where width is measured in cycles per visual degree (cpd) can be used to quantify visual resolution. The higher the frequency, the better the acuity.

Optotype acuity

Standardised symbols or letters made up of lines of different widths can also be used to quantify acuity. Grating acuity (resolution) and optotype acuity (resolution *and* recognition) are not equivalent, as the higher level cognitive visual functions have an as yet unclear role in the recognition of the shapes used to test acuity. Good grating acuity in early infancy is not a guarantee of good optotype acuity in later life, and optotype

acuity matures faster than grating acuity in the first five years of life. [27] Optotype acuity is measured using one of two scaling systems:

- The LogMAR scale uses a logarithmic conversion of visual resolution to create a linear scale of vision, which allows for statistical analysis of visual outcome. As $\log_{10}(\mathbf{1})=0$, a LogMAR acuity of 0.0 is 'normal' acuity, whilst 1.0 LogMAR signifies a tenfold decrease in resolving power ($\log_{10}(\mathbf{10}) = 1$). Thus each 0.1 step signifies a linear decrease in resolving power. A negative LogMAR score indicates a 'better than normal' acuity.

- The Snellen scale uses a geometric scale to quantify resolving power, expressed as a fraction or as a decimal. A child who at a distance of 6 metres can only see and read a symbol which a 'normally' sighted child would have been able to see at 60 metres distance will have a vision of 6/60. The Snellen fraction can be converted into a LogMAR 'score' by taking the logarithm of the inverted snellen fraction (thus 6/60 Snellen acuity is equivalent to $\log_{10}(\mathbf{60/6})$ or $\log_{10}(\mathbf{10})$, that is1.0 LogMar, and 6/6 Snellen is equivalent to 0.0 LogMar, table 1).

There is often confusion between the Snellen and LogMAR scales and the Snellen and 'LogMAR' charts (charts which give LogMAR acuity scores without the need for conversion). For example, in the United Kingdom, the charts most commonly used to measure adults acuity use the Snellen scale. These Snellen charts (there is no one standardised Snellen chart) use variable numbers of symbols per line, with irregular progression of letter sizes between lines and irregular line spacing.[28;29] Consequently, it is difficult to use acuity scores as measured by Snellen charts in the statistical analysis of visual outcome.

A more qualitative or gross measurement of vision is useful when vision is too poor for such assessment scales. Subjects can be described as having perception up to the level of 'counting fingers' 'hand movements perception' or 'perception of light' (Table 1).

Table 1. A comparison of the different acuity scales in use
Snellen, LogMAR and grating acuity.

Optotype acuity			*Grating acuity equivalent*
Snellen (geometric scale)	**LogMAR (linear scale)**		**Cycles per degree (geometric scale)**
6/4.8	*-0.1*		-
6/6	*0.0*		-
6/7.5	*0.1*		-
6/9	*0.2*		-
6/12	*0.3*		*15*
6/15	*0.4*		*13*
6/18	*0.5*		*10*
6/24	*0.6*		*8*
6/30	*0.7*		*6*
6/36	*0.8*		*5*
6/48	*0.9*		*4*
6/60	*1.0*		*3*
Count fingers (CF) - Able to count fingers at a given distance			
Hand movements (HM) - Able to perceive a hand waved near the face			
Perception of light (PL) - Able to perceive the presence or absence of light			
No perception of light (NPL) or absolute blindness			

2.2.a.iii. Other visual functions

The other components of normal visual function include:

Depth perception or *stereopsis*, which requires correspondence between the vision in both eyes and between the movements of both eyes. Ocular deviation, or strabismus ('squint'), is associated with loss of stereopsis (and in children strabismus is often associated with significantly poorer vision in the deviated eye).

Visual field, which is the total area of space perceived when the eyes and head are stationary. The sensitivity of the field is greatest centrally and drops off towards the periphery.

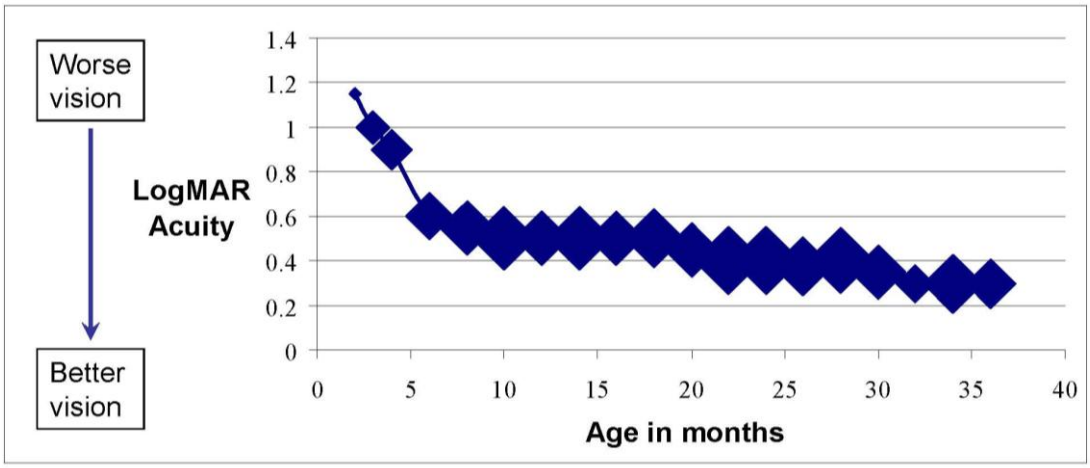
Contrast sensitivity is the ability to discriminate between areas of difference luminance. Discerning black images on a white background requires less contrast sensitivity than discerning grey images on a slightly lighter grey background: visual function may be very different in differing illumination conditions for children with abnormal contrast sensitivity.

The perception of *colour* is also part of vision, as are higher level visual functions such as *motion perception* and *face recognition.*

2.2.b. **The development of vision**

Vision improves rapidly over the first few years of life. Newborns have an average acuity of approximately 1.5 LogMAR, which improves to an average acuity of 0.5 LogMAR by 12 months of age, and 0.35 LogMAR by 24 months of age [30;31] (Figure 6).

Figure 6. Visual maturation in childhood showing the rapid improvement in the first year of life
and the slower rate of improvement as the child ages. Modified from Salomao et al.[30]. The size of the data point reflects the number of tested children in each age group (total 646 children)



2.2.b.i. The sensitive periods of visual development

Hubel and Wiesel's Nobel prize-winning studies in the 1950s' described the result of experimental monocular visual deprivation of kittens of different ages. They demonstrated that following deprivation during a 'susceptible' period, there was a sharp decline in the number of visual system neurons driven by the deprived eye, resulting in unequal cerebral ocular dominance.[32]

The development of mammalian sensory modalities involves a crucial sensitive period, a time window during early development when experience has a profound effect on the consequent structure and function of the brain. Prior to the sensitive period is the latent period, during which the earliest phases of visual development are independent of visual stimuli.[33;34] Within the sensitive period is a critical period, during which experience is absolutely necessary for the creation of neural networks and subsequent normal function (box 1).[33] Normal development of the visual communication pathways thus requires the presentation of a focused image to the higher level systems during a sensitive developmental period. There may be overlapping sensitive periods for the different visual modalities such as form perception, ocular dominance, face perception, or motion perception.[33;34]

Box 1. The phases of plasticity which define the sensitive period*. Modified from Hooks et al[33].*

Pre critical latent period: the initial formation of neuronal circuitry that is not dependent on visual experience

Critical period: distinct onset of plasticity in response to visual stimulus, so that visual experience is absolutely necessary for normal development and subsequent normal function

Sensitive period: the window of development during which initially formed circuitry can be modified by experience, with less plasticity exhibited with the duration of the window

Should the image presented to the retina and higher level systems during the sensitive period be defocused, due to uncorrected refractive error, or blurred, due to cataract, the visual system will fail to develop to its full potential. This failure to achieve visual potential is called *amblyopia*.

2.2.b.ii. Amblyopia

Amblyopia can arise secondary to blur from defocus (*refractive amblyopia*, which may be related to *anisometropia*), a failure to maintain a straight gaze (*strabismic amblyopia*) or structural disorders of the eye, such as cataract, which obscure incoming images, (*form deprivation amblyopia*).

Amblyopia can be bilateral, but is much more commonly unilateral, with the visual cortex "preferring" the eye which presents the least blurred or defocused image during the sensitive period. The treatment of amblyopia requires early management of the cause of reduced vision, and management of unilateral amblyopia also requires visual penalization of the better seeing fellow eye. This can be achieved with an adhesive eye patch or contact lens to occlude the non-amblyopic eye, or chemical penalization of vision in that eye (using topical cycloplegic eye drops which paralyse the eye's accommodative ability, thus preventing focused viewing).

In humans, the critical sensitive periods for ocular dominance and form perception start just after birth.[35] The duration of the critical period is unclear, although some evidence from children born with treatable visually obscurative defects suggests that the critical visual development windows close sometime during or after the second month of life,[36-38] and that the critical windows for ocular dominance open and close earlier than the window for development of resolution/acuity.[37;39-41] The development of the visual systems remains progressively less sensitive until the age of 8. As evidenced by studies of amblyopia treatment in late childhood, in some individuals, the period of plasticity extends beyond this age.[33;42;43]

In order to detect a child's response to amblyopia management, or to any intervention aimed at improving vision, some assessment of visual function is necessary.

2.2.c. **Assessing vision in childhood**

As described earlier, visual ability develops over time (figure 5), accompanied by the development of other capabilities with intellectual and motor function maturation. Methods for the assessment of visual function therefore differ with the stages of development in early childhood.

2.2.c.i. Neonates

A normally sighted neonate will have a **C**entral, **S**teady gaze which she can **M**aintain for brief periods (sometimes abbreviated to CSM fixation), but she will have limited ability to maintain sustained fixation on objects, or to perceive fine detail or colour. Over the first days of life children develop first the ability to fix their gaze on visual stimuli and then to pursue moving stimuli (**Fix** and **Follow** vision).[44] Highly contrasting images, such as black and white stripes or checkerboard patterns, are most visually stimulating.

2.2.c.ii. Infants and toddlers (and other pre or non-verbal children).

The preferential interest which infants display in high contrast (black and white) patterned images can be used to quantify acuity in pre-verbal children from the second week of life. Boards with a window of gratings (of progressively higher frequency / thinner width) on one half and gray background on the other are presented to infants. Acuity can be tested with both eyes open (binocular acuity), or tested individually for each eye (monocular acuity) with grating acuity card systems such as the *Teller* cards (Figure 7, page 41) giving acuity levels in cycles per degree (as discussed in section 2.2.a.ii). A child aged 12 months should be able to achieve at least 0.8 LogMAR (the

average vision being 0.5 LogMAR), whilst a three year old should be able to achieve 0.5 LogMAR using the Teller preferential looking cards (Table 2, page 41).

The normative data cited above arise from two studies: a study of 646 children aged from 2 to 36 months of age who were assessed by one of 8 examiners who themselves had been assessed as achieving 'errorless performances' in the grating card technique[30] and a study of 460 children aged between 1 month and 4 years old who were each assessed twice by two study examiners. [31] The latter study demonstrated excellent between-examiner and between-testing reliability (no clinically or statistically significant variation in test findings).

Grating acuity cards may not be interesting enough to keep the attention of toddlers (children aged 1 year to 3 years).[45] Preferential looking techniques can also be used with optotype image boards such as the *Cardiff* cards, which use white shapes bordered by black bands situated on either the top of bottom half on of a grey board (Figure 7). Cardiff cards were originally designed to bridge the gap between 'resolution and recognition'[46]and have been validated for use in children aged 12-36 months.[45;46]. Acuity levels are recorded either as Snellen fractions or as LogMAR scores. A child aged 12 months should be able to achieve at least 0.8 LogMAR, whilst a three year old will be able to achieve 0.3 LogMAR using Cardiff card testing (Table 3, page 41).

The Cardiff card acuity norms arise from a 1994 study estimating the acuity in 231 children aged between 12 and 36 months. Binocular and monocular acuity levels were assessed by a single examiner, but the generalizability of the findings are somewhat adversely affected by the investigator's success rate for monocular acuity assessment, which was 41% for children aged 12-18 months and no higher than 73% for children aged18 to 30 months.[46]

Figure 7. Preferential looking tests
for acuity / resolution. A.Teller cards and B. Cardiff cards

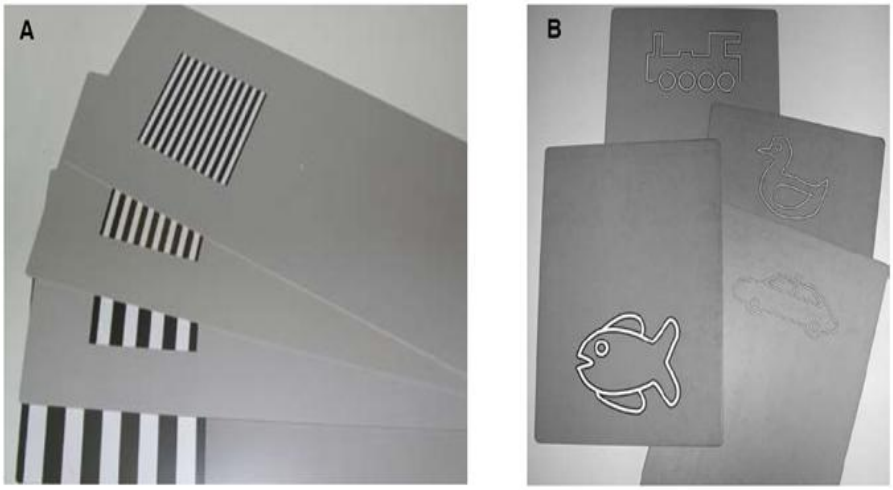


Table 2. Mean and lower limit of normal range of acuity for children aged 12 to 36 months on Teller grating card preferential looking assessment
Adapted from Salamao1995[30]

Age (months)	***Monocular acuity (LogMAR)***		***Binocular acuity (LogMAR)***	
	Mean acuity	***Lower limit of 95% normal range***	***Mean acuity***	***Lower limit of 95% normal range***
12	0.5	0.8	0.4	0.8
18	0.5	0.7	0.4	0.8
24	0.4	0.7	0.3	0.7
30	0.3	0.7	0.2	0.6
36	0.3	0.3	0.2	0.5

Table 3. Mean and lower limit of normal range of acuity for children aged 12 to 30+ months on Cardiff acuity card assessment
Adapted from Adoh 1994[46]

Age (months)	***Monocular acuity (LogMAR)***		***Binocular acuity (LogMAR)***	
	Mean acuity	***Lower limit of 95% normal range***	***Mean acuity***	***Lower limit of 95% normal range***
12	0.6	0.8	0.6	0.9
18	0.4	0.7	0.4	0.6
24	0.2	0.5	0.3	0.4
30	0.1	0.3	0.2	0.3

2.2.c.iii. Older children – object or optotype recognition

Several different optotype methods are in use, including the Cardiff cards, Kays picture cards, Lea symbols and the Snellen and **E**arly **t**reatment **d**iabetic **r**etinopathy **s**tudy charts for literate children (as indicated by its name, the ETDRS test was designed by ophthalmic investigators to overcome the deficiencies of Snellen charts in the analysis of visual outcome, as discussed in section 2.2.a.ii, 31). Due in part to the recognition skills required, optotype acuity testing is unreliable in children under two years old.[30]

2.2.c.iv. The comparability of different acuity tests

The different tests used to measure acuity in young children measure different functions (resolution with or without recognition) and therefore are not directly comparable.[27;45] When undertaken in the first years of life, the normative values of these tests can, however, be used to determine whether a child falls outside an expected level of acuity, [30;31;45;46] although the Teller acuity test may underestimate visual loss in amblyopic children.[47;48]

2.2.c.v. The predictive power of early childhood acuity tests

Longitudinal studies have provided evidence of the good predictive power of normal Teller acuities for children without ocular or neurological conditions,[47;48], although there is no longitudinal evidence of the predictive power of Cardiff card acuity assessment undertaken in early childhood.

2.2.c.vi. Qualitative assessments of visual function in early childhood

Due to developmental and behavioural constraints, it may not always be possible to quantify the acuity of infants and toddlers. In these cases, other signs may be used to determine the presence of a significant visual functional problem:

- The absence of vision dependent or vision-directed behaviour – such as smiling in response to silent parental smiles
- An infant's strong and prolonged objection to occlusion of one eye over another may provide a clue to the possible presence of uniocular reduced vision. In cases of severe uniocular visual impairment, this objection to occlusion can make the assessment of uniocular acuity challenging.
- Strabismus (with deviation of the poorer seeing eye), an associated finding in cases of unilaterally or bilaterally poor vision.
- Nystagmus (involuntary movements of the eyes), an associated finding in bilateral visual loss.

2.2.c.vii. Electrodiagnostic testing

Electrodiagnostic testing (*electroretinograms, ERGs,* which record activity within the retina and *visual evoked potentials*, *VEPs*, which record activity through the post-retinal pathways) can be used to estimate visual potential. Visual stimuli are presented, and the child's physiological response is evaluated. The level of activity is compared to normative data to provide an indication of the child's visual potential.

2.2.d. **Visual impairment and blindness**

In adults and older children acuity levels (and to a lesser degree the visual field) are used in the official definition of visual impairment. The World Health Organisation (WHO) defines visual impairment as *blindness* if vision is worse than 3/60 with both eyes open, *severe visual impairment* if vision is worse than 6/60 or there is severe peripheral field loss, and *moderate visual impairment* if vision is worse than 6/18 or there are moderate visual fields defects.[49]

Whilst there is no legal definition of sight impairment in the UK, government guidelines state that impairment is '*substantial and permanent handicap (due to) defective vision caused by congenital defect or illness or injury',* and children can be registered as having partial or severe sight impairment using the criterion described in Table 4. Registration of a child's visual impairment enables family access to financial benefits and other practical support including assessment of the child's educational needs and possible future vocational need (although registration is not a pre-requisite for a vision-related educational needs assessment). As vision in the better seeing eye is used to formally define impairment, a child with poor visual outcome from unilateral cataract and a normal contralateral eye would not be formally registered as visually impaired.

Table 4. UK criteria for the registration of individuals as visually impaired

	Best achievable acuity with both eyes open
Sight impairment (previously termed *partially sighted*)	3 / 60 to 6 / 60 with a full field of vision
	Up to 6 / 24 with moderate reduction of field of vision or central blur
	Up to 6 / 18 with very reduced field of vision or hemianopia
Severe sight impairment (previously termed *blindness*)	Less than 3 / 60 with a full visual field
	Between 3 / 60 and 6 / 60 with severe reduction of field of vision
	6 / 60 or better with very reduced field of vision

2.2.d.i. The impact of visual impairment

Visual impairment and blindness (VI/BL) impacts on society as well as the individual due to the cost of medical and social support for the child and the adult she becomes, as well as the loss of potential employment related income.

Although individuals with unilateral impairment have good acuity with both eyes open, when compared to individuals with bilaterally normal vision those with unilateral amblyopia have an increased lifetime risk of bilateral visual impairment due to loss of acuity in their better-seeing eye.[50;51]

2.2.e. **Summary**

Children have a finite developmental window during which the visual system must be presented with a clear and focused image to enable them to fulfil their visual potential. If this development is interrupted by disorders which affect the presentation of a good visual image, permanent visual impairment may occur (amblyopia).

Normal vision requires the integration of a number of visual functions. However acuity, arguably the most important modality, forms the basis of the taxonomy for the classification of individuals as non-impaired, impaired, severely impaired or blind.

Accurate assessment of visual acuity in infants and toddlers is difficult, and a there exists a variety of different tests for use in children under 5 years old.

2.3. Congenital and infantile cataract

Childhood cataract can affect the child from birth (congenital cataract) or in the first year of life (infantile cataract). Cataract can be unilateral or bilateral, with some individuals exhibiting asymmetric bilateral cataract.

2.3.a. **Incidence of congenital and infantile cataract in the United Kingdom**

The estimated UK incidence of cataract in the first year of life is 2.5 per 10,000 (95% confidence interval 2.1 – 2.9), and by the age of 5 the cumulative incidence of congenital and infantile cataract is 3.2 / 10,000.[52] These estimates are drawn from a 1995/96 population based study involving two national active surveillance schemes, which identified 248 children (aged under 16 years) newly diagnosed with congenital or infantile cataract in one year, of which 66% had bilateral disease. 188 of the 248 children were diagnosed in the first two years of life.[52]

2.3.b. **The global burden of congenital and infantile cataract**

It is estimated that 15% of the world's blind children are blind due to cataract.[53] Determining the burden of childhood cataract in developing countries is made difficult by the lack of infrastructure and methodological challenges of conducting population based research. Some evidence of the burden of childhood cataract comes from investigations into the causes of impairment in children educated at schools for the blind (Table 5).

Table 5. The proportion of childhood blindness due to cataract in low and middle income countries
using the prevalence of cataract blindness within schools for the blind

	Number of children examined	*Proportion*
Indian subcontinent		
North India, 2008[54]	703	10%
Northeast India, 2003[55]	376	11%
Bangladesh, 2007[56]	1935	33%
West India, 2007[57]	1985	6%
Rest of Asia		
Malaysia, 2001[58]	358	22%
Indonesia, 2007[59]	165	13%
Sub-saharan Africa		
Nigeria, 2003[60]	142	30%
Ethiopia, 2003[61]	260	9%

The wide range in proportion of blind school students with cataract reported in Table 5 (from 6-33%) is indicative of the wide variety in both the frequency and causes of visual impairment across the world, reflecting the global patterns of the overall health and survival of children as well as the socio-economic developmental status of the region

2.3.c. **Aetiology of congenital and infantile cataract**

Cataractous opacity of the naturally clear lens due to disturbance of the biochemical or physical structure of the crystalline lens fibres occurs secondary to a range of genetic, developmental or traumatic insults, and children with congenital and infantile cataract form a heterogeneous group (Table 6), although for the majority of children with congenital and infantile cataract in the UK, the aetiology remains unknown (*idiopathic* disease).

Table 6. The causes of congenital and infantile cataract in the United Kingdom in order of decreasing incidence
Adapted from Rahi et al 2000[62]

I. Idiopathic isolated* cataract (*no other disorder)
II. Idiopathic cataract with associated ocular disorder
eg: microphthalmia, persistent fetal vasculature
III. Hereditary isolated* cataract (*isolated =no systemic disorder)
Autosomal dominant, autosomal recessive, or X-linked
IV. Hereditary or sporadic genetic cataract with associated disorder (including chromosomal)
eg. Trisomy 21, oculo-renal disorder of Lowe, Cockayne syndrome
V. Prenatal biological or environmental exposure
eg: prenatal rubella, maternal corticosteroid exposure

The underlying aetiological factors differ for bilateral and unilateral cataract: whilst over 90% of unilateral cataract identified by Rahi et al was idiopathic, only 38% of children with bilateral cataract had idiopathic disease. Conversely hereditary disease was more common in bilateral cataract (56%) than unilateral cataract (6%).[63] Hereditary cataract can be passed on through dominant, recessive or X-linked inheritance (most commonly autosomal dominant) and can consist of isolated cataract, or cataract seen with associated ocular or systemic disease.[64] Cataract is also a feature of non-inherited genetic disorders such as trisomy 21 (also known as Down syndrome).[65]

Intrauterine insult to fetal lens development through infectious agents (cytomegalovirus, herpes or rubella viruses, for example) is now an uncommon cause of congenital cataract in industrialised countries, but important due to the preventable nature of the disease (eg through immunisation programmes). Globally, infectious causes of cataract have more significance.[66] Intrauterine hyperglycaemia (due to gestational diabetes)[67] is another possible cause.

2.3.d. **Phenotypic classification of cataract**

Rather than an exhaustive list of the possible morphological variations of early childhood cataract, an effective classification system for visually significant cataract can be created using the area, degree and type of opacity seen.[2;3;68] The phenotype or morphology of lens opacity is partly dependent on the timing of the insult to the lens within the period of lens development.[2;3;68;69]

- *Nuclear* cataract is opacity of the central fetal lens, which indicates an insult to the developing lens at an early embryological stage
- *Lamellar* or zonular cataract is shell like opacity of the secondary lens fibres in the layers or zones around the nucleus, indicative of an insult to the lens at a later embryological stage
- *Anterior* cataract, which can involve the anterior face of the capsule
- *Posterior* cataract which can again involve the capsule, and may involve fetal vascular remnants
- *Cortical* cataract, opacity of the outer cortex, is usually indicative of post-natal insult to the lens
- *Total* cataract, where the opacity involves the whole of the lens. This may be as a result of the progression of a different form of cataract

Other structural abnormalities of the anterior or posterior segment can be seen with congenital cataract: thus another classification system of cataract involves the presence or absence of an associated ocular abnormality. The most common abnormalities seen with cataract are microphthalmos, microcornea and persistent fetal vasculature.

In some cases, the opacity is not of a sufficient degree to affect vision. These visually insignificant cataracts have a wide range of possible phenotypes, ranging from blue dots scattered across the lens to Y shaped opacities at the points where the lens fibres meet to form suture lines.

2.3.d.i. Microphthalmos

Microphthalmos is an abnormally short eye due to a failure of globe development, and is defined as an axial length less than two standard deviations from normal, or an axial length outside of the 95% range of normality.[2;3;70] This has been broadly defined as an axial length of less than 19mm in a 1 year old or less than 21mm in adults.[2] As the axial length of a child's eye changes significantly in the first two years of life, age at axial length measurement is an important factor in determining whether the child's eye is microphthalmic (box 2). Many previous investigators who have reported on the frequency of microphthalmos in congenital and infantile cataract or outcomes following cataract surgery have failed to use the existing normative data on infant axial length (Table 7) to define microphthalmos, or have failed to give a definition [71-80;80-84] making it difficult to undertake comparisons.

Box 2: Age related definition of microphthalmos*, using the norms as reported in Fledelius 96 [10] Larsen 1971:[85] Mutti 2005, Blomdahl 1979 and Gordon 1985*

<20mm if aged 2 years or older

<19mm if aged 6months or older

<18mm if aged 3months or older

<17.5mm if aged 1month or older

Axial length <15.5mm at any age

As well as cataract, other structural globe anomalies affecting the iris, retina and optic nerve are associated with microphthalmos. The condition can be bilateral or unilateral, and may be hereditary, with almost 50% of children with microphthalmos having an associated systemic disorder.[86]

2.3.d.ii. Microcornea

Again, the definition of microcornea is dependent on age at measurement of horizontal corneal diameter (HCD). Microcornea has been defined as HCD <9.5mm, or <10mm in a child over 1 month old [87] or HCD <10.5 in a child under 4 months old.[5;79;81] However, as microcornea has been described as a significantly small cornea which is more than two standard deviations from normal or outside the 95% predicted normal range[2;81;87;88], using the existing normative data (Table 7) microcornea should be classified as a horizontal corneal diameter of <9.5mm at any age, HCD <10 if aged over 1 month old, or HCD <10.5mm in children over 6 months old, in an eye with a normal axial length (as almost all microphthalmic eyes have similarly abnormally small corneal diameters).[2;89] Microcornea may be inherited, and may again be associated with other globe abnormalities including persistence of the fetal vasculature.

Table 7. Summary of the findings of studies of the normative values of ocular axial length and horizontal corneal diameter in the first 2 years of life

Description	Longitudinal study	Cross sectional studies			Cross sectional studies			
Study	Mutti et al 2005[12]	Larssen 1970[85]	Blomdahl 1979[90]	Gordon et al 1985[11]	Kiskis et al 1985[89]	Blomdahl et al 1979[90]	Hymes et al 1929[91]	Wallace & Plager 1996[5]
Age	***Mean axial length in mm, standard deviation SD of children / eyes examined)***			***(and number***	***Horizontal cornea diameter in mm, standard deviation SD (and number of children / eyes examined)***			
Term	-	16.8, 0.6 SD (43 children)	16.6 (28 children)	16.7, 0.6 SD (23 children)	-	9.8 mean (28 children)	10.04 / 9.9 mean boys / girls, 0.2 SD (17 eyes)	9.75 mean (n not reported)
1 month	-	-	-	19.2, 0.7 SD (11 eyes)	9.4 (2.5% lower limit) (33 children)	-	10.6 mean, 0.1 SD (19 eyes)	-
2 months	-	-	-	-	-	-		-
3 months	19.0, 0.6 SD (222 children)	-	-	-	-	-		-
6 months	20.2, 0.6 SD (222 children)	18.2 (2 eyes)	-	-	10.5 (2.5% lower limit) (33 children)	-		-
9 months	-	19.1 (4 eyes)	-	-	-	-	-	-
12 to- 24 months	-	20.6, 0.5 SD (36 eyes)	-	20.2, 0.3 SD (8 eyes)	10.5 (2.5% lower limit) (33 children)	-	-	-

2.3.d.iii. Persistent fetal vasculature

Persistent fetal vasculature, or PFV, is a spectrum of clinical features caused by failure of the normal regression or apoptosis of the intraocular fetal vasculature (Figure 3, page 22).[92] PFV is a common ocular abnormality in unilateral cataract, reported to occur in almost a fifth of cases.[62] Bilateral cases of PFV, which are much less common, are often hereditary, and often associated with systemic abnormalities.[92;93]

PFV was previously termed persistent hyperplastic primary vitreous (PHPV), due to the characteristic feature of a plaque of remnant tissue sitting on the posterior face of a cataractous lens, attached to a persistent stalk of hyaloid vasculature. However, any part of the fetal vasculature can persist, resulting in iris, pupillary, or optic nerve vascular remnants. [92] More severe manifestations involve fibrosed, tightened remnant tissue dragging the ciliary processes centrally with resultant detachment of the retina or dislocation of the lens.[92;93] Rarely, cataractous eyes with PFV also develop destructively high pressures within the eye due to abnormal drainage of aqueous (*glaucoma*) resulting in a painful blind eye.[94] In these cases, cataract extraction may be undertaken in order to prevent a painful condition rather than to improve visual function.

Other congenital ocular anomalies associated with cataract include anterior segment developmental anomalies (ASDA) in which the cornea, iris and angle structures fail to develop normally, and congenital glaucoma.

2.3.e. **The natural history of congenital and infantile cataract**

Without surgery, children with visually significant cataract (opacity sufficient to obscure incoming visual information) have little chance of good form vision in that eye.

2.3.f. **The prevention of childhood cataract blindness in the United Kingdom**

2.3.f.i. Primary prevention

Primary prevention of cataract blindness in the UK involves genetic counselling of affected families, counselling of mothers of children with Trisomy 21, and the rubella immunisation programme to prevent the occurrence of maternal gestational infection. However, as the majority of congenital and infantile cataract in the UK is of unknown aetiology, the scope for primary prevention is currently limited and secondary and tertiary strategies play a greater role in the prevention of childhood cataract blindness due to cataract.

2.3.f.ii. Secondary prevention

Early detection and early treatment is key to the prevention of blindness in the management of congenital and infantile cataract.

Detection

Although prenatal and ultrasound and MRI diagnosis of cataract is possible from gestational week 14[95], there is no evidence on the sensitivity or specificity of prenatal radiological diagnosis of cataract.[96-98] Thus, the earliest time that visually significant cataract can be excluded reliably is post-natally. Detection of cataract depends on the examination of the 'red reflex', this being the unobscured orange-red glow when light shining into an eye is reflected back by the retina. Lens opacity prevents this reflection. The importance of the early detection of cataract is reflected by the Department of Health's formal inclusion of the red reflex test within the neonatal and 6 week postpartum infant health checks.[99] In the British 95/96 cohort 66% of children diagnosed in the first 2 years of life were detected by 8 weeks.[100]

Cataracts which develop later in infancy or which are not detected by screening may also be detected through frank leukocoria (white pupil due to a dense cataract) a change in visual behaviour or development of a strabismus in unilateral cases with the visually deprived eye turning in or outwards.[2]

Treatment

Approaches to treatment are described below. However surgical intervention may be considered inappropriate in cases where the visual potential of the eye is poor due to dense amblyopia following delayed diagnosis of congenital unilateral cataract, or due to

ocular or neurological disease, or where there is concurrent life-threatening systemic disease. In some situations, for example cataract with glaucoma due to persistent fetal vasculature, removal of the lens is necessary for other clinical indications despite no visual potential.

2.3.f.iii. Tertiary prevention

Once a child has developed established visual impairment or blindness due to cataract, management involves minimising the limitations imposed on the child, with continued specialist ophthalmic input, provision of low vision care, special and specific educational support, and habitation and mobility training to assist activities of daily living.

2.3.g. **Surgical management of congenital and infantile cataract**

2.3.g.i. Recent history of surgical management

Prior to the 1960s, ophthalmologists considered it safer to delay surgery until the infant eye was larger and more developed, in order to reduce the risk of the technical challenges and per operative complications associated with surgery on a small eye, and the potential post-operative complications of operating on immature eyes.[101] Improved understanding of visual development and the sensitive period led to surgeons undertaking earlier surgery, and in particular a greater emphasis on post-operative visual rehabilitation for children with unilateral cataract.[102]

The next challenge was the achievement of safe but thorough removal of the cataractous lens in order to prevent the physical and inflammatory mediated damage caused by lens remnants.[1] The eye is a watertight structure: when a surgical wound is made in order to enter the eye, aqueous leaks out, leading to a loss of anterior chamber depth. Thus, safe cataract surgery requires the continuous maintenance of pressure in the anterior chamber, in order to keep a space in which to operate. This is achieved using irrigating fluid, pumped into the eye to balance fluid lost from the wounds, or lost when the lens is removed from the eye. In the mid 70's, an automated *vitrector* cutting machine, designed to remove the gelatinous vitreous gel by 'cutting and sucking' simultaneously, was cautiously used to remove the lens in paediatric cataract surgery. In children, the lens is often thick and 'gummy', and the ability to 'cut and suck' using a vitrector hand piece, which is also has an irrigation function, led to improved removal of the cataractous lens. The use of the vitrector also made possible the safe removal of the anterior section of the vitreous gel, which could move forwards following paediatric cataract surgery, leading to complications such as glaucoma and retinal detachment.[103;104] Other developments, such as *ophthalmic viscoelastic gel devices* (OVDS) capable of maintaining the shape of the anterior chamber,[105] improvements in operating microscopes and surgical techniques for dealing with the

capsule of the lens[106] have all resulted in further improvements in the risk / benefit ratio for early intervention for congenital and infant cataract.[106-108]

2.3.g.ii. Modern surgical management

Paediatric cataract surgeons

In the United Kingdom, currently, paediatric ophthalmic surgeons first train in adult surgery before sub-specialising in paediatric surgery. Cataract surgery is the most common procedure undertaken by general ophthalmologists, accounting for over a half of all ophthalmic procedures undertaken in the UK,[109] and progression within the junior levels of ophthalmic training requires the achievement of a quota of completed adult cataract procedures. This is the background of all paediatric ophthalmic surgeons in the UK and (many of the paediatric surgeons in the developed world), and there is a resultant diffusion of techniques and instrumentation from adult cataract surgery into paediatric practice.

Paediatric cataract surgery

In paediatric cataract surgery the surgeon is aiming to create entrance points into the eye and a space in which to operate in order to remove the lens, whilst simultaneously limiting post-operative inflammation.

The pupil is dilated pre-operatively with topical medication to allow access to the lens. The main surgical wound is created either through the periphery of the cornea or through the sclera, following which irrigation fluid, or an oculoviscous device (OVD) is used to maintain anterior chamber depth.[105;107;108] The OVDs are classified by their level of viscosity: low, medium, high viscosity or fracturable (fracturable being

superviscous OVD, analogous to the fracturable nature of chocolate cooling within a fridge, becoming more viscous until it reaches a stage where it snaps under pressure) . The use of higher viscosity OVDs (such as Healon®5 and Healon GV ®) have been associated with ocular hypertension due to inadequate removal following adult intraocular surgery.[110]

The lens is accessed via an opening in the capsule – a *capsulotomy*. Uncontrolled capsulotomy results in irregular edges to the capsulotomy, which can become radial tears which extend to the zonules, creating an unstable lens body from which safe lens removal is extremely difficult. Several different capsulotomy methods are in use in modern paediatric cataract surgery, including

- *diathermy*, in which heat used is used to rent the capsule beneath a layer of supportive oculoviscous gel which also acts as protection against thermal corneal trauma

- *vitrectorhexis*, where the vitrector is used to punch through the capsule[111-113]

- *capsulorhexis*, a technically demanding manual circular tearing of the capsule face undertaken beneath a layer of supportive oculoviscous gel; capsulorhexis results in a smooth edged circular opening

Following capsulotomy, the lens is removed either through an automated method (with the vitrector) or a manual method of aspiration, leaving the eye in an aphakic (literally, 'without lens') state.[105]

In children the posterior face of the capsule invariably and rapidly opacifies following cataract extraction.[1;3;105;107;114;115] Thus, many surgeons undertake removal of the central portion of the posterior capsule at primary surgery. This is accompanied by removal of the anterior section of the vitreous gel (*anterior vitrectomy*). The ideal timing for *posterior capsulotomy*, that is whether primary capsulotomy or later secondary capsulotomy is best, has been a subject of debate, with some investigators arguing

that, as secondary capsulotomy can be undertaken as a non-invasive procedure using laser, it is safer and less traumatic than primary capsulotomy, and may reduce the risk of further complications.[80] However, laser capsulotomy is not always successful and further intraocular surgery may be needed. Other investigators argue that the amblyogenic potential of an opaque posterior capsule necessitates primary removal, which also avoids the possible need for a second intraocular procedure.[104-106;108;116;117]

Following surgery, antibiotics may be injected into or around eye as prophylaxis against infection. Steroids are also injected into and / or around the eye to reduce inflammation. Post operatively topical (eyedrop) steroid and mydriatic (pupil dilating) medications are used to control inflammation and prevent the formation of inflammatory pupil adhesions (*synechiae*). [105]

2.3.g.iii. Per operative complications

Iris trauma

Per operative iris trauma may occur directly, through instrumentation, or indirectly, through acute fluctuations of pressure caused by the flow of fluid into and out of the eye during surgery (*barotrauma*). The iris may also prolapse through the operating wound during surgery. Iris trauma results in inflammation,[118] may result in bleeding from iris vessels (*hyphaema*) which leads to further inflammation, and may results in damage to the drainage systems in the iridocorneal angle.

Anterior and posterior capsule tears

Tears to the anterior and posterior capsule during capsulotomy do not in themselves lead to adverse outcomes for children, but the tears may lead to further complications due to inability to safely remove lens material.

Other per operative complications

Other complications include corneal trauma, which can result in vision-threatening cloudiness of the cornea, vitreous haemorrhage, which can result in increased inflammation and obscuration of vision.

2.3.h. **Visual (re)habilitation following surgical management**

2.3.h.i. Occlusive therapies for amblyopia

Children with unilateral cataract (or with significantly asymmetric bilateral cataract) require therapy for amblyopia following cataract extraction, in the form of eye patch occlusion of the better seeing eye. Children who resist patching may require other methods such as insertion of an occlusive contact lens or cycloplegic penalisation of the non-amblyopic eye. The amount of occlusion (measured in hours per day, or percentage of waking time) depends on the degree of amblyopia and the age of the child,[119;120] and treatment is prescribed until the amblyopia improves, or until the sensitive window effectively closes (between 7-9 years of age).[120] The optimal amount and duration of post cataract surgery occlusion is unclear. The first few years of life, the time at which the child's neuroplasticity is greatest, and thus her potential response to occlusion is highest [119-121] is also the time during which the accurate assessment of acuity is most challenging.

2.3.h.ii. Refractive correction

The post-operative focusing power of the natural lens must be replaced so that a focused image is presented to the higher visual systems. Even relatively short periods of deprivation within the early sensitive period can result in severe or dense amblyopia in aphakic infants. Whichever method is chosen to correct aphakia, the changing dimensions and consequent changing refractive state of the growing infant eye need to be considered.

Aphakic glasses

Glasses are a relatively inexpensive option for the replacement of lens focusing power. However, the necessary density and thickness of these lenses make them heavy and cumbersome for the infant face. There are also optical problems, as these high power lenses magnify centrally by 20% to 30% resulting in orientation problems due to poor depth perception[122;123] and blurring of the peripheral field.[122;124] This makes them unsuitable for monocular aphakia, as the differing magnification of image size is challenging when the child has both eyes open.

Aphakic contact lenses

Aphakic contact lenses enable an improved and more constant visual rehabilitation, resulting in better central vision and field of vision than aphakic glasses.[71;124] Lenses are usually cleaned, inserted and replaced by parents, the majority of whom describe initial difficulty with insertion and removal although most quickly become adept at handling them.[125-127] However difficulty of use and high costs can lead to failure to use aphakic contact lenses in up to a third of families in industrialised countries.[125;126;128]

Child resistance to contact lens insertion is a particular issue in those children aged 2-5 years,[125] as maturing self-awareness and improving manual dexterity conspire to make life difficult for the parents of aphakic toddlers. Centres which focus on parental education and support do report improved concordance with contact lens use.[125] Serious complications of contact lens use such as infection and corneal opacity are rare.[125;128] However, contact lenses are expensive and require frequent changes and follow up checks.[126;129] A further obstacle to their wider adoption in low income countries is the need for a clean water supply to ensure hygienic use.[129]

Intraocular lens implantation

In theory, artificial intraocular lens (IOL) implantation offers a permanent state of full or partial refractive correction. Implantation of an IOL into the emptied capsular bag can occur as part of primary surgery (i.e. immediately following cataract extraction), or secondary implantation can occur later in childhood or in adulthood, greatly reducing the required corrective refractive power. Secondary IOL implantation can be technically demanding due to intraocular inflammatory capsular bag changes following primary surgery, and the remaining practised options, anterior chamber IOLs or the suturing of IOLs into place, can result in IOL dislocation or significant inflammation and glaucoma due to iridocorneal angle trauma. [130-133]

The potential benefits of primary intraocular lens implantation are better visual rehabilitation without the visual field defects of glasses and amblyogenic risk of poor compliance or refitting needs of contact lenses, less long term expense for populations in the developing world and the removal of the need for later secondary surgery to implant an IOL. However, there is limited robust evidence that these benefits are realised in young children

2.3.i.**Summary**

Congenital and infantile cataract is a rare disease which adversely impacts on visual development, and which often co-exists with other ocular disorders and systemic disorders which further impact on visual and global development.

Adult cataract surgery is the dominant procedure in ophthalmic practice, and is a force for technical innovations which have often diffused into paediatric cataract surgery.

Due to the amblyogenic nature of congenital/infantile cataract early intervention is essential, but visual rehabilitation is key. Focusing power needs to be replaced, and over the past few decades, for children aged under 2 years, this has been achieved predominantly with aphakic contact lenses and glasses.

2.4. Outcomes following congenital and infantile cataract surgery

2.4.a. **Evaluating the existing evidence on outcomes**

It is challenging to place the study reported in this thesis within the context of the existing literature on outcomes following congenital and infantile cataract surgery. Comparisons with the existing evidence are difficult due to the methodological variations and limitations of the published studies. These limitations include misclassification bias, selection bias, confounding and lack of statistical power to determine the role of chance

2.4.a.i. Bias

Selection bias: Misclassification and varying definitions of disorders and outcomes

The misclassification of non-diseased / non-affected individuals as diseased / affected (or vice versa) has a profound effect on the subsequent analysis of the frequency of disease or the associations with possible causative factors. For example, microphthalmos, microcornea and glaucoma following cataract surgery have all been defined in numerous ways in the existing literature.[75;78;134]

Selection bias: heterogeneity of study populations

Children with congenital and infantile cataract form a varied group, and the populations investigated within the literature reflect this heterogeneity. Investigators have either limited their study populations to children with isolated cataract (no other ocular or systemic disorder)[80;87;135-138] or to children with cataract associated with microphthalmos,

microcornea or persistent fetal vasculature.[70;139;140] Included (or excluded) children may have different risk factor profiles for the development of different post-operative outcomes, differences which are not always appropriately dealt with at analysis. This case mix adversely impacts on attempts to compare the findings of different studies, and on the generalisablity of individual study findings.

The majority of the studies on outcomes have been retrospective and most have failed to report how many children were lost to follow up, or on the case mix of those children.[5;70;72;73;77;79-84;87;135;137-169] Consequently, these studies are at risk of ascertainment bias.

2.4.a.ii. Confounding

Prior investigations of the potential associations of child and surgery specific factors with favourable and adverse outcomes following congenital and infantile cataract have not always considered the issue of confounding.[80;166] In order to reduce the risk of confounding, the possibilities of complex relationships between clinical variables and outcomes must be considered and investigated during analysis. Methods used to address confounding include stratification, but the most robust way of investigating the relationship between multiple, possibly interrelated clinical variables such as age, ocular findings and family history is to undertake multivariate analysis.[79;170;171] In this way, the independent effect of one variable on the risk of a particular outcome once other variables have been taken into account can be ascertained, as can the direction and size of effect one variable has on another variable's association with the risk of the outcome.

2.4.a.iii. Levels of evidence

The hierarchy of evidence (reflecting the hierarchy of study methodology) can be used to consider the strength of the evidence on outcomes following surgery. Methods used in the study types at the “top” of the hierarchy are more likely to minimise bias and confounding (Table 8). However, the hierarchy is not an inflexible construct, as study methodology is no guarantee of study quality: the level within the hierarchy of an individual study may be graded down on the basis of ‘study quality, imprecision, indirectness’,[172] and the level of a review of studies may be graded down because of inconsistencies between studies, or because the size of the reported effects are very small. Conversely, the level may be graded up if there is a large effect size.

Table 8. Levels of evidence
from the Oxford Centre of evidence based medicine[172]

Level of evidence	Outcomes investigated	Study methodology
1 (Highest level)	Prognosis	Systematic review of inception cohort studies
	Treatment benefits Treatment harms	Systematic review of randomised trials
	Rare treatment harms	Systematic review of case control studies or studies revealing dramatic effects
2	Prognosis	Inception cohort study
	Treatment benefits	Randomised trial or observational study with dramatic effect
	Treatment harms	Systematic review of nested case control or dramatic effect
	Rare treatment harms	Randomised trial or observational study with dramatic effect
3	Prognosis	Cohort or control arm of randomised trial
	Treatment benefits Treatment harms Rare treatment harms	Non randomised controlled cohort / follow up study
4	Prognosis	Systematic review of case-series
	Treatment benefits	Systematic review of case-control studies, historically controlled studies
	Treatment harms Rare treatment harms	Case-control studies, historically controlled studies
5 (Lowest level)	Prognosis Treatment benefits Treatment harms Rare treatment harms	Opinion without explicit critical appraisal, based on limited / undocumented experience, or based on mechanisms

2.4.a.iv. Chance

Congenital and infantile cataract is rare, and adverse outcomes following surgical treatment are rarer. When a disease or an outcome is uncommon, it can be a challenge to obtain the sample size needed to demonstrate statistical significance for even potentially large effects. Much of the existing literature on outcomes following surgery consists of case series on relatively small numbers of children and hence is prone to chance findings. [71;82;83;83;84;139;150;153;157;173-184]

2.4.b. **Visual outcomes following congenital and infantile cataract surgery**

There now follows a summary of the existing evidence on visual outcome following surgery for bilateral and unilateral congenital or infantile cataract. The terms used for the database searches for this review are appended (Appendix N).

2.4.b.i. Bilateral cataract

Whilst the majority of children with bilateral disease will not have normal vision post operatively,[64;171] surgery can prevent visual impairment in approximately a third of children[64;71;176] (table 6). Severe visual impairment or blindness affects up to 33% of children following surgery.[64;176;177] In Chak et al's[171] follow up study of 113 children initially identified by UK surveillance in1995/6,[52] five years following bilateral surgery the median visual acuity was 6/18 Snellen. Although children had been aged between 5 days and 12 years at surgery, the median age at surgery of 4 months indicated that the majority of these children underwent surgery early in life.

2.4.b.ii. Unilateral cataract

Compared with those with bilateral cataract, children with unilateral disease generally experience worse visual outcomes in the operated eye due to the additional amblyogenic drive of competition from the better-seeing eye.[171;177;178;185] Post operatively, between a third and a half of children will have severely impaired vision or worse, and moderate to severe visual impairment in the operated eye is the usual outcome (table 7).[171;174;177;179-181;185] Chak et al reported that for the 40 children who had undergone surgery following diagnosis of cataract in 1995/6 (with a median age at surgery of 3 months) the median acuity in the operated eye five years after surgery was 6/60.[171] Parental concordance with occlusion of the fellow eye is of key importance.[120;171;186]

Table 9. Visual outcome following bilateral cataract surgery
binocular acuity or acuity in better eye

Study	Level of evidence	N (children)	Age at surgery	Follow up	Visual outcome		Notes
					no impairment	severe impairment or worse	
Chak 2006[171]	2a	113	4.6 months (median)	7 years (median)	Median acuity 0.6 (moderate impairment)		
Magnusson et al 2002[78]	3a	28	<1 year	> 12 years	Mean acuity 0.3 (no impairment)		
Hing et al 1990[71]	3b	26	<12 months	3 years (mean)	54% achieved vision better than 6/24		No visual impairment in 83% of children operated on in first 2 months of life
Robb et al 1992[187]	3b	30	<24 months	> 3 years	37%	7%	
Kugelberg et al 1992[188]	3b	7	< 3 months	5 years (mean)	43%	29%	
Neumann et al 1993[174]	3b	11	8 months (mean)	60 months (mean)	64%	9%	
Bradford et al 1994[176]	3b	23	<6 months	6 years (mean)	43%	14%	
Lesueur et al 1998[177]	3b	11	4 months (mean)	77 months (mean)	17%	11%	Mean vision 0.7 (moderate impairment)
Lundvall et al 2002[84]	3b	13	<12 months	> 4 years	54%	8%	Also studied 9 children with other systemic / ocular abnormality: 56% severe visual impairment
Francis et al 2001[64]	3b	172	< 2 years	Not reported	34%	33%	
HeHua [189] *et al 2007*	3b	38	<12 months, mean 5.6m	9 years (mean)	Mean vision 0.25 (no impairment)		All children had secondary IOLs after 2 yrs of age
Birch [190] *et al 2009*	3b	37	10 weeks (mean) <31 weeks	10 years (mean)	Mean vision 0.4 (no impairment)		Worsening of visual outcome with every 1 week increase in age up to age of 14 weeks
Lorenz et al 1991[191]	4	9	< 1 year	> 5 years	32%	22%	

Table 10. Visual outcome in operated eye following unilateral cataract surgery

Study	Level of evidence	N (children)	Age at surgery	Follow up	Visual outcome		Notes
					no impairment	severe impairment or worse	
Chak et al 2006[171]	2a	40	3 months (median)	7 years (median)	Median visual outcome 1.0 (severe impairment)		
Lambert et al 2004[180]	3a	13	9 weeks (mean)	4 years (mean)	17%	-	27% blind in operated eye
Drummond et al 1989[179]	3b	14	< 6 months	>5 years	43%	37%	
Wright et al 1992[181]	3b	13	< 9 weeks	>1 year	13%	-	
Neumann et al 1993[174]	3b	11	4 months (mean)	5 years (mean)	18%	73%	all children with good visual outcome underwent surgery in first month of life
Thompson et al 1996[192]	3b	12	< 13 weeks	> 4 years	Mean acuity 1.3 (severe impairment)		
Birch et al 1998[178]	3b	17	< 30 weeks	>7 years	Aged under 8 weeks at surgery mean vision 0.4 (no impairment); age over 8 weeks vision 0.9 (moderate impairment)		
Lundvall et al 2002[83]	3b	30	< 12 months	>4 years	20%	80%	All children with 0.1 vision or better underwent surgery aged <3 months
Birch et al 2005[185]	3b	5	4 months (mean)	4 years (mean)	Mean visual outcome 0.4 (no impairment)		
Chen et al 2010[193]	3b	15	<6 weeks	>5 years	50%	25%	
Allen et al 2010[74]	3b	62	5 weeks (mean)	>7 years	6%	27%	Children who underwent surgery aged ≤2weeks had vision 0.4 (no impairment)
Lesueur et al 1998[194]	4	9	6 months (mean)	3 years (mean)	11%	56%	mean outcome 1.0 (severe impairment)

2.4.b.iii. Age at surgery and other determinants of good visual outcome

The age at surgery has consistently been reported to be the most important determinant of visual outcome: the later the surgical intervention, the worse the visual outcome.[64;71;171;174;178;185]. The highest level evidence on the impact of age on outcome comes from Chak et al's study, which reported that decreasing age at surgery results in reduced relative odds of poorer visual outcome: relative odds = 0.99 **unilateral** cataract (CI 0.96 – 1, n=40) and 0.98 **bilateral** (CI 0.94 – 1, n=109).[171] Another smaller prospective study reports that between 0 and 14 weeks of age visual acuity decreases by 1 LogMAR line for each 3 weeks of delay in undergoing **bilateral** surgery. [195] The idea of a window of developmental sensitivity, which gradually closes over the first years of life, fits well with this evidence of the importance of early intervention for cataract. However, the start point and the duration of the critical window within the sensitive period (see box 1, section 2.2.b, page 36) is unclear. If there is a critical period during which visual stimulus is absolutely necessary for development of function, then restoration of clear focused vision before the end of this period will give the child the best chance of good vision, and surgery during the latent pre-critical phase would theoretically help the child to escape the risk of amblyopia altogether.

The critical periods for form perception and for cerebral ocular dominance (at particular risk in unilateral cataract) may close before the 8th week of life, as evidenced by reports from small retrospective case series studies. These suggest that normal vision in the operated eye is more common in children with **unilateral** cataract operated on before 7 weeks of age (4/11, 36%) versus children operated on after 7 weeks (0/12) [180]; further, strabismus and nystagmus is more common in children with **unilateral** and **bilateral** cataract undergoing surgery later than 7-8 weeks of age versus surgery before 7 weeks of age [166]. A weakly bilinear relationship between increasing age at surgery and the decreasing level of post-operative visual outcome has been reported in two small

retrospective studies (45 children with unilateral cataract, and 37 with bilateral cataract) with a steeper decline in outcome with increasing age (suggesting closure of a critical window for form perception) beginning at 6 weeks old for unilateral cataract, [36] and 14 weeks for bilateral cataract.[195] However, the possibility of a non-linear relationship was not investigated. The latent pre-critical periods may end within the first month of life: surgery before 3-4 weeks of age is associated with a lower rate of the indicators of poor visual acuity, strabismus and nystagmus.[195;196]

Visual outcome after paediatric cataract surgery also depends on several other factors including the:

- co-existence of other ocular anomalies – abnormalities which directly impact on acuity, such as retinal disorders or microophthalmos,[70;197] , and abnormalities which are associated with poorer outcome vision due to the increased risk of per and post-operative complications following cataract surgery such as persistent fetal vasculature.[176;198;199]

- effectiveness of and concordance with amblyopia treatment, especially for children with unilateral cataract[119]

- effectiveness of and concordance with refractive correction[74]

2.4.c. **Early post-operative complications of congenital and infantile cataract surgery**

2.4.c.i. Inflammation

Post-operative anterior segment inflammation, the immune response to the trauma of intraocular surgery, is much brisker in children than in adults following cataract surgery.[1;115] Inflammation can result in the deposition of inflammatory proteinaceous fibrin membranes in the eye, adhesions between the iris and capsule (pupil synechiae), and inflammatory damage to the trabecular meshwork (trabeculitis). Post-operative drops are used to control inflammation, and excessive inflammation (as indicated by membranes, synechiae or congested iris vessels) is treated with intensive topical steroid regimes, periocular steroids or intraocular anti-inflammatory agents, depending on the severity.[105] Inflammatory membranes may require surgical removal.

2.4.c.ii. Post-operative iris prolapse

The iris muscle may prolapse through a surgical wound which re-opens following surgery, with consequent post-operative inflammation and possible trauma to the angle through tension on the root of the iris at the iridocorneal uveal meshwork.[9]

2.4.c.iii. Endophthalmitis

A very rare but devastating complication of intraocular surgery is intraocular infection, endophthalmitis.[200] The estimated UK incidence following adult cataract surgery is

0.14%, or one case per 700 procedures.[201] The incidence in children is unknown. Endophthalmitis is difficult to treat, and generally has a very poor visual prognosis.[201;202]

2.4.c.iv. Acute pupil block

The anterior vitreous gel or retained lens matter (which, when released from the containment of the capsule, becomes hydrated and swollen) may move forwards, shallowing the anterior chamber and blocking the pupillary opening and '*closing*' the iridocorneal angle. This prevents the egress of aqueous fluid, thus causing an acute rise in intraocular pressure. If sustained, the intraocular hypertension results in destructive changes to ocular tissue, in particular the optic nerve (*glaucoma*). Pupil block is treated with surgical removal of the blocking material. In the longer term, the iridocorneal angle may remain closed despite surgical treatment, due to inflammatory adhesions formed between the iris and cornea during the acute phase.

Over the past few decades, rates of post-operative *closed angle* glaucoma following early childhood surgery have declined following the introduction of vitrectomy techniques allowing more thorough removal of the cataract and anterior vitreous.[9;183]

In adults, incomplete per-operative removal of the superviscous OVD gel types (Healon GV, Healon 5) has been associated with early transient elevations in intraocular pressure.[110]

2.4.d. **Late post-operative complications of congenital and infantile cataract surgery**

Late post-operative complications are those which occur after the first post-operative month.[2] The most significant sight threatening complications following early childhood cataract surgery are glaucoma, and the formation of opacification across the visual axis. Other possible late complications include detachment of the retina. [64;71;106-108]

2.4.d.i. Post-operative visual axis opacity

Although primary posterior capsulotomy and anterior vitrectomy removes the central section of the capsule and anterior gel, post-operative opacification across the central axis of vision can still develop due to the proliferation of microscopic populations of remnant lens fibres. [1;203]

Definition and classification

Visual axis opacity (VAO) can occur due to proliferation at the anterior or posterior capsular planes, and can take one of two forms:

- Pearls, or swollen lens fibre remnants which form bladder like cells, which are semi-opaque
- Fibrosis, with opacified metaplastic lens fibre remnants which have constrictive as well as proliferative properties, thus leading to phimosis (narrowing) of the anterior or posterior capsulotomy openings.[1]

In addition, following significant post-operative inflammation the visual axis can be obscured by membranes of organised inflammatory material crossing the pupil margin.[1;115]

Prevalence

It has been reported that between 9% and 22% of children will develop VAO during the first post-operative year.[114;165;204]

Associated factors

Post-operative inflammation (which may be due to surgical iris trauma), and inadequate removal of lens matter increases the risk of proliferative and inflammatory VAO. [1;117;204-208]

Treatment

Once VAO develops, prompt treatment with laser therapy or, more commonly, further intraocular surgery [114;117;165;180;209] is indicated to prevent the development of amblyopia. Where inflammatory membranes cover and occlude the pupil, urgent treatment may be necessary to release pupil block. [105]

2.4.d.ii. *Post-operative ocular hypertension and glaucoma*

Paediatric post-operative glaucoma is a sight threatening disease in which ocular damage occurs secondary to elevated intraocular pressure (ocular hypertension) which is in turn secondary to damage to the aqueous drainage pathways in the iridocorneal angle. The damage to the angle can either be of a *closed angl*e type, where there is loss of access to the drainage angle due to apposition / adherence of the iris and / to cornea (as seen in pupil block episodes), or *open angle* type, where there is an open but dysfunctional drainage pathway.[2;9;137;158;183] Since the 1980s, rates of post-operative closed angle glaucoma following early childhood surgery have reduced following the introduction of microsurgical and vitrectomy techniques which allow safer and more thorough removal of the cataract and anterior vitreous. The problem of open angle glaucoma, which presents more insidiously, has gained increased attention.[210]

Definition and classification

Ocular Hypertension

The average infant intraocular pressure ranges from 5mm of mercury (mmHg) to 21mmHg varying with the method used to measure pressure, whether the child is awake, and the use of certain anaesthetic agents.[2;211;212] Ocular hypertension is therefore an intraocular pressure of >21mmHg. However, as individuals who have undergone early childhood cataract surgery have thicker corneas than 'normal' individuals, which results in artificially elevated measurements of intraocular pressure, [141;142;213] a measured ocular hypertension may not reflect a 'true' ocular hypertension.

Glaucoma

The British Infantile and Childhood Glaucoma study group, which consists of paediatric ophthalmologists specialising in glaucoma, has concluded that the appropriate definition of childhood glaucoma should put the emphasis on the destructive sequelae of ocular hypertension on the ocular structures, rather than the degree of hypertension diagnosed (box 3).

Box 3. The British Infantile and Childhood Glaucoma study group definition of glaucoma:

'the presence of a combination of clinical signs consistent with high IOP (≥21mm Hg), such as: optic disc cupping ≥0.3 (signifying optic atrophy) or disc asymmetry ≥0.2, progressive disc cupping (thinning), buphthalmos, enlarged corneal diameter, corneal oedema, Descemet's membrane splits / Haab's striae (signs of corneal stretch), visual field defects (due to the neuropathy), and progressive myopia'. [214]

Prevalence

Due to the different definitions in use within the literature on secondary glaucoma after cataract surgery, including those listed in box 4 overleaf, it can be difficult to compare studies to determine with certainty the prevalence of secondary glaucoma after childhood cataract surgery. However, following childhood cataract surgery, it is likely that between 10% and 25% of aphakic eyes will develop glaucoma by the 10th post-operative year.[79;80;166;170;215;216] The population based and large scale longitudinal studies of outcomes following congenital and infantile cataract surgery consistently show that the frequency of glaucoma increases with the duration of follow up,[78;216] with approximately 5% of operated eyes developing secondary glaucoma each year.[170] In addition, secondary glaucoma is now the most common sight threatening post-operative outcome of childhood cataract surgery, accounting for a third of all secondary childhood glaucoma in industrialised countries such as the United Kingdom.[214]

Box 4. Differing definitions of glaucoma within the existing literature

the presence of 'elevated pressure (IOP>21mmHg) **AND** signs of that elevated pressure'[5;82;134;136;139;157-160;217;218]

the presence of 'elevated pressure (IOP>25mmHg) **AND** signs of that elevated pressure'[75;78;165;166]

the presence of 'elevated pressure (not defined) **AND** signs of that elevated pressure'[80;156]

'elevated intraocular pressure (<21mmHg)'[162-164]

'elevated intraocular pressure (<25mmHg)'[9;72;73;79;87;137;140;167-169;183])

'elevated IOP **OR** signs of elevated pressure'.[77;81;161]

Associated factors

As stated earlier, in a large number of studies, there has been a misclassification of the outcome of interest (with isolated ocular hypertension considered as glaucoma) with subsequent possible biased analysis of the clinical associations of aphakic glaucoma. There is, however, robust evidence that increasing age at surgery is protective against the risk of glaucoma.

Age at surgery – the key risk factor for developing secondary aphakic glaucoma?

A 10 fold increase in age at surgery (for example, from 3 days old to 30 days old at surgery) may be associated with a 60% reduction in the risk of developing glaucoma. When other factors have been accounted for (using multivariate analysis) age at surgery is either the only significant or the most significant risk factor for developing glaucoma. [72;79;87;88;170;170]

It is increasingly recognised that determining the 'ideal' age at cataract surgery for an individual child requires balancing the risk of amblyopia with the risk of glaucoma, but there is no robust evidence of a 'threshold' age for early life cataract surgery, that is, an age at which the risk of developing subsequent glaucoma drops significantly. The strongest available evidence puts a threshold age well beyond the age of the postulated 'critical period': Rabiah et al and Swamy et al used an ad hoc cut off of 9 months of age, and reported that age under 9 months conferred an increased risk of glaucoma (n=322 children, hazard ratio =7.0 [CI 3/6 – 13.7] and n=234 children, hazard ratio=2.9 [CI 1.3 – 7.7] respectively following multivariate analysis).[79;87]

Other risk factors for developing aphakic glaucoma

Microphthalmos and microcornea have been reported as risk factors for glaucoma following univariate analysis, [78] but not following multivariate analysis, suggesting that when the age of the child is taken into consideration, the size of the eye is not a significant independent risk factor for the future development of aphakic glaucoma. However, this may also reflect the small study populations in these studies, and the resultant lower power to detect statistically significant clinical associations.

Persistent fetal vasculature (PFV) has not consistently been found to be a significant risk factor,[87;166] but the phenotypology of PFV is so variable that the case mix may be responsible for the absence of robust reported associations.

Treatment

The treatment of paediatric glaucoma involves topical and oral anti-hypertensive medication, laser ablation of the ciliary body to shut down aqueous production, and intraocular surgery which may involve the implantation of a drainage device to lower IOP.[210] Secondary glaucoma following cataract surgery is difficult to manage, and the majority of children require multiple interventions.[136;158;210] It can result in severe visual impairment in almost a half of affected children with the outcome in some cases being worse than the outcome in un-operated cataract.[78;136;137]

A paper reporting the detailed findings of a systematic review, undertaken as part of the research for this thesis, of the existing evidence on secondary glaucoma following childhood cataract surgery is appended to this thesis (Appendix A) as are the search terms used for the review (Appendix N).

2.4.d.iii. Other complications

The other potential late complications of early childhood cataract surgery include:

- decentralisation of the pupil due to iris trauma or inflammatory iris adhesions,[107;219] which can impair vision should the pupil edge obscure the visual axis

- detachment of the retina due to tractional forces acting through the vitreous gel: an uncommon complication following modern cataract surgery involving more controlled manipulation of the vitreous gel[220]

- macular oedema: swelling of the central area of the retina is an uncommon and usually self-limiting complication[107]

2.4.e. **Refractive change following surgery**

Cataract extraction in infancy, the period of relatively rapidly occurring changes in ocular structure, can impact on the further growth of the eye and consequently the emmetropisation process. Although animal models of the outcome of lens extraction demonstrate retardation of ocular growth, in human infants the impact of lens extraction is usually in the direction of a myopic shift due to excessive axial elongation.[221;222 223;224] The mechanisms behind this alteration in ocular growth are unclear, and will remain so until the process of emmetropisation in normal eyes is more fully understood. This abnormal elongation may be in response to visual blur due to uncorrected myopia, but has been shown to occur in aphakic eyes with 'normal' vision.[225] It may be due to postoperative complications, either directly (in glaucomatous eyes) or indirectly (where the complication leads to visual derivation). It may also be a consequence of the impact on emmetropisation of the loss of accommodation with removal of the crystalline lens. Or, it may simply be that cataractous eyes are essentially abnormal and thus exhibit abnormal growth patterns.

2.4.f. **Summary**

The heterogeneity of disease and outcome classification as well as study design and study populations within previous observational studies of outcomes following cataract surgery in early childhood have made comparisons or systematic review difficult, and meta-analysis extremely difficult.

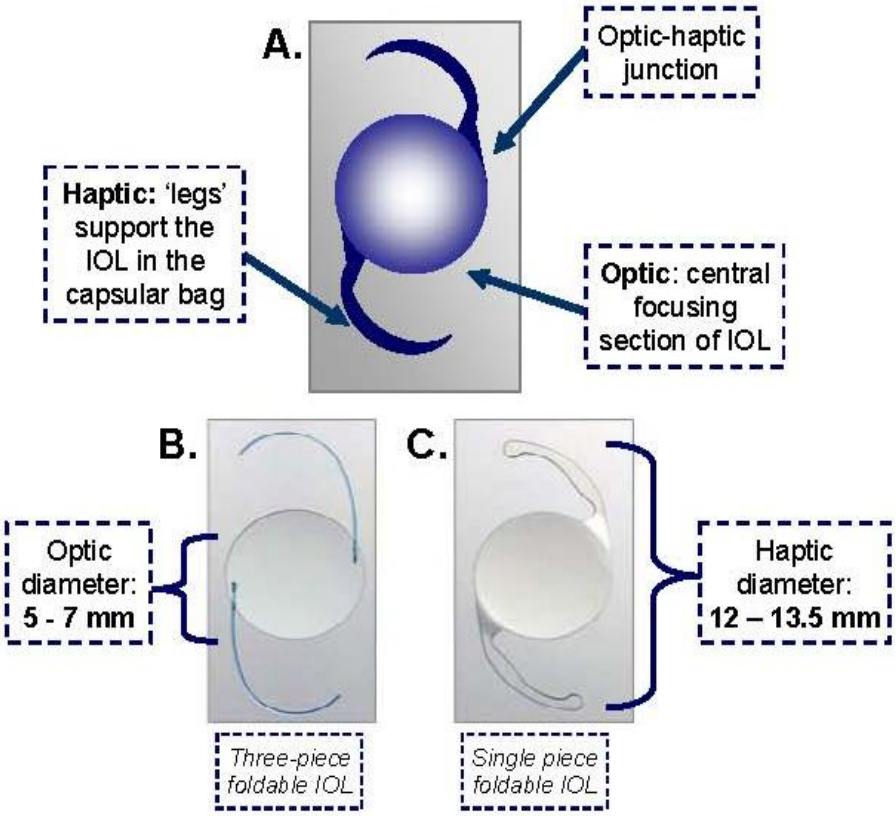
However, there is good evidence that with current treatment approaches just over 50% of children will have some visual impairment following surgery for bilateral cataract, and over 50% of children will have severe visual impairment in the operated eye following surgery for unilateral cataract. Aphakic glaucoma is the most important complication following paediatric cataract surgery, with surgery during the first two years of childhood resulting in a lifetime increased risk of the development of this sight threatening and challenging condition. Age at surgery is the probably the most significant risk factor for glaucoma, but this risk should be balanced by the risk of dense amblyopia if surgical intervention is delayed.

2.5.Primary intraocular lens implantation

IOLs consist of a central optic section, and flexible haptic 'legs' which provide the intraocular support (Figure 8) The optic and haptics may be made up of the same (one piece IOL) or different (three piece IOL) materials. Biocompatibility is the ability of a material implanted in the body to 'exist in harmony with the surrounding tissue without causing deleterious change'.[226] Cataract extraction has been practised since 1000BC, but patients with cataract had to wait until the 1950s for a biocompatible, manipulable material capable of safely replacing the lens' lost focusing power. As with the development of penicillin, tetanus immunisation and blood transfusion,[227] warfare was the driving factor behind the development of a biocompatible intraocular material: modern intraocular materials (box 5) are descendants of the fragments of blown-out Perspex windscreen which were observed to stay inert within the eyes of injured World War II RAF pilots.[228]

Age related cataract is the most common cause of impaired vision in adults aged over 65 years old, and in 2009, in England, 320,000 adults underwent implantation with an intraocular lens.[229] Primary IOL implantation is routine practice in adult surgery, who can expect excellent visual results following surgery, with 95% of otherwise healthy eyes achieving 6/12 vision or better, [109] and sight threatening complications occurring in less than 5%.[109] However, intraocular lens implantation has until recently been exceptional practice in paediatric cataract surgery (specifically in children aged under 8 years old) due to the difficulties inherent in the safe and effective implantation of an IOL within an environment which is at its most pro-inflammatory stage, a structure which is undergoing significant change, and a child who is experiencing rapid visual and global development.[107]

Figure 8. Intraocular lenses
(A) showing the optic and flexible supportive haptic portions, and (B) & (C) showing the optic and haptic dimensions for the IOLs most commonly in use in the developed world. [105]



Box 5: Modern IOL materials

- *PMMA, or poly methyl methacrylate: Rigid, less biocompatible than silicone acrylic, the most economic IOL material, and most in use in the developing world*[226]
- *Hydrophilic acrylic: Foldable (therefore require a smaller wound for implantation), less capsule biocompatibility than other hydrophobic acrylic*[203;230]
- *Hydrophobic acrylic: Foldable, highest biocompatibility*[231]
- *Silicone: Foldable, less capsule compatibility than hydrophobic acrylic*[232]

2.5.a. **The issues surrounding surgical planning for IOL implantation in children versus implantation in adults**

2.5.a.i. Intraocular lens sizing

Modern IOLs (such as those illustrated in Figure 8) measure from 12-13.5mm in haptic diameter, and have been designed so that they are able to sit securely within the adult capsular bag (which is approximately 10.5mm in diameter) without causing undue stretch or distortion.[203]

Whilst the adult capsule measures 10.5mm in adulthood, however, the mean neonate capsule diameter is considerably smaller at 7mm, although it grows to 9mm by 2 years of age and 10mm by 5 years.[226] As such, most IOLS designed for use in adults are too large for the infant eye, however IOL implantation in post mortem infant eyes, show 'acceptable' levels of stretching with smaller IOLs (haptic diameters of 12mm and optic diameters 5-6mm across).[233]

2.5.a.ii. Patient selection

At present, any adult who is able to undergo cataract surgery is selected for IOL implantation in all but the most exceptional cases, for example, where there has been traumatic damage to the capsular bag and iris with no resultant secure positioning possible for the IOL.[2]

There is at present no consensus on the children most likely to benefit from or most likely to experience complications following primary IOL implantation. However, some practitioners have argued that children at a greater risk of glaucoma (such as children with Lowe oculorenal syndrome associated cataract) should not receive IOLs.[107;234] Other children unlikely to receive IOLs are those with small eyes (although there is no

consensus on which size of eye is ‘too small’ for safe IOL implantation) or those in whom the capsule is too unstable to support the lens, such as those with significant persistent fetal vasculature.[105;106;235]

2.5.a.iii. Refractive planning

Biometry

In adults, the selection of the power of the implanted IOL is dependent on the pre-operative dimensions or biometrics of the eye. Biometry, a non-contact scanning of the eye which measures the curvature of the cornea and length of the globe, is undertaken, and these various parameters are entered within one of several eponymous formulae in order to calculate the necessary prosthesis power. Four different formulae are in use in adults in the UK: the Sanders, Retzlaff and Kraff third generation (SRK/T), Holladay, Haigis and Hoffer Q [236 237 238] equations, with the Hoffer Q and Haigis equations being recommended by the Royal College of Ophthalmologists for adult eyes less than 22mm in length. These formulae have been developed and refined using the parameters and outcomes of adult eyes. The most commonly used formulae, the Hoffer Q and the SRK/T, have been designed to be further individualized for patients using either ocular data (specifically anterior chamber depth for the Hoffer Q[238]) or a surgeon specific adjustment (the A constant) derived from refractive outcome data from previous patients [236].

Whilst biometry in adults is a fast, simple non-contact procedure, requiring adults to focus on a fixation light whilst the automated measurements take place, young children cannot be expected to comply in this way. Thus, contact methods of measuring the eye whilst the child is held securely, sedated or anaesthetised have been developed. Ultrasonic axial length measurement, which is necessary for biometry, requires contact with the ocular surface either with a probe or through a globe immersion device.

Contact methods have been shown to have reduced accuracy when compared to immersion techniques, possibly due to inadvertent flattening of the front of the eye.[239] Paediatric cataract surgeons have not yet reached a consensus regarding the best method of choosing a power calculation formula. The four different formulae in use are all based on assumptions about the shape of the adult eye and the position of the IOL implant after surgery in adults.[237;240] These formulae are less accurate in predicting outcomes for children,[241;242 242;243] as the shape of the eye differs significantly in infancy and changes as the eye grows, with significantly less accuracy at the extremes of axial length and corneal curvature. The relationship between the biometrics, the formula choice and the accuracy of the power calculation are unclear.

Power selection

In adults, the lens power and refractive outcome is selected following discussion with the patient regarding whether they would prefer to be focused for distance work (emmetropia) or focused for near work (mild myopia). Following surgery adults either use reading or distance / driving glasses for additional post-operative focusing respectively.

In paediatric surgery, the surgeons can either select a lens power which leaves the eye emmetropic or one which leaves the eye in the normal infant state of hypermetropia, so that the growth of the eye and 'myopic shift' will result in a final refractive state near emmetropia.[106;244]

The myopic shift in paediatric pseudophakic eyes is larger than that seen in aphakic eyes, due in part to the optical effect of a fixed lens power in a growing eye: as the eye becomes larger, the IOL shifts further away from the retina, inducing myopia to a degree relative to the power of the lens. Axial elongation following paediatric cataract surgery has been reported by several small scale studies to be, however, more

variable in pseudophakic eyes than in aphakic eyes,[245-250] which may indicate some other impact of IOL implantation on ocular growth and emmetropisation.

It is difficult to judge which eyes will develop a significant refractive surprise following IOL implantation in infancy. A child's pre-operative axial length, post operative keratometry, the power of the implanted IOL and the presence of other ocular disorders do not appear to correlate well with the degree of myopic shift.[251-253] Age has been shown to be an influencing factor: the younger the patient, the larger and the more unpredictable the myopic shift.[252;254;255]

Due to the uncertainties regarding which IOL power formula to use and the degree of the paediatric pseudophakic myopic shift, investigators have reached differing conclusions regarding the most appropriate refractive outcome to aim for in primary IOL power selection for children undergoing surgery in the first two years of life. For example, the suggested refractive goals for children aged under 2 months old range from +10 dioptres[105] to +8 dioptres[106] to +7D[256], whilst the goal for children aged 5 years old is +5 dioptres.[105;182;219;257]

2.5.a.iv. Per operative procedure

In paediatric and in adult eyes the intraocular lens is ideally placed within the capsule: however, this is technically demanding and may be made impossible by per-operative capsular bag damage. In these cases, if an IOL is to be used, surgeons may place the haptics in the sulcus, the space between the peripheral iris and the anterior capsular face.[105] It is unclear if this intraocular fixation method, which if undertaken in early childhood results in contact between the IOL haptics and the immature iris and irido-ciliary area, is associated with adverse outcomes.

2.5.a.v. Management of post-operative inflammation

Following routine adult cataract surgery with or without intraocular lens implantation, four times daily to twice daily topical corticosteroid drops are used over the first post-operative month in order to control inflammation (Royal College of Ophthalmology guidelines, 2009). Following cataract surgery in the first two years of life, the particularly pro-inflammatory state of early childhood necessitates more frequent instillation of post-operative steroid drops.[107] In addition, despite the biocompatibility of IOL materials, IOL implantation may result in increased post-operative inflammation, due to the inevitable iris trauma inflicted when attempting to insert an IOL with a 5-6mm optic diameter through an infant pupil which even at maximal dilation is less than 7.5mm in diameter.[258] Most surgeons advocate additional intraocular or periocular steroid medication following IOL implantation in early childhood. [105;106;259;260]

2.5.b. **Post-operative visual re(habilitation)**

Amblyopia is not an issue in the post-operative management of cataract in adults and children over 8 years old, in contrast with its particular importance for children who undergo surgery in the first two years of life, a time when amblyopia intervention is most effective. Whilst occlusion therapy remains the same for children undergoing surgery with IOL implantation for unilateral cataract,[261] refractive correction following surgery for unilateral or bilateral is different, as pseudophakic children do not require the full refractive power of the natural crystalline lens. However, where post-operative hypermetropia or emmetropia has been achieved, pseudophakic children, who are unable to accommodate, will require refractive correction in order to focus on near objects such as toys, parental faces or print. Refractive correction will also be needed if there has been a 'refractive surprise', an unexpected refractive result following IOL implantation.

2.5.c. **Visual outcomes following primary IOL implantation in children ≤2 years old**

The existing studies on outcomes for children under 2 undergoing primary IOL implantation are generally limited by relatively small numbers, with the majority of these studies involving fewer than 20 children,[177;182;185;186;253;262-266] and retrospective study designs with resultant incomplete datasets necessitating narrow focus on particular outcomes or inability to fully investigate child or surgery specific determinants of outcomes.[144;153;247;267-271]

Nevertheless, it appears that visual outcomes following primary IOL implantation in children under 2 compares favorably to outcomes with aphakic contact lenses.[185;186;272] Vision is either not significantly different or, in children with unilateral cataract, is slightly better, as the reduced refractive difference between the two eyes is thought to reduce the amblyogenic drive.[253;185] However, there is often a selection bias at play, as the cohorts undergoing primary IOL implantation are carefully selected and thus tend to be those with a better visual prognosis due to absence of other ocular anomaly or development of cataract at later stages of infancy outside the critical sensitive period.[185;247;152; 270; 148; 153]

Two groups have undertaken a more systematic and direct comparison of outcomes with and without IOLs and have exclusively studied infants with unilateral congenital cataract undergoing surgery in the first 6 months of life.[272, 180] Autrata et al[272] reported improved vision in 18 infants implanted with IOLs (0.43 LogMar) versus 23 children managed with contact lenses (0.53 LogMar), but the postoperative interocular difference in vision between the cataract and fellow eyes was significantly higher in the contact lens group (0.48 Log MAR versus 0.23 LogMar) in this non randomized prospective cohort study. This suggests a stronger amblyopic drive in the contact lens group which could explain the poorer visual outcome in this group.

The infant aphakia treatment study

Recently, investigators have reported the findings of a randomized controlled trial, the Infant Aphakia Treatment Study (IATS).[273] The IATS group involved 20 surgeons across 12 centres which allocated 114 children aged less than 7 months at the time of surgery to either cataract surgery and contact lens correction, or surgery with primary IOL implantation. The median age at surgery was 1.8 months within both groups, and the surgical procedure consisted of a vitreous cutter or manual tear capsulotomy, lens aspiration, posterior capsulotomy and anterior vitrectomy. Acrylic hydrophobic IOLs were used in all pseudophakic eyes. Following surgery children received topical steroids four times daily for one month.

At one year following surgery, following training and formal assessment of examiner performance, travelling study examiners assessed the visual acuity of recruited children using Teller grating acuity cards. IOL implantation was not associated with better acuity at this early stage – there was a trend towards better acuity for children within the aphakic group but this did not reach statistical significance (median LogMAR acuity contact lens group, 0.80; IOL group, 0.97; p=0.19).

As a randomized controlled study, the IATS is able to provide evidence at the highest level on the impact of IOL implantation in infancy within the context of surgical practice within the included North American hospitals, but is not able to provide information on if and how the other potential determinants of post-operative vision impact on children undergoing surgery with IOL implantation. These determinants, which may impact differentially on children undergoing surgery with and without IOL implantation, include refractive planning (refractive outcome and biometry method and degree of post-operative refractive correction), surgical technique, IOL type, the use of anti-inflammatory medication (and their impact on adverse outcomes such as glaucoma and visual axis opacity) and ocular parameters such as axial length and corneal diameter. The IATS is also unable to report on outcomes following bilateral primary IOL implantation

In summary, although the IATS has created a valuable source of clinically relevant information for the practice of IOL implantation in infants with unilateral cataract, the study does not inform practitioners in the British Isles as to the national patterns of practice of IOL implantation following bilateral and unilateral cataract surgery, the frequency of adverse events following IOL implantation, or the child and treatment specific factors which impact on outcomes following primary IOL implantation in early life.

2.5.d. **Adverse outcomes following primary IOL implantation in children ≤2 years old**

2.5.d.i. Post-operative open angle ocular hypertension and glaucoma

Despite initial speculation, intraocular lenses (IOLs) have not been found to confer protection from the risk of secondary glaucoma.[170] Papers which have reported a lower prevalence of glaucoma following IOL implantation have been based on children who have been carefully selected for surgery , commonly those who are older at surgery, [144;161;167] and in whom glaucoma is less likely to develop. It could be theorised that the presence of an intraocular foreign body could adversely affect the development of the aqueous drainage pathways through inflammation mediated damage to the angle, but it could also be theorised that the IOL protects the anterior segment from any damaging factors released from the vitreous body, and that it offers some support to the developing angle structures. It is however also possible that IOL implantation in very young children may be associated with a greater risk of glaucoma, possibly due to the increased inflammation which may result. The IATS investigators have reported that whilst glaucoma occurred in more pseudophakic eyes than aphakic eyes following surgery for unilateral cataract, (12% IOL eyes, 5% aphake eyes), this difference did not reach statistical significance (p=0.32).[274 273] As described earlier, the IATS is unable to comment on the impact of other variables such as different surgical methodologies and post-operative steroid regimens on the risk of developing post-operative glaucoma. Another group has recently reported an increased risk of glaucoma following due to aborted IOL implantation necessitating explantation at primary surgery. [81]

2.5.d.ii. Post-operative visual axis opacity

Capsular opacity is more common, and occurs earlier following surgery with IOLs,[180;186;208;270;275] as a consequence of the pro-inflammatory state of infancy and scaffold effect of an intraocular foreign body.[1;276] Between 54% and 94% of children implanted with an acrylic hydrophobic lens (the most biocompatible) develop visual axis opacity in the first year of life.[144;180;182;203;267;277] Primary IOL implantation thus commits the child, family and surgeon to secondary surgical procedure(s) in the majority of cases. The consequence of further surgery to remove capsular opacity, with regards to visual results and incidence of further complications, is unclear.[180;186;208;270;275]

The IATS randomized trial investigators reported that visual axis opacity occurred in 43% of pseudophakic children versus 2% of aphakic children, and that pupillary inflammatory membranes occurred in 30% of pseudophakic children but did not occur at all in the aphake group.[274]

2.5.d.iii. Post-operative refractive change: the 'myopic shift'

The myopic shift is a normal process, in which refractive change ideally results in an emmetropic result for the initially hypermetropic infant (as described in section 2.1.d, page 26) The aphakic eye also undergoes this shift, which can be described either as the gross refractive change in dioptres, or described as the rate of refractive change (the gross myopic shift adjusted by the change in age over the period in which change occurs).

Pseudophakic children who are aged less than 2 years old at surgery appear to undergo an exaggerated myopic shift, with a resultant myopic state, which may be severe. As with the normally developing eye, and the aphakic eye, the primary effector of the myopic shift seen in pseudophakic children is globe axial elongation.[248;253;254] The pseudophakic myopic shift is not only large[252;254] but also shows considerable variance.[246-249;251-255;257] The reported mean myopic shifts range from three[257] to seven[251] dioptres, with follow up ranging from one[253] to seven years.[254]. The shift is devoid of consistent correlation with either a child's preoperative axial length or the implanted IOL power.[251-253] Age at surgery is the significant influencing factor with younger children exhibiting larger and more unpredictable myopic shifts.[251;252;254;255] Other possible causes of myopic shift in pseudophakic children include glaucoma, amblyopic visual deprivation, and normal axial elongation in the presence of a fixed lens power. However, reported studies only examine a small number of children each – between 11 and 34 children, with resultant loss of ability to examine putative associations between clinical factors and refractive outcome.

The adoption of paediatric IOL implantation

The critical dynamics which may promote the adoption of new medical technologies include the patients' demand for change (such as the difficulties which some parents have with aphakic contact lenses and glasses), the low cost to surgeons and hospitals of learning and using the new technology (IOLs are already in widespread use within the UK).[278] IOL implantation has gradually become accepted practice for older children.[279] In 1966, Binkhorst undertook primary IOL implantation in a 2 year old girl. The visual outcome was poor, and the surgery was later complicated by retinal detachment.[280] In 1977, Hiles described poor outcomes with the use of IOLs in children aged 1-2 years old: traumatic bleeding in the anterior chamber and severe inflammation.[281] These surgeons used anterior chamber fixation of intraocular lenses, with lenses fixed to the iris anterior to the pupil. These early cautionary tales dissuaded surgeons from implanting IOLs in early childhood.[104;107] In the early 1990s, as surgical technological advances made it possible to retain a child's capsule in order to retain support for a posterior chamber IOL, practitioners again began to use IOLs in the youngest children, despite the challenges of size, immaturity and inflammation.

In 1993, a survey of members of the American Society of Cataract and Refractive Surgery and the American Association for Pediatric Ophthalmology and Strabismus reported that only 19% of respondents would advise IOL implantation for a child under 2 years old.[282] By 2003, up to 89% of members of the same societies would recommend IOLs for these children although only 12% of surgeons who had used an IOL in a child aged less than 2 years had implanted a child aged less than 7 months old.[283]

2.5.e. **Summary**

Surgical innovation consists of either a new procedure which uses an existing device, or a new device used in an existing procedure. Intraocular lens implantation for children under 2 years old has aspects of both: although IOLs are the most commonly implanted medical prosthesis, and have a strong safety record for the population for which they were first designed (adults aged over 65 years old) an IOL within the small, immature and pro-inflammatory eye of early childhood is a device which is fundamentally different from an IOL within a mature eye.

IOL implantation has been used in children aged over 2 years old since the 1950s, with initial uptake only by surgical ‘innovators’ or ‘evangelists’, followed by gradually increasing uptake due to improvements in managing inflammation, IOL design and refractive planning. IOLs are now being used in children under 2 years old, with evidence of a more rapid adoption pattern despite unanswered questions surrounding the refractive changes in the first two years of life, patient selection and possible adverse outcomes. Standardised information on practice and outcomes is needed in order to ensure the best results for these children.

2.6. Epidemiological investigation into outcomes following cataract surgery in children under 2: methodological issues

2.6.a. **Rare diseases and rarer outcomes: the challenges of chance, bias and confounding**

Rare diseases are those with a prevalence of less than 5 in 10,000 of the population. Together they number 6,000 - 7,000 disorders and collectively they affect 5% of the population.[284] The great challenge of any study into outcomes following surgery for an uncommon diseases such congenital and infantile cataract is the creation of a study population which is representative of the total population at risk.

2.6.a.i. Chance

In order to investigate outcomes following interventions for rare disorders, study designs which increase the number of potential cases are necessary, to increase sample size and reduce sampling error.

2.6.a.ii. Bias

Children with rare diseases tend to cluster in specialised centres, enabling study recruitment, but these centres also tend to manage the more complex cases. As these centres may either have better outcomes due to more experienced clinicians, or worse outcomes due to a case mix with the more severe cases, selection bias may result. Cases of early childhood cataract must therefore be recruited as widely as possible.

Whilst multicentre studies can increase the sample size, there is still a potential for bias. Selection bias can result due to non-participation, and measurement bias can result if

different outcomes and data are assessed within different centres. Uniform and systematic collection of information can strengthen the validity of findings.

Another source of bias is in the classification of outcomes: systematic collection of information with clear, consistent diagnostic or outcome (for example, glaucoma) definition is imperative.

2.6.a.iii. Confounding

Investigation of factors associated with outcomes following a rare intervention can be at risk of confounding. A randomised control trial would limit the risk but it would be an expensive and time consuming undertaking and it is unclear how willing families and clinicians would be to participate in a clinical trial of IOLs versus contact lens management.

Whilst standardised data collection from a multi-centre collaborative network enables a larger and broader sample, management differences within the network introduces further variables which may affect the outcomes of interest, although regression analysis with models using surgery specific variables can help to address potential confounding . The use of a clinical research network brings other challenges, in particular ensuring that the methodology of case identification, recruitment and data collection is fit for purpose when applied diverse and/or numerous clinicians participating in the network.

2.6.b. **Identifying cases**

2.6.b.i. Centralised national databases of activity

NHS information centres which collect data from NHS trusts on the activities undertaken within their hospitals are a potential method of ascertaining information about congenital and infantile cataract surgery.

Hospital Activity Statistics

The United Kingdom National Health Services (NHS) publish annual summary measures of hospital activity through the Hospital Episode Statistics (HES) agency for NHS England,[285] Patient Episode Database for Wales (PEWD) agency for NHS Wales[286] and Hospital Activity Statistics (HAS) agencies for NHS Scotland and Northern Ireland.[287;288] These summary measures are used in a variety of administrative and financial pathways, including Government Treasury negotiations for NHS funds, the allocation of funds within the NHS, and the identification of trends in specific conditions or performance of operative procedures.[289] As the information collected for individuals includes the primary diagnosis and the treatment received in hospital, these centralised measures of activity within UK hospitals are a potential source of data on children ≤2 years old undergoing cataract surgery, and undergoing intraocular lens implantation.

The information on treatment and diagnosis returned to the central database is first entered into hospital databases by hospital administrative staff using diagnostic codes taken from the International Classification of Diseases[49] and operative codes defined by the Office of Population Censuses and Survey.[290] The codes are recorded by medical staff within the medical records, or are derived by administrative staff from recorded clinical information. With regards to potentially bilateral surgical procedures such as ocular surgery, separate episodes are recorded for each eye rather than a single episode for a single individual undergoing bilateral surgery.

The 2008/9 Department of Health audit into clinical coding accuracy for the NHS England HES identified an overall clinical coding error of 12.8%, with poor clinical documentation, inadequate training of hospital coders and inadequate involvement of clinical staff in the coding process contributing to in inaccurate or incomplete data entry.[289] Thus, the HES, PEWD and HAS databases may not be a robust source of data on the number of children.

Coding of cataract surgery

The Office of Population Censuses and Survey (OPSC)-4 four character coding system consists of one letter followed by three digits. Whilst the letter indicates the anatomical site for the procedure, the following two digits indicate the procedure type, with a third digit adding a more precise description. The letter 'C' is used to indicate ophthalmic surgery, 'C7' indicates surgery on the anterior chamber of the eye and on the lens, the codes C71, C72, C74, C75 and C77 indicate the different possible surgical lens extraction and IOL implantation methods. Within in each of these three character groups there is further subdivision. Thus, there are at least 13 possible codes for cataract surgery in children ≤2 years old, and 4 codes for the description of IOL implantation (Table 11).

Table 11. Three character and four character Office of Population Censuses and Survey classification codes
for adult and paediatric cataract removal and IOL implantation.

Three character OPSC code	Four character OPSC subcodes
C71: Extracapsular extraction of lens	C71.1 Simple linear extraction of lens C1.2 Phacoemulsification of lens C71.3 Aspiration of lens C71.8 Other specified extracapsular extraction of lens C71.9 Unspecified extracapsular extraction of lens
C72: Intracapsular extraction of lens	C72.2 Suction extraction of lens C72.8 Other specified intracapsular extraction of lens C72.9 Unspecified intracapsular extraction of lens
C74: Other extraction of lens	C74.3 Mechanical lensectomy C74.8 Other specified other extraction of lens C74.9 Unspecified other extraction of lens
C77: Other operations on lens	C77.8 Other specified other operations on lens C77.9 Unspecified other operations on lens
C75: Prosthesis of lens	C75.1 Insertion of prosthetic replacement for lens C75.4 Insertion of prosthetic replacement for lens using suture fixation C75.8 Other specified prosthesis of lens C75.9 Unspecified prosthesis of lens

There is no national guidance as to which code to use for the most commonly performed types of cataract extraction in children (lens aspiration or lensectomy, with or without vitrectomy).

In summary, although there exists a centralised database of procedures undertaken in NHS hospitals (including cataract surgery in children ≤2 years old), its nature makes it unsuitable as a data source for the ascertainment of cases for a prospective study, and incomplete or inaccurate coding and possible regional variation in coding of surgery may make it inappropriate as a robust source for assessing activity.

2.6.b.ii. Surveillance network: the British Isles Congenital Cataract Interest Group

Surveillance, or the "systematic collection and collation of data on a health related event with dissemination of analysis and findings", is a key weapon in the epidemiological arsenal. The state of 'continued watchfulness' described by Langmuir in 1963[291] is especially useful when investigating rare diseases. Whilst passive surveillance involves only the reporting of relevant cases, active surveillance is the ongoing monitoring of the entire population at risk, providing a more precise description of distribution. Both forms of surveillance are 'active' processes for the reporting clinician, but true active surveillance requires the establishment of a collaborative network with a central monitoring unit searching for cases or the confirmation of the *absence* of cases through peripheral units which are able to identify and report on the population at risk. Active surveillance, whilst more costly than passive surveillance, is less likely to result in the under-reporting of cases and thus gives a more representative clinical picture.

Active surveillance systems are well established in the UK and have been successful in both the paediatric and ophthalmic fields, (the British Paediatric and British Ophthalmic Surveillance Units, BPSU and BOSU). 1n 1995, the British Congenital Cataract Interest Group was created (Appendix B; this collaborative research network, made up of consultants with an interest in the disease, has published work on the detection, distribution and management of congenital and infantile cataract.[63;170;171;292;293] As many of the BCCIG members perform surgery on children with cataract, this network is well suited to forming the reporting base for a national study of early childhood cataract surgery and primary intraocular lens implantation.

2.6.c. **Statistical analysis of hierarchical data**

In a child with bilateral cataract, the outcome of the right eye is more likely to be associated to the outcome of the left eye than to the outcome of another eye in another individual. If these correlations are not taken into account, there may be resultant errors in study findings, usually in the form of inaccurately small p values and narrow confidence intervals. Some studies have dealt with this by ignoring one eye of an individual with bilateral disease, or pooling information from both an individual's eyes, but in the study of a rare disease, these options are unsatisfactory. Tools for dealing with the '2 eyes, 1 person' inter-eye correlation issue include regression analysis modelling of outcome in one eye adjusting for the outcome in the fellow eye, or modelling the inter-eye correlation separately. Multilevel or random effect modelling can explicitly deal with the issue of within participant clustering of data, by differentiating between the 'ocular' and 'individual' level data during analysis. There is also correlation between repeated measures within an individual over time, as recorded in longitudinal case studies, and this can also be addressed using a multilevel modelling approach.

2.6.d. **Investigating outcomes following intervention in early childhood**

In the management of congenital and infantile cataract, as in much of paediatric ophthalmology, vision is the primary functional outcome of concern. As vision develops over many years following the intervention concerned, an investigation of outcomes needs to take into consideration whether a longitudinal design can be achieved and maintained, in particular the challenges of maintaining collaborative research groups and the continued involvement of participating families and children.

3. AIMS

The research reported in this thesis was undertaken to investigate factors associated with visual outcomes and complications following primary IOL implantation in a nationally representative cohort of children undergoing congenital / infantile cataract surgery in the first two years of life.

The primary objectives were to address the following questions:

In relation to visual outcome:

- What are the early visual outcomes following bilateral or unilateral primary intraocular implantation in the first two years of life?
- What are the child or treatment specific factors associated with good visual outcome following surgery with and without intraocular lenses?

In relation to complications:

- What is the incidence of per-operative complications with primary IOL implantation, and what are the associations with child and treatment specific factors?
- What is the incidence of glaucoma and visual axis opacity in the first year following surgery with and without IOL implantation, and what are the child and treatment specific variables associated with these complications?
- What is the incidence of other complications such as severe post-operative inflammation, IOL dislocation and infection in the year following primary IOL implantation?

In relation to refractive outcome:

- What are the refractive outcomes following primary IOL implantation?
- What are the associations between initial refractive outcome and treatment-specific and child-specific factors?

- What are the patterns of refractive change of the infant eye following cataract surgery with a primary IOL?

Finally, in undertaking this study it was intended to establish a novel inception cohort of children in whom investigations of long term visual, educational and psychosocial outcomes can be undertaken in the future.

4. METHODS

4.1. Introduction

This chapter describes study design, with case ascertainment through a national active surveillance network, standardised data collection and analyses undertaken.

4.2. National survey of current practice of primary intraocular lens implantation in children under 2 years old

4.2.a. **Introduction**

Although the BCCIG had been established in 1995, it was necessary to update the network and to ensure the completeness of the reporting base. In addition, although practices in North America regarding the use of intraocular lenses in early childhood in have been reported,[283] the current patterns of practice relating to primary IOL implantation in children ≤2 years old in the UK and Ireland were not known.

Consequently, at the outset of this study a postal survey was carried out to establish how many children ≤2 years old were undergoing cataract surgery annually, which specialists (other than those who are already members of the BCCIG) were managing these children, and which consultants were undertaking primary IOL implantation in these children. The survey also sought information on the current management practices with regards to primary IOLs: these findings were intended to inform the design of the study data collection forms.

The paper reporting the findings of this survey is appended (Appendix C), but the details are summarised here.

4.2.b. **Methods**

In October 2008, 960 consultants comprising all members of the BCCIG (renamed the British **Isles** Congenital Cataract Interest Group to acknowledge the contribution of consultants from the Republic of Ireland), all consultant members of the Royal College of Ophthalmologists and Irish consultant ophthalmologists with a known interest in congenital cataract, were contacted using postal questionnaires accompanied by hand addressed cover letters and postage paid reply envelopes. Members of the BCCIG who did not respond to the mailing were sent reminders.

Respondents were asked:

- Do you manage children aged ≤2 years with congenital/infantile cataract?
- In the past year, approximately how many children aged ≤2 years with newly diagnosed congenital/infantile cataract have you managed?
- In the past year, in approximately how many children aged ≤2 years with congenital/infantile cataract have you undertaken cataract surgery?
- In the past year, in approximately how many children aged ≤2 years with congenital/infantile cataract have you undertaken primary intraocular lens implantation?
- which IOL(s) and IOL power calculation formula(e) do you use, and where do you place your IOL?
- which surgical techniques or approaches do you prefer?
- Do you routinely measure axial length post operatively?
- If you DO undertake primary IOL implantation in these children what are your exclusion criteria for IOL implantation in children under 2?

The last question, on exclusion criteria, requested a free text answer format, whilst the other questions had pre-defined categorical, numerical or binomial yes/no answers with a tick box format.

4.2.c. **Statistical analysis**

Descriptive analysis of responses was undertaken. Free text answers on exclusion criteria were coded to enable descriptive analysis.

4.2.d. **Results**

32 of the 960 distributed questionnaires were returned as undeliverable. 709 (76%) of the remaining 928 contacted consultants replied to the survey between October 2008 and January 2009. 47 (7%) of the 709 respondents stated that they operated on children ≤2 years old, estimating that over the preceding year they had operated on a total of 301 children altogether. 6 (13%) of the 47 surgeons did not perform primary IOL implantation in any child ≤2. The 41 surgeons who did perform primary IOL implantation estimated that in the preceding year they had operated on 268 children (116 with unilateral, 152 with bilateral cataract), undertaking primary IOL implantation in 65% (Table 12).

Table 12. Surgical management of children ≤2 with cataract
number of children undergoing surgery as estimated by respondents

How many children ≤2 years old have you operated on over the last year? (47 surgeons)			
	Unilateral cataract	**Bilateral cataract**	**Total**
Median	2	2.5	5
Range (min to max)	0-10	0-15	0-25
Total	133	168	301
In how many children ≤2 years old have you performed primary IOL implantation over the last year? (41 surgeons)			
	Unilateral cataract	**Bilateral cataract**	**Total**
Median	2	1	2
Range	0-8	0-14	0-19
As a proportion of children undergoing surgery	75% (87/116)	57% (86/152)	65% (173/268)

4.2.d.i. Exclusion criteria

Exclusion criteria for primary IOL implantation in children ≤2 were provided by 36 of the 41 respondents. 6 (17%) surgeons did not mention any ocular anomaly amongst their stated exclusion criteria. 23 (64%) described specific anomalies which would prevent them from implanting an IOL. Of these, 16 cited short axial length or microphthalmos, with 5 specifying different lengths below which they would not implant (16, 18 and 20mm). Anterior and posterior segment anomalies were exclusion criterion for 12 and 14 respondents respectively. 7 (19%) respondents considered the presence of any co-existent ocular anomaly to be sufficient cause for exclusion. Thus, microphthalmos is an exclusion criteria for 64% (23/36) of respondents, anterior segment anomaly 53% and posterior segment anomaly 58%. 9 (25%) cited microcornea, with surgeons again specifying differing corneal diameters, either below 9mm (3 respondents) or 10mm (3 respondents). 7 (19%) cited persistent fetal vasculature (PFV) or persistent hyperplastic primary vitreous (PHPV), with 5 of the 7 specifying 'significant' PHPV. Other stated exclusion criteria included abnormal capsular support (10/36 or 28%), glaucoma (7/36, 19%) and previous intraocular inflammation (uveitis, 3/36, 8%).

The age of the child was cited by 6/36 (17%) of the 36 respondents. Different minimum age limits were used: 12 months, 6 months and 1 month old minimal ages by 3, 2 and 1 respondent respectively. Thus, 25% (9/36) of respondents would not perform primary IOL implantation in any child under 1 year old. 7 (19%) of the consultant ophthalmologists commented on parental preference as an exclusion criterion for primary IOL implantation.

4.2.d.ii. Details of routine surgical management

All respondents used a hydrophobic acrylic IOL, with 90% using one of four 'Acrysof' model IOLs (Table 13). 70% reported using the SRK/T formula for IOL power calculation, with 37% using it in combination with the Hoffer Q formula. 6 respondents

specified that they used either formula, dependent on the axial length of the child. With regards to routine surgical technique, 90% of surgeons used limbal / corneal wounds for surgery; manual capsulotomy techniques were used by 88%; posterior capsulotomies were created by all but 1 surgeon. Of those using posterior capsulotomies, 78% also performed anterior vitrectomy with 16%. The majority of respondents (71%) do not routinely post-operatively measure the axial lengths of pseudophakic children.

Table 13. Details of surgical management

Number of respondents (n=41)		
IOL model		
	Acrysof acrylic hydrophobic lens	37
	3 piece (MA60 or MA30 models)	*27*
	Single piece (SA60, SN60 models)	*8*
	AMO acrylic hydrophobic lens	4
	HoyaVA acrylic hydrophobic lens	1
IOL power calculation formulae		
	SRK/T	28
	Hoffer Q	21
	SRK/T + Hoffer Q	*14*
	Holladay I	6
	SRK II	3
	Haigis	1
IOL placement		
	In the bag	40
	Optic capture	1
Wound creation		
	Limbal / corneal	36
	Scleral	8
	Limbal or scleral	2
Anterior capsulotomy technique		
	Manual	36
	Diathermy	4
	Vitrectorhexis	3
Posterior capsulotomy and vitrectomy		
	No posterior capsulotomy	1
	Posterior capsulotomy without vitrectomy	9
	Vitrectomy	42
Post-operative axial length routinely measured post operatively		
	Yes	12
	No	29

4.2.e. **Discussion**

The findings indicated that at the start of the present study, primary intraocular lens implantation in children ≤2 had been adopted by the majority of the responding surgeons who manage children with cataract in the United Kingdom / Ireland. There existed concordance of surgical approach, with most surgeons choosing an AcrySof hydrophobic acrylic IOL, manual curvilinear anterior capsulorhexis, limbal or corneal wound access and posterior capsulotomy with anterior vitrectomy: this uniformity would enable a robust examination of outcomes following surgery.

However, the variability with regards to exclusion criteria suggests that there was disparity of opinion on which children would benefit from primary IOL implantation, and which children were at least risk of complications and poor outcome. Whilst this disparity may have been be due to differing personal preferences within a relatively new and evolving field, it may also have been a reflection of absences within the evidence base on the practice of primary IOL implantation in children ≤2.

The estimated total of 301 children undergoing cataract surgery over the preceding year, as reported by the consultants, may have been an overestimate: previous work undertaken by Rahi et al identified 165 children undergoing cataract surgery in the first two years of life between 1995 and 1996.[293] However, the findings of this survey indicated that it should be possible to obtain at least 200 children undergoing surgery over a two year recruitment period for the present study.

4.3. Establishment and maintenance of the surveillance network

Consultants who managed children under 2 with cataract but who were not yet members of the BCCIG were invited to join the group and to contribute to the study. Preferred contact details (telephone, email or postal) were established, and contact was made with allied ophthalmic clinical staff (orthoptists, opticians, or clinical nurse specialists) at the core study hospitals (those which reported that they had operated on over 9 children with cataract over the preceding year). Pre-paid addressed response envelopes were used throughout, enabling more efficient postal communication within the network.

Draft study protocols and other study documentation (eg participant information sheets and consent forms) were distributed to all members of the network for comments.

The study research fellow had the responsibility for the maintenance of the network during the case ascertainment and data collection phases of the study, through the regular communication with consultants.

4.4. Case definition

The case definition for the study was: any child resident in the British Isles undergoing cataract surgery in the first two years of life with or without primary intraocular lens implantation undergoing primary surgery between 1st January 2009 and 31st December 2010.

4.5. Case identification and ascertainment through the BCCIG reporting base

Consultants were asked to use study identification sheets (Appendix D) to inform the research team of eligible children under their care due to undergo cataract surgery through active surveillance: consultants were contacted at least every two months and asked to report on whether they had recently managed an eligible child, or to confirm that they had not managed an eligible child. In addition the core centres were visited at least three times during the recruitment period, and theatre booking or operating records were checked by the study research fellow to ensure full case ascertainment.

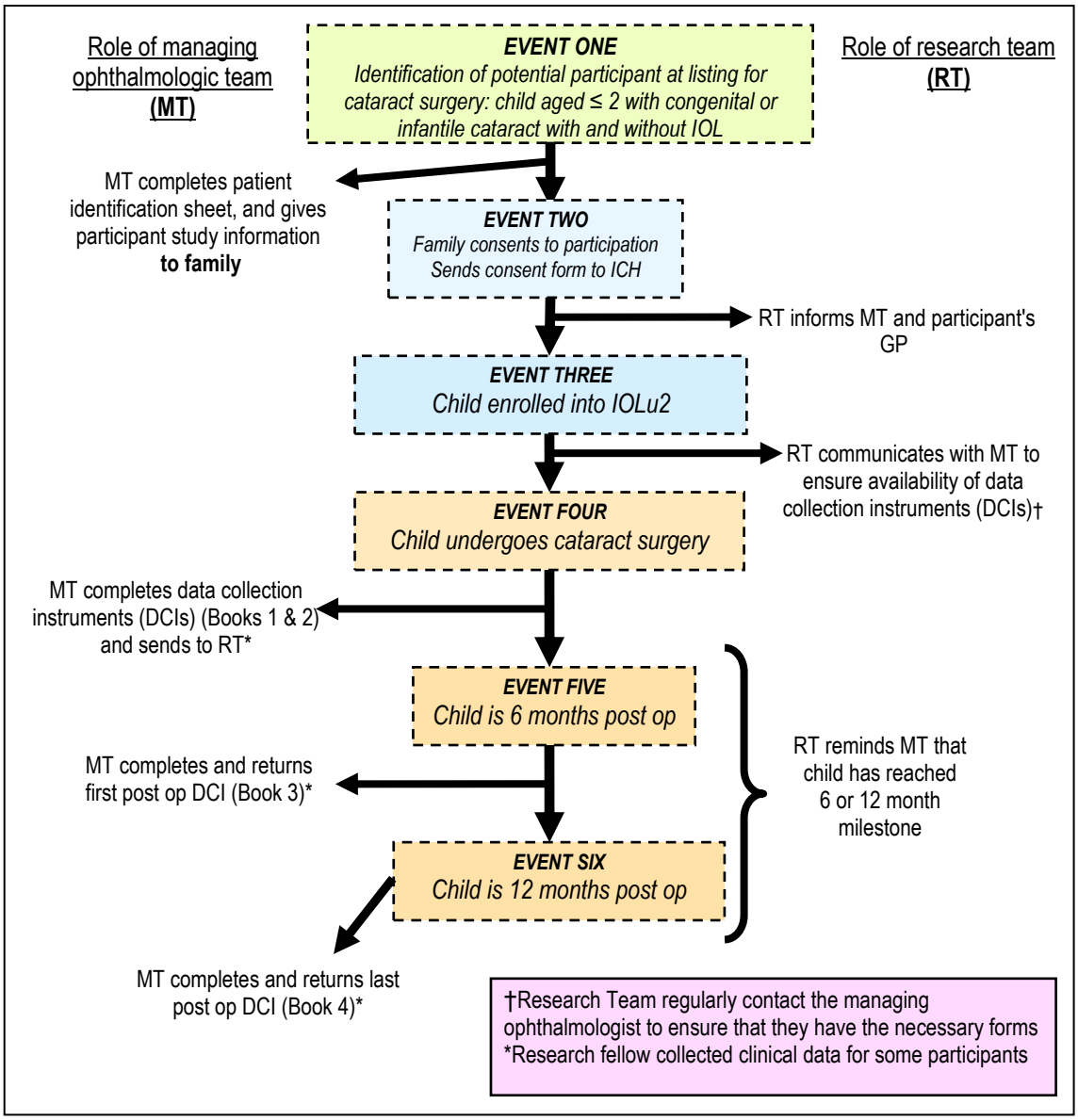
Consultants also used electronic mail to notify the research team of an eligible child. Case ascertainment for children managed at Great Ormond Street Hospital and Moorfields Eye Hospital was primarily performed by the study research fellow, with support from the managing consultants, through regular surveys of hospital theatre planning records. In some cases, the research team were first notified of an eligible child through the receipt of a completed family consent form.

4.6. Recruitment and consent

The families of eligible children were first approached by their managing consultants, either in person or postally. Consultants advised the parents of the aims and design of the study, and gave parents recruitment packs containing information sheets, consent forms and family background questionnaires as well as contact details for the research team (Appendix E). The background questionnaires, which elicited socio-demographic details, were developed through previous work by the BCCIG. Consent forms and questionnaires were returned to the research team using provided pre-paid response envelopes (thereby limiting the burden on participating families). Families of children cared for at the Great Ormond Street and Moorfields Eye Hospitals were also approached by the study research fellow. Following receipt of a completed consent

form, the research team informed the managing ophthalmic team of the family's consent so that formal data collection could begin (Figure 9).

Figure 9. The process of recruitment and data collection



4.7. Data collection

Information was collected using at preoperative and specified postoperative time points using specially designed proforma.

4.7.a. **Data collection instruments**

The data collection instruments are appended to the thesis (Appendix F). The information needed to answer the research questions comprised the following:

- Demographic information

including child's date of birth, ethnicity, hospital and NHS number.

- Pre-operative clinical information

including age at diagnosis and at surgery, aetiology of cataract, visual function, (including presence of pre-operative strabismus or nystagmus) and co-existence of ocular disorders and systemic disorders.

- Operative planning information

including use of an intraocular lens, and reasons for not using an IOL, biometric parameters, formula used for IOL power calculation and the expected post-operative refractive outcome

- Per operative clinical information

including surgical techniques used (wound position, anterior and posterior capsulotomy, method of lens aspiration, anterior vitrectomy), IOL model and power, use of prophylactic anti-inflammatory and antibiotic medication, and details of any intra-operative complications

- Post-operative clinical information

including occlusion therapy, contact lens and glasses use, visual outcome, refractive outcomes, and any post-operative complications (time of occurrence, severity and management)

4.7.a.i. Development of the data collection instruments (DCIs)

The DCIs were kept concise to improve response rates from clinicians. Ease of completion was aided by the use of tick boxes where possible, with the selection options for tick box answers being informed by the results of the national survey of practice (section 4.2.d, page120).

Piloting of the forms was initially carried out by the study research fellow, using the clinical records of children who had previously undergone cataract surgery. The forms were then further piloted by experienced trainee ophthalmologists, who were asked to comment on the wording of the questions and the length and format of the questionnaire. Also, these trainees were asked to enter data using the same sets of clinical notes in order to determine inter-observer variation. Following this process, the layout and content of the form was altered to more closely follow the structure of clinical case notes. Information for right and left eyes was more explicitly organised into right and left handed columns, reflecting clinical note convention. Date formats were defined (DD/MM/YY). Questions which requested unnecessary information were refined (for example, questions on IOL material type and IOL design were replaced with a single question on IOL model type). More tick box choices were introduced to limit free text entry wherever possible. In addition, the time points of post-operative data collection were reduced (from 3, 6, 9 and 12 months) to 6 months and 12 months.

Further refinement of the content and layout took place firstly through consultation with the consultants at the core study hospitals, and then within the wider collaborative network. Following this, study specific nosology was developed. For example, post-operative visual axis opacity was to be recorded as pearls, fibrosis or inflammatory membrane using tick boxes, and a definition of glaucoma was included within the form to limit misclassification. Concordance with occlusion therapy or the wearing of refractive correction was graded as poor, good or very good, with definitions again given within the form. The finalised forms were then re-distributed within the BCCIG, and consultants were asked to confirm that they routinely collected the dataset which was intended to be captured by the data collection instruments.

The DCIs were printed onto carbonless copy paper to enable the instant creation of duplicates to be kept by the managing consultants. Pre and per operative forms were combined into one form (Book 1), as certain pre-operative investigations (measurement of horizontal corneal diameter, biometry) were often undertaken immediately prior to cataract surgery.

4.7.b. **Data collection process**

All consultants were regularly sent additional copies of the pre and per operative data form (Book 1 and Book 2), and were sent the 6 month (Book 3) and 12 month (Book 4) post-operative collection forms as required (figure 9). DCI were completed either by the managing consultant or by a senior trainee ophthalmologist, and completed forms were posted to the research team. Data collection was also undertaken by the research fellow where necessary. In these cases, surgeons were asked to prospectively enter the full dataset of required information into the notes.

To assist the prospective entry of per operative data, a pro-forma for paediatric cataract surgery was created for the use of study centres (Appendix G). These proforma were subsequently adopted for the formal routine recording of paediatric cataract surgery within clinical notes by three hospitals (Great Ormond Street Hospital, Moorfields Eye Hospital and Birmingham Children's Hospital), and have also been adopted within these Trusts to document surgery for children not recruited to this study.

4.8.Ethics and research governance

4.8.a. **Ethics approval**

The study was approved by the UCL/UCLH type III research ethics committee. Ethics approval for research within the Republic of Ireland was granted separately by the relevant Health Authorities in Cork and Dublin.

4.8.b. **Research governance approval**

Following identification of the centres at which early childhood cataract surgery took place, and confirmation of the consultant's interest in joining the research network, governance approval was sought locally from each relevant Health Care Trust. This was a laborious process due to considerable variation in the documentation requested by the research and development departments at 42 different Trusts, despite the standardisation of the process as intended by the National Research Ethics Services. For example, trusts asked for a median of 4 (range 0 – 10) other forms or pieces of documentation. The median time from first contacting the research department to last request for further documentation was 15 days (maximum 126) and from first response from the research department to the granting of local governance approval 70 days (maximum 174 days).

4.9. Data management

4.9.a. **Data protection**

Paper forms with identifiable data were held in a different location to paper forms containing clinical data. All clinical study data were anonymised by assigning unique identification numbers for study documents and for the study database. All electronic and paper data files were held in secure conditions and identifiable individual level data were never transferred by email. The study personal computer was password protected, and the electronic databases were password protected and encrypted.

4.9.b. **Data validation**

Data collection forms were checked on receipt by the study research fellow, and inconsistencies or omissions were followed up with the relevant clinician.

4.9.c. **Database design**

Demographic, pre, per and, post-operative information databases, based on the data collection form layout, were designed in Microsoft Access. Relationships were created between the databases using the study ID numbers.

4.9.d. **Data entry**

Data were entered into the databases by the study research fellow. Free text data were entered verbatim.

4.9.d.i. Validation of entered data

Validation rules were created within the Access database to prevent data entry errors, such that entered numerical values (e.g. horizontal corneal diameter, biometric parameters) and dates were limited to a reasonable range. Drop down lists were created for variables where there were more than two tick box options.

Prior to analysis, dates of referral, presentation to team, biometry, surgery and post-operative event were checked for chronological consistency. Minimum and maximum values were checked for numerical data to ensure that the data were plausible. Free text information was checked for inconsistency prior to coding for analysis.

4.9.d.ii. Data verification

The study research fellow rechecked a random sample of incoming data, cross-referencing the paper data collection forms, electronic database and edited 'cleaned' datasets within the computer analysis programme. The random sample was selected using the Microsoft excel random list generator. 10% each of pre-operative, per operative and 6 and 12 month post-operative data were checked. Of the 58 forms reviewed, only 4 had errors which had not been dealt with by the in-built validation rules: for one date, the month and day had been transposed; in one child, the refractive outcomes for the right and left eye had been transposed on data entry, and the other two errors were spelling mistakes within the free text section. As the 58 forms had a total of 23,432 entries, the error rate was 1.7 per 10,000, much lower than the generally accepted error rate of 10 per 10,000[294]

4.9.e. **Data coding: the creation of variables for analysis**

In all cases, although the creation of new derived variables was undertaken in order to aid analysis, the original variables were also retained within the dataset.

4.9.e.i. Demographic and parental background data

There were two ethnicity data sources: hospital or clinician based descriptions, (as entered into the data collection instruments), and self-reported descriptions (as entered into the parental background questionnaire). Self-reported parental ethnicity has been used to describe the child's ethnicity for the children described in this study.

4.9.e.ii. Pre-operative data

Date of birth

Gestational age at birth was used to adjust date of birth to give a corrected gestational age for axial length or horizontal corneal diameter measurement. This enabled differentiation between eyes which were small due to the age of the child versus eyes which were small due to a developmental abnormality. Ages at surgery, diagnosis of post-operative complications or measurement of post-operative ocular biometrics were determined using actual date of birth (i.e. not corrected for gestational age).

Aetiology and associated non-ocular disorders

Three mutually exclusive categories were created for the analysis of associated factors: idiopathic, hereditary ocular, and hereditary with systemic features / chromosomal aetiology.

The presence of a non-ocular disorder was dichotomised, with additional binomial variables created for the presence of a ‘significant’ systemic disorder: a cardio-respiratory, metabolic or neurological disorder.

Phenotypic classification

Cataract morphology was coded into primary and secondary morphological categories. For primary morphology, the categories were nuclear, posterior, lamellar, anterior and cortical, and additional non locus-specific categories (partial, dense, total) where opacity loci was indeterminable.

Axial length

Although microphthalmos was coded as a binary yes/no variable using the definition given in section 2.3.d.i, page 53, two additional derived variables were created:

‘significant microphthalmos’ (axial length <16mm) and interocular axial length difference. Also, the numerical value of axial length was used as a quantitative trait.

Horizontal corneal diameter (HCD)

Although microcornea was also coded as a binomial yes / no variable using the definition given in section 0, page 54, an additional variable was created, ‘significant microcornea’ (HCD <9.5mm), and horizontal corneal diameter was also used as a quantitative trait.

Persistent fetal vasculature (PFV)

PFV was classified as one of these three mutually exclusive categories:

1. Isolated posterior capsular plaque / persistent posterior tunica vasculosa
2. Anterior PFV only (persistent iridohyaloid / pupillary membrane / anterior tunica vasculosa)

3. Complex PFV (‘posterior plaque plus other sign’).

Within the complex PFV category, the presence of other signs (anterior PFV, persistent hyaloid artery, centrally dragged ciliary processes, optic nerve head hypoplasia / dysplasia, macular abnormalities, retinal detachment) were dichotomised as present or absent.

Anterior and posterior segment abnormalities

As well as anterior and posterior segment anomalies being dichotomised separately as absent / present, anterior segment and posterior segment PFV were classified as anterior and posterior segment abnormalities respectively. Pre-operative pupil synechiae were also classified as an anterior segment abnormality.

Significant co-existent ocular abnormality

Children’s eyes were also classified as either having or not having a significant co-existent ocular abnormality: ‘HCD<9.5mm, axial length <16mm, anterior PFV or complex PFV, or other anterior segment or posterior segment abnormality’.

4.9.e.iii. Per operative data

Surgeon

A new dichotomised variable was created based on the level of the surgeon's exposure to cataract surgery in children under 2 over the 2 year study period. Surgeons were categorised as 'high exposure / experience' if they had operated on at least 10 eyes over the study period. All eyes of children who had been ascertained during the study period were included for the generation of this variable independent of whether the children were or were not recruited into the study.

Surgical techniques

As the survey of practice had indicated that the majority of surgeons used the same combination of surgical techniques, a new combination binary variable 'standard surgery' was created (*'standard' surgery = limbal or corneal wound + manual capsulorhexis + automated lens aspiration + primary capsulotomy + anterior vitrectomy*).

Eyes which had undergone surgery were also categorised by the type of viscoelastic device (OVD) used: No OVD; low or medium viscosity OVD; high viscosity OVD; or fracturable high viscosity OVD.

Per operative complications

Per-operative complications were additionally coded as either sight threatening or non-sight threatening complications whilst retaining the original variables. The only complication classified as non-sight threatening was an anterior capsular tear not extending past the lens equator.

Per- operative corticosteroids

Eyes were categorised into one of four groups: those receiving no per-operative steroid; those receiving one of either intraocular or subconjunctival or other per-orbital steroids; those receiving intraocular plus subconjunctival or other per-orbital steroid; and those receiving intraocular plus subconjunctival plus other per-orbital steroid.

Post-operative corticosteroids

Eyes were categorised as receiving either more than/equal to or fewer than 2 hourly drops with nightly steroid ointment following surgery. The use of systemic steroid post operatively was dichotomised (yes / no).

4.9.e.iv. Visual outcome

Visual acuity

Teller acuity in cycles per degree (cpd) was converted into Teller logMAR (logMAR=$\log_{10}$(30/cpd)) and Cardiff card snellen scores were converted into Cardiff card logMAR (logMAR= $\log_{10}$(1/snellen fraction)). Due to the difficulty of comparing results from disparate visual acuity tests, whilst the original data were retained as an ordinal variable, acuity was categorised into an ordinal scale (using the normative age related values described in section 2.2.c.ii, page 39) as follows:

5. Better than mean acuity for age

4. Worse than mean acuity but within normal range for age

3. Worse than lower limit of normal range but able to fix on visual target on quantitative visual assessment, or able to follow visual stimuli on qualitative visual assessment

2. Showing no interest in quantitative visual assessments, unable to follow on qualitative visual assessment, but showing behaviour which suggests some ability to fix on visual stimuli ('Fix' on fix and follow testing)

1. Will not take up fixation, but perceives light

0. No perception of light

4.9.e.v. Adverse outcomes

Glaucoma

Children were classified as having either

no glaucoma

ocular hypertension

glaucoma with pupil block event

open angle glaucoma

Visual axis opacity

Dichotomous categories were created for the presence of pearls, fibrosis, anterior capsular contraction or inflammatory membranes. Children were then also dichotomised as either having or not having 'true' visual axis opacity (pearls, fibrosis, and contraction).

4.9.e.vi. Refractive outcome

A variable measuring prediction error (PE) was created through the subtraction of the actual immediate refractive outcome (spherical equivalent of refraction carried out within 1 month of surgery) from the planned refractive outcome.

4.10. Analysis

Findings of descriptive analysis on outcomes and possible associated factors are presented as proportions for binary or categorical data, with 95% confidence intervals where appropriate, and medians, standard deviations, ranges and interquartile ranges for continuous data.

Statistical analyses were performed using STATA SE 10/11 (Stata Corp, Chicago Illionois). Children with unilateral cataract were analysed separately from those with bilateral disease. In children with bilateral cataract the correlation of paired eye data in the analysis of visual outcomes, refractive and post-operative adverse events were dealt with by clustering within-child variables.

If the following assumptions are made:

recruitment of at least 250 children, of whom 60% have undergone surgery for bilateral cataract, and of whom two thirds have undergone IOL implantation (as suggested by the national survey of practice)

a frequency of glaucoma of up to 32% of children with bilateral cataract at eight years following surgery without IOL implantation in the first two years of life[88;138;170]

this study will have a statistical power of 42% (with a significance level of 0.05) for the detection of a doubling of the odds of glaucoma by the eighth post-operative year following bilateral cataract surgery (odds ratio 2.0) with IOL implantation as compared to aphakia at the level of the child, and statistical power of 75% for the detection of an association at the level of each operated eye (without within child clustering). Thus, the probability of false negative findings lies somewhere between 25% and 58%.*

(*power calculation undertaken using Epi Info™ 7 (Centers for Disease Control and Prevention, Atlanta USA).

4.10.a. **Visual outcome**

The association between visual outcome and child / treatment specific factors was analysed using ordinal regression for vision as an ordered categorical outcome.

The factors considered were:

IOL implantation, age at diagnosis, time from diagnosis of cataract to surgery, socioeconomic status, (gestational) age at surgery, age at visual assessment, axial length, horizontal corneal diameter, compliance with occlusion and correction, surgeon and the presence or occurrence of microphthalmos, interocular axial length difference, a significant ocular anomaly, pre-operative nystagmus or strabismus, medical disorder or impairment, standard surgery, per-operative complication, post-operative visual axis opacity, glaucoma, other complication or secondary intraocular procedure. For outcomes following bilateral cataract surgery, asymmetry of opacity was also considered as a potential predictor of outcome.

Prior to univariate regression analysis, correlations between the potential predictors of visual outcome were investigated using non-parametric tests ($\chi 2$, Mann Whitney U, Kruskal-Wallis and Spearman's correlation coefficient) with test outcomes associated with p values of <0.05 considered to be evidence supporting a correlation.

Multivariate models were then created first using the most significant variables from the univariate analysis, as judged by the estimated size of the effect of the potential predictor on visual outcome as well as the p value. Wald values were examined to determine the change to the fit of the model with the addition of each new variable to the model. The aim was to create the simplest multivariate model, and significant correlations between potential predictors were used to determine the predictor which was most appropriate / biologically plausible for inclusion into the model. Once all significant variables were added to the model, they were dropped in turn and the consequent effect on model fit was examined. Variables which did not change the fit of

the model on removal from the model were considered on the basis of biological plausibility before being removed from the final model.

4.10.b. **Per and post-operative events**

The associations between potential predictors and the occurrence of per operative complications, 'true visual axis opacity (VAO)', inflammatory VAO and glaucoma were estimated using logistic regression. A similar method to that used to undertake univariate and multivariate regression on acuity outcomes was used, with *a priori* consideration of correlation between potential predictors estimated using non-parametric tests.

The potential predictors of per-operative complications considered in the analysis were:

(gestational) age at surgery, axial length, significant interocular axial length difference, horizontal corneal diameter, surgeon, the presence of persistent fetal vasculature, microphthalmos, microcornea, significant ocular abnormality, the use of oculoviscous devices and IOL implantation.

The potential predictors of visual axis opacity considered were:

(gestational) age at surgery, axial length, horizontal corneal diameter, surgeon, the presence of persistent fetal vasculature , per op iris trauma, per op IOL explantation, post-operative inflammation, the use of manual anterior capsulotomy, posterior capsulotomy, IOL implantation, IOL power, single piece IOLs, IOL fixation position, per operative heparin, post op intensive steroid drops, and post op systemic steroid.

The potential predictors of glaucoma are:

(gestational) age at surgery, cataract morphology, axial length, significant interocular axial length difference, horizontal corneal diameter, surgeon, the presence of persistent fetal vasculature, per op iris trauma, per op IOL explantation, post-operative inflammation, post-operative inflammation or post-operative intraocular surgery, the use of posterior capsulotomy, oculoviscous devices, IOL implantation, post op intensive steroid drops, and post op systemic steroid.

The estimated effect of clinical factors on the immediate post-operative refractive outcome (prediction error) for children undergoing primary IOL implantation were modelled using linear regression methods.

The potential predictors of refractive prediction error considered were: (gestational) age at surgery, corneal curvature, corneal astigmatism, anterior chamber depth, axial length, significant interocular axial length difference, horizontal corneal diameter, surgeon, the presence of anterior segment abnormality, and the use of oculoviscous devices, posterior capsulotomy, anterior vitrectomy, wound suture, single piece IOL, and IOL fixation position, IOL power and calculation formula.

4.11. Identification of cases of cataract surgery and intraocular lens implantation in children under 2 years old in the United Kingdom using the National statistical database

In order to compare the level of ascertainment achieved by the active surveillance network with the ascertainment of cases achieved through data collection undertaken by NHS Trusts and returned to a central database, requests for data on the number of children undergoing cataract surgery were made to the NHS information centres for the four member states of the United Kingdom. The Central Statistics Office Ireland does not collect this level of data from publicly funded hospitals in the Republic of Ireland.

4.11.a. **Identification of eligible codes**

As discussed in section 2.6.b.i page109, there is no national agreement on which OPCS code to use for children undergoing cataract surgery (either lens removal from the capsule, or lens removal with posterior capsulotomy / anterior vitrectomy). Thus, all of these codes for lens removal were used in the data request.

4.11.b. **Data request**

England

An HES data extraction request was made to the NHS Information Centre for health and social care (NHSIC) through the Hospital Episode Statistics online service (enquiries@ic.nhs.uk). Data were extracted to these specifications:

Data year: 2009 & 2010

Measures: Clinical data: Number of episodes with a main or secondary Procedure/Intervention

With the fields: Number of patients aged 0 -1 years and 1-2 years; 4 digit OPCS code; Primary care trust area of treatment

Limited to the following OPCS codes: Procedures under 'C71' (EXTRACAPSULAR EXTRACTION OF LENS); Procedures under 'C72' (INTRACAPSULAR EXTRACTION OF LENS); Procedures under 'C74' (OTHER EXTRACTION OF LENS); and Procedure 'C75' (INSERTION OF PROSTHETIC REPLACEMENT FOR LENS).

A tabulated HES data extract was then created by the NHSIC and provided as an encrypted electronic tabulation.

Northern Ireland

An email request was made through the NHS Northern Ireland Hospital Information Branch [statistics@dhsspsni.gov.uk] for the 'totals' reports for procedures under the three digit OPCS codes 'C71', 'C72','C74', and 'C75' for children aged 2 years or under at surgery, for the years 2009 and 2010.

Scotland

An email request was made through the NHS Scotland Information Services Division [NSS.isdSCT@nhs.net] for the 'totals' reports for procedures under the three digit OPCS codes 'C71', 'C72','C74', and 'C75' for children aged 2 years or under at surgery, for the years 2009 and 2010.

Wales

An email request was made to PEWD through NHS Wales Informatics [PDIT.Requests@wales.nhs.uk] for the 'totals' reports for procedures under 'C71', 'C72','C74', and 'C75' for children aged 2 years or under, for the years 2009 and 2010.

5. RESULTS

5.1. Introduction

The distribution of the surveillance network and characteristics of the families of the children on whom data have been collected are described here.

Descriptive analyses are presented regarding the clinical features of the children undergoing surgery, the practices undertaken, and outcomes following surgery with and without IOL implantation. These findings are followed by multivariate analysis of the factors associated with good visual outcome and adverse outcomes following surgery, and refractive changes following IOL implantation.

Findings of a comparison between the ascertainment of cases through the surveillance network, and the national databases of clinical activity are presented.

5.2. Case ascertainment and recruitment

5.2.a. **Distribution of recruiting centres**

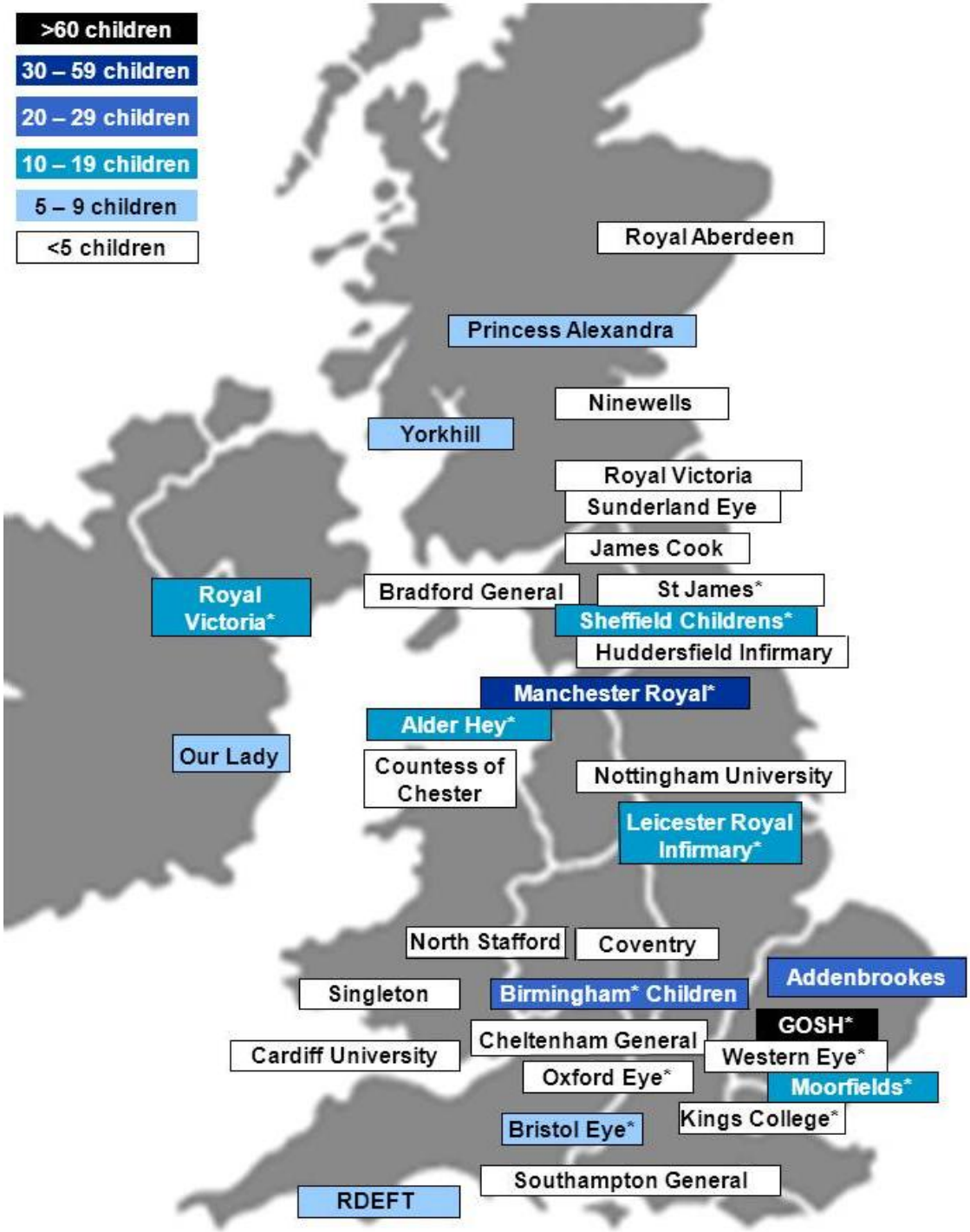
Participant identification was undertaken by 45 of the 47 paediatric ophthalmologists initially identified by the national survey of practice (section 4.2). A further six consultants were identified afterwards (3 through late responses to the national survey, 1 through existing members of the BCCIG, and 2 consultants who started their posts after January 2009).

Thus, a total of 51 surgeons across 32 centres identified children for recruitment to this study: 1 centre in the Republic of Ireland, 1 in Northern Ireland, 2 in Wales, 4 in Scotland and 24 in England. The distribution of these centres is shown in Figure 10.

Figure 10. Distribution of the recruiting centres, with a colour code for the number of children identified by the centre during the 2009/2010 study period

(GOSH: Great Ormond Street Hospital; RDEFT: Royal Devon and Exeter Hospital)

*At asterixed centres ascertainment was checked by the study fellow (ALS)



5.2.b. **Case notification**

334 children undergoing surgery for cataract were reported between January 2009 and January 2011. 19 of these children were ineligible for inclusion (due to being aged over 2 years at surgery, diagnosis of secondary cataract or non-residence in the British Isles). Thus 315 eligible children underwent surgery for congenital and infantile cataract (Figure 11).

5.2.c. **Consent and recruitment to study**

306 of the 315 families of eligible children were approached for consent. 243 of the 306 (79.4%) families had consented to their child's inclusion within the study (Figure 11) by the time of the submission of this thesis (August 2011). Nine families were not approached for consent, due to social / care issues or inability of the managing consultant to collect the full study dataset. 6 children underwent surgery after the end of the recruitment period (December 2010): however, the families of these children were identified and approached by their consultants during the study period.

The proportion of families giving their consent at each recruiting centre ranged from 100% to 0% (Figure 12, page 155).

Figure 11. Case ascertainment and recruitment flow chart

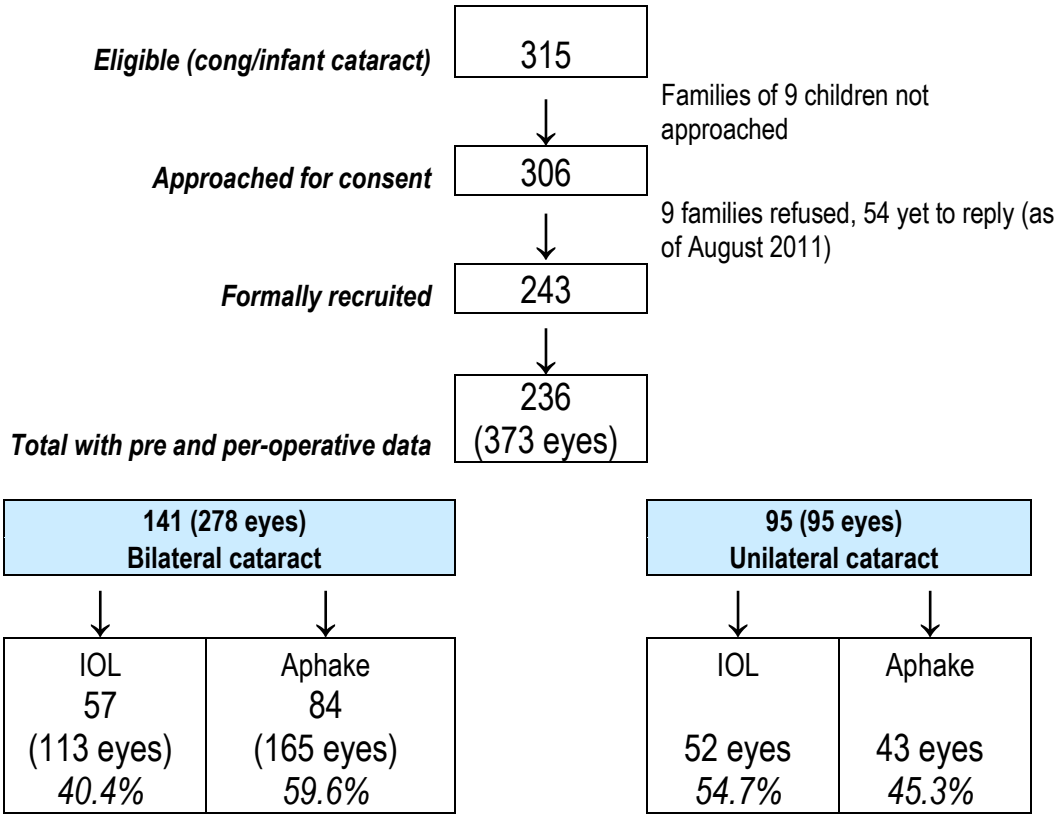
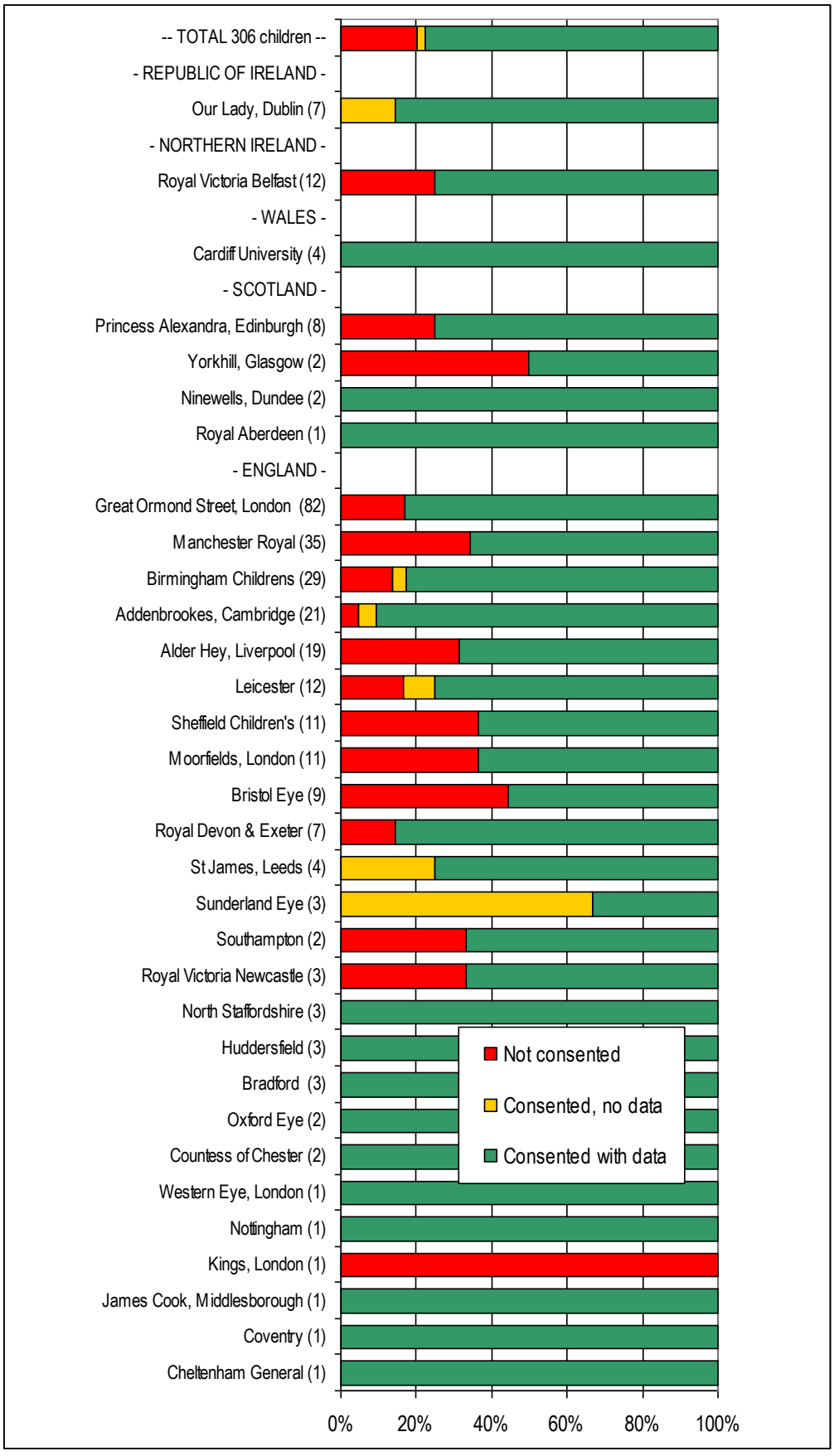


Figure 12. Recruitment and data collection across the collaborating hospitals



5.3. Data collection

As of August 2011, pre and per operative data collection instruments have been completed for **236** of the 243 recruited children. The proportion of consented children at each recruiting centre for whom data has been collected ranges from 33% to 100% (Figure 12).

Of these 236 children, **141 had bilateral cataract, 95 had unilateral cataract**. 57, 40% of children with bilateral cataract underwent primary IOL implantation, as did 52, 55% of children with unilateral cataract. These 236 children comprise the study sample for the descriptive analyses undertaken on demographic, pre-operative clinical and per-operative clinical characteristics, and the statistical analyses of per operative adverse events.

5.4. Comparison of IOLunder2 United Kingdom ascertainment with national databases of hospital activity

Of the 326 children reported by the BCCIG as having undergone cataract surgery aged ≤2years, 320 underwent surgery between January 2009 and December 2010 for unilateral (135 children) or bilateral (185 children) cataract (total 501 eyes, or episodes of cataract surgery).

At the time of submitting this thesis, data were available from the NHS Hospital Episode Statistic database (England) and the NHS Wales information centre on the numbers of episodes of cataract surgery in children age 2 years and under occurring during 2009 and 2010 and data were unavailable from the NHS information centres for Scotland and Northern Ireland for episodes which occurred during 2010. Over these periods, 187 episodes of 'extracapsular' cataract surgery, 274 episodes of 'other extraction of lens' and 1 case of an 'intracapsular' cataract surgery were reported by NHS Trusts to their central national database centres, making a total of 462 episodes. Over the same period, 477 episodes of cataract surgery were identified through active surveillance undertaken through the BCCIG (Table 14).

Table 14. Comparison of ascertainment through national database and through IOLu2 surveillance

		England	Scotland	Northern Ireland	Wales	Total
NHS information centre ascertainment of episodes cataract surgery						
	2009 & 2010	2009	2009	2009 & 2010		
C71 – Extracapsular extraction	161	8	9	9	187	
C72 – Intracapsular extraction	1	0	0	0	1	
C74 – Other extraction of lens	256	7	1	10	274	
Total cataract extraction	**418**	**15**	**10**	**19**	**462**	
C75 – Intraocular lens implantation	**134**	**9**	**9**	**4**	**156**	
IOLunder2 active surveillance						
	2009 & 2010	2009	2009	2009 & 2010		
Ascertainment of episodes of cataract surgery	**436**	**18**	**11**	**12**	**477**	
Cases of IOL implantation recruited through active surveillance and included within this study sample	**146**	**3**	**5**	**4**	**158**	

As shown in Table 14, in England, Scotland, and Northern Ireland, more cases were ascertained by collaborating clinicians within the BCCIG network than were ascertained through hospital data returns to the NHS, whilst in Wales, fewer cases were ascertained. This under-ascertainment is due to failure to enrol one hospital in Wales at which paediatric cataract surgery was undertaken.

Within the Republic of Ireland, only one of the three eligible centres identified by the bi-national survey of practice were enrolled to the study. Thus, children undergoing cataract surgery in the first 2 years of life in Ireland are under-represented within this study.

5.5. Descriptive analysis

5.5.a. **Demographic characteristics of the study population**

5.5.a.i. Gender

47% (111/236) of children who underwent surgery are female.

5.5.a.ii. Self-reported ethnicity

The majority of children (73%) come from families of White ethnicity, as shown in Table 15. Whilst there are no significant differences between children who underwent surgery with or without IOL implantation, in comparison to national data on the ethnicity of children born between 2005 and 2008 (which is the latest available dataset for the national patterns of ethnicity of live births) a higher proportion of children within the described cohort are from families of Asian ethnic origin ($p<0.05$, 95% confidence interval of difference between proportions 0.05% - 6.4%). However, over the past decade there has been an annual increase in the proportion of national live births born to non-White ethnicity families, so more recent data may reveal that the ethnicity distribution of this cohort is not significantly different from the national distribution.

5.5.a.iii. Family structure and socioeconomic status

In comparison to the national average, a higher proportion of recruited families were 2 parent families (89% versus 75%, $p<0.05$, 95% CI 9.1% - 17.9%) and a higher proportion of parents / carers had achieved degree or higher degree level education ($p<0.005$, 95% CI 14.3 – 27.6%). However, a higher proportion of mothers of recruited children were aged under 21 years ($p<0.05$, 95% CI 2.2 – 8.5%), although 17%

(40/236) of parents declined to answer this question. Again, there were no significant differences socio-economic parameters between children who had undergone surgery with or without IOL implantation.

Table 15. Demographic characteristics for included children

Data sources for population references: Office of National statistics (ONS), NHS numbers for babies (NN4B)

	IOL, n=109	Aphake, n=127	Total, n=236	Population reference
Gender: *Female*	49, 45% (35.9 - 54.1%)	62, 48.8% (40.3 - 57.4%)	111, 47% (40.8 - 43.4%)	48.7% **ONS 2009**[295]
Ethnicity: *Missing*	5, 4.6% (1.7 - 10.5%)	13, 11.4% (6.6 - 18.7%)	18	**NN4B/ONS 2008**[296]
White	83, 81.4% (72.7 - 87.8%)	89, 78.1% (69.6 - 84.7%)	172, 72.8% (66.9 - 84.6%)	70.1%
Mixed	1, 1% (0 - 5.8%)	3, 2.6% (0.6 - 7.8%)	4, 1.9% (0.6 - 4.8%)	
All Asian / Asian British	14, 13.7% (8.2 - 21.9%)	15, 13.2% (8.0 - 20.7%)	**29, 13.4% (9.5 - 18.7%)***	9.0%
Indian	1, 1% (0 - 5.8%)	5, 4.4% (1.6 - 10.1%)	6, 2.8% (1.1 - 6.7%)	
Pakistani	9, 8.8% (4.5 - 16.1%)	6, 5.3% (2.2 - 11.2%)	**15, 6.9% (4.2 - 11.2%)**	3.7%
All Black / Black British	1, 1% (0 - 5.8%)	5, 4.4% (1.6 - 10.1%)	6, 2.8% (1.1 - 6.7%)	5.1%
Family structure: parental				**ONS 2009**[297]
Missing	15, 13.8% (8.4 - 21.6%)	22, 17.3% (11.7 - 24.9%)	37	
Lone parent family	14, 11.7% (6.5 - 19.9%)	8, 7.6% (3.7 - 14.5%)	**22, 11.1% (7.4 - 16.2%)***	25.3%
Family structure: children				**ONS 2009**[297]
Missing	3, 2.8% (0.6 - 8.1%)	7, 5.5% (2.5 - 11/1%)	10	
>2 children	20, 18.9% (12.5 - 24.4%)	23, 19.2% (13.1 - 27.2%)	43, 19% (14.4 - 24.7%)	22.7%
Accommodation type: *Missing*	5, 4.6% (1.7 - 10.5%)	13, 11.4% (6.6 - 18.7%)	18	**2001 census households with dependents**
Self own / private rent	81, 79.4% (70.5 - 86.2%)	83, 72.8% (63.9 - 80.2%)	164, 75.9% (69.8 - 81.2%)	80.8%
Parental education: *Missing*	10, 9.2% (4.9 - 16.2%)	15, 11.8% (7.2 - 18.7%)	25	**ONS 2001**[298]
None	7, 7% (3.2 - 14.15)	13, 11.6% (6.8 - 18.9%)	20, 9.5% (6.2 - 14.3%)	20.1%
Olevel/Alevel/Cert/Other	47, 47.5% (37.9 - 57.2%)	44, 39.3% (30.7 - 48.6%)	91, 43.1% (36.6 - 49.9%)	57.6%
Degree /Higher Degree	45, 45.5% (36 - 53.3%)	55, 49.1% (40 - 58.2%)	**100, 47.4% (40.8 - 54.1%)***	22.1%
Maternal age: *Missing*	11, 10.9% (5.6 - 17.3%)	29, 22% (16.4 - 30.4%)	40	**ONS 2009**[297]
<21 years	3, 3.2% (0.7 - 9.3%)	7, 7.1% (3.3 - 14.3%)	**10, 5.2% (2.7 - 9.4%)***	0.6%
21 - 30	42, 44.2% (34.6 - 54.2%)	49, 48% (38.3 - 57.7%)	89, 46.1% (39.2 - 53.2%)	46.7%
31 - 40	45, 47.4% (37.6 - 57.3%)	39, 39.8% (30.4 - 49.7%)	84, 43.5% (36.7 - 50.6%)	43.3%
41+	5, 5.3% (2 - 12%)	5, 5.1% (1.7 - 11.7%)	10, 5.2% (2.7 - 9.4%)	3.8%

*statistically significant difference to national proportion p<0.05)

In comparison to the national measures of multiple indices of deprivation, a larger proportion of families of children recruited to the study lived within areas of relative deprivation, with 28% living in areas which fell within most deprived national quintile (Table 16, difference from national proportion reaches statistical significance p=0.05).

Table 16. Postcode-derived deprivation measure for family residence (index of multiple deprivation quintile)
*difference between study population and national distribution reaches statistical significance
**difference between IOL and aphake groups reaches statistical significance

	Total, n=236	95% CI of proportion	IOL, n=113	Aphake, n=127	95% CI of difference in proportions
Missing	28, 12%	-	18, 16%	14, 11%	
Living in the most deprived areas (highest deprivation score quintile)	**59, 28%**	**21.9 - 34%* (p=0.05)**	***17, 18%***	***41, 36%***	***-30 to -6%** (p<0.01)***
2nd quintile	39, 18.5%	13.2 - 23.8%	19, 20%	19, 17%	-7 to +14%
3rd quintile	37, 17.5%	12.4 - 22.7%	17, 18%	19, 17%	-9 to +12%
4th quintile	32, 15.2%	10.2 - 20%	15, 16%	17, 15%	-9 to +11%
Living in the least deprived areas (lowest deprivation score quintile)	44, 20.8%	15.3 - 26.4%	**27, 28%**	**17, 15%**	**+2 to +25%** (p=0.03)**

IOL implantation was associated with the postcode derived index of deprivation for recruited children for whom these data were available, with a higher proportion of children from least deprived areas, and lower proportion from the most deprived areas undergoing IOL implantation (Table 16).

5.5.a.iv. Summary

Children have been recruited through 51 managing consultants across 30 hospitals in the United Kingdom and 1 hospital in the Republic of Ireland, and 79.4% of the approached families of eligible children have to date agreed to their child's inclusion to this study.

Of the 236 children who form the study sample for the analyses described here, 109 underwent IOL implantation. There were no significant differences in the demographic characteristics of the families of children selected for surgery with IOL implantation compared to those who underwent surgery without IOL implantation with regards to ethnicity, family structure or parental education. However, children from families living in the most deprived areas of the UK were less likely to have undergone primary IOL implantation.

5.5.b. **Pre-operative clinical characteristics**

5.5.b.i. Laterality

Of the 141 children with bilateral cataract significant asymmetry of lens opacity was noted in 26 children or 18% (more dense in the right eye in 15 children with asymmetric cataract, 58%, and in the left eye in 11 children).

Of the 95 children with unilateral cataract, 46 were affected by cataract in the right eye (48%).

5.5.b.ii. Morphology

For the majority of children (187/236, 79%) cataract morphology was described according to lens strata (nuclear, posterior, lamellar, anterior or cortical) (Table 17). For the remaining 49 children, cataract was described as dense, total or partial.

Nuclear cataract was the most common morphology in bilaterally affected children (73, 52%). Posterior opacity or nuclear cataract were the most common morphologies amongst children with unilateral disease.

Amongst children who underwent IOL implantation (in comparison to children who did not undergo IOL implantation) posterior lens opacity was a more common morphology in bilaterally affected children, and nuclear lens opacity was a less common morphology in both bilaterally and unilaterally affected children (Table 17).

Table 17. Morphology of lens opacity in bilateral and unilateral cataract

	Bilateral cataract				Unilateral cataract			
	Total	**IOL**	**Aphake**	**p***	**Total**	**IOL**	**Aphake**	**p***
Nuclear	73 51.8%	**23** **40.4%**	**50** **59.6%**	**0.03**	29 30.5%	20 38.5%	9 20.9%	0.08
Posterior	20 14.2%	12 44.4%	8 9.5%	0.08	37 39%	17 32.7%	20 46.5%	0.2
Lamellar	13 9.2%	7 12.3%	6 7.1%	0.4	5 5.3%	2 3.9%	3 6.9%	0.7
Anterior	4 2.8%	2 3.5%	2 2.4%	0.99	5 5.5%	4 7.7%	1 2.3%	0.4
Total lens	8	4	4	0.7	7	5	2	0.5
Cortical	1	0	1	0.99	0	0	0	-
Dense*	22	9	13		8	1	7	
Partial*	0	0	0		4	3	1	
Total	141	57	84		95	52	43	

*p values for test of significant difference between IOL and Aphake groups

5.5.b.iii. Associated ocular abnormalities

The most common co-existent ocular abnormalities were microphthalmos (152/236 children, 64.3%, with 56/236 or 24% children having severe microphthalmos), microcornea (affecting 25% of children without microphthalmos) and persistent fetal vasculature (24%, 56/236 children).

As shown in Table 18, in comparison to children in the aphake group, amongst the bilaterally affected children who were selected for primary IOL implantation there were significantly lower proportions with co-existent microphthalmos, microcornea or anterior segment ocular abnormalities.

Table 18. Frequency of co-existent ocular abnormalities in children with bilateral cataract

	IOL 57 children	Aphake 84 children	p	95% CI of difference between proportions
Microphthalmos	**64.9%** ***(95% CI 51- 76%)***	**96.3%** ***(86.7 - 99.7%)***	***<0.001***	***18.7% - 44.7%***
Axial length <16mm	**3.9%** ***(0.3 - 13.%7)***	**42.7%** ***(30.2 – 55%)***	***<0.001***	***26.3% - 50.3%***
Microcornea	**0%** **(0 - 10%)**	**50%** **(29.0 - 70.9%)**	**<0.001**	**37.8% - 60.5%**
Persistent fetal vasculature	7% *(2.3 - 17.2%)*	9.5% *(4.7 - 17.9%)*	*0.76*	-
Anterior segment abnormality	7% *(2.3 - 17.%2)*	19% *(11.9 - 28.8%)*	*0.051*	*0.1% - 22.6%*
Posterior segment abnormality	3.5% *(0.3 - 12.6%)*	6% *(2.2 - 13.5%)*	*0.7*	-

Similarly, for children with unilateral cataract (as shown in Table 19), amongst the children who were selected for surgery with primary IOL implantation, there were significantly lower proportions with co-existent microcornea and anterior segment ocular abnormalities. There were also fewer children with persistent fetal vasculature.

Table 19. Frequency of co-existent ocular abnormalities in children with unilateral cataract

	IOL 52 children	Aphake 43 children	p	95% CI of difference between proportions
Microphthalmos	28% *(17.4 - 41.8%)*	44.8% *(28.4 - 62.5%)*	0.13	-
Axial length <16mm	20% *(0 - 11.5%)*	17.2% *(7.1 – 35%)*	0.79	-
Microcornea	**6.9% (0.9 – 23%)**	**33.3% (16.1 - 56.4%)**	**0.003**	**8.9% - 40.5%**
Persistent fetal vasculature	**30.8% *(21 - 45.5%)***	**65.1% *(40 - 77.6%)***	**0.001**	***14.2% - 50.9%***
Anterior segment abnormality	**11.5% *(5 - 23.3%)***	**44.2% *(30.4 - 58.9%)***	**<0.001**	***14.8% - 48.6%***
Posterior segment abnormality	5.8% *(1.4 - 16.3%)*	7% *(1.7 - 19.3%)*	0.99	-

These co-existent ocular abnormalities will now be described in more detail.

Axial length and microphthalmos

Bilateral cataract

Ultrasound axial length measurement was undertaken in significantly more children who were selected for surgery with IOL implantation: 57/57, 100%, versus 61/84, 72.6%, p<0.0001, 95% CI difference in proportion between the two groups or CIDIP 16.9% - 37.8%).

Axial length, uncorrected for age, ranged from 15.04mm to 24.3mm for those who underwent IOL implantation, and between 12 and 21mm for the children in the aphake group.

114 children underwent bilateral axial length measurement. 89 (78.1%) were affected by microphthalmos in either both or one eye (Table 20) with a significantly higher proportion of microphthalmic children within the aphake group than within the IOL group: 96.3% versus 64.9% (p=0.005, 95% CIDIP 11.3% - 40.2%).

Only 4 children (4%) had an interocular axial length difference greater than 1.5mm.

Of the 114 children, 26 (22.8%) had axial lengths of less than 16mm, with again a significantly higher proportion of children in the aphake group having this degree of microphthalmos: 42.1% versus 3.9% (p<0.0001, 95% CI DIP 24% - 51.8%).

Table 20. Microphthalmos and severe microphthalmos in eyes of children with bilateral cataract
in the a) IOL group and b) aphake group

a) IOL group, n=57		Left eye		
		Not affected	Microphthalmos	Severe Microphthalmos
Right eye	Not affected	20	4	0
	Microphthalmos	1	30	0
	Severe Microphthalmos	0	0	2

b) Aphake group, n=57		Left eye		
		Not affected	Microphthalmos	Severe Microphthalmos
Right eye	Not affected	5	0	4
	Microphthalmos	0	28	0
	Severe Microphthalmos	0	2	18

Unilateral cataract

As with children with bilateral cataract, ultrasound axial length measurement was undertaken in significantly more children who were selected for surgery with IOL implantation: 49/52, 94.2%, versus 30/43, 69.8% (p=0.002, 95% CI DIP 9.2% - 39.8%).

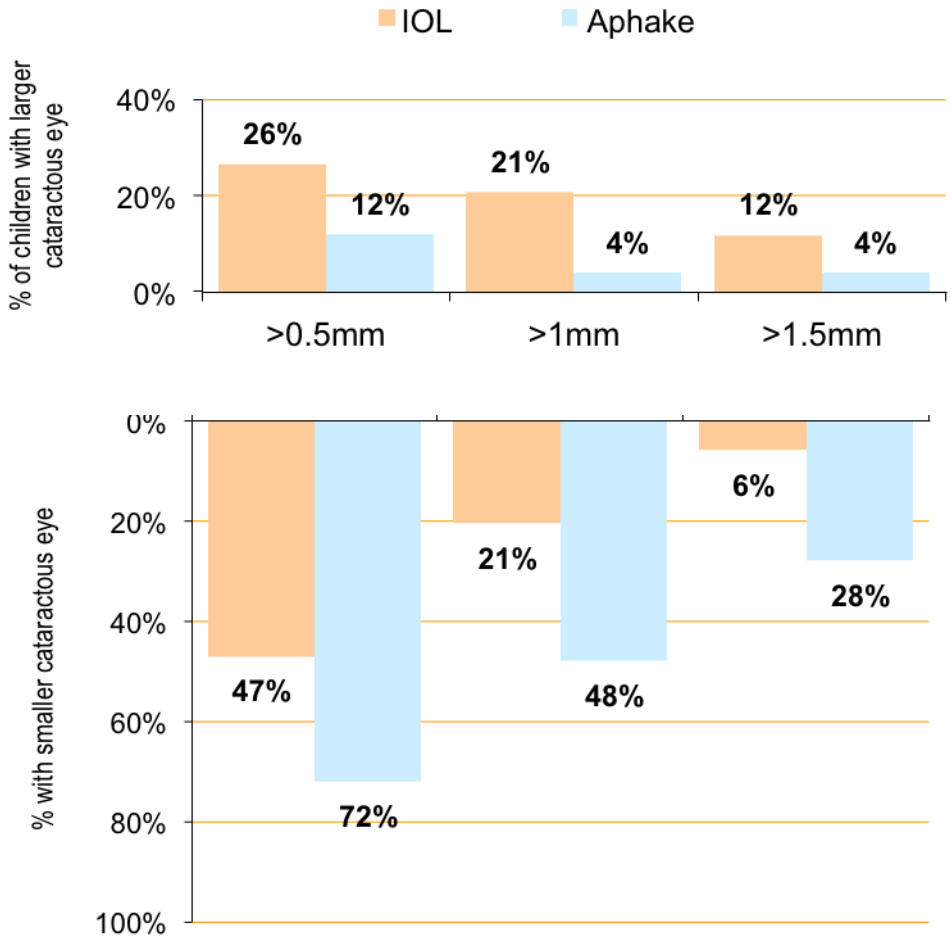
Axial length, uncorrected for age, ranged from 15.6 to 23.9mm (contralateral non-cataractous eye 16 – 22.3mm) for those who underwent IOL implantation and between 15 and 20.8mm for the aphakic group (contralateral non-cataractous eye 17.3 – 20.2mm).

27 children had microphthalmic eyes on ultrasound measurement (34.2%) and 6 had axial lengths <16mm (7.6%). A smaller proportion of the children who were selected for IOL implantation had axial lengths <16mm (2% versus 17.2% in the aphake group, p=0.02, 95%CI DIP 4.2 – 28.9%) and had microphthalmic cataractous eyes (28% versus 44.8% in the aphake group, but this difference does not reach statistical difference, p=0.14).

All children who were aged under 1 month at diagnosis of unilateral cataract had a smaller cataractous eye, whilst half (52%) of the oldest children in the group (those aged over 6 months at diagnosis) had a larger cataractous eye at the time of biometry.

More children in the aphake group had a cataractous eye which was 1.5mm smaller than the contralateral non-cataractous eye (Figure 13). However, this difference did not reach statistical significance.

Figure 13. Interocular axial length difference in children with unilateral cataract



Clinical microphthalmos versus USS (ultrasound scan) axial length

Of the 197 children who underwent USS measurement, 31 children were diagnosed with ‘clinical microphthalmos’ by managing consultants, but 2 of these 31 children were found to have normal axial lengths for age. When compared to the classification system of microphthalmos on USS measurement, clinical determination of microphthalmos in bilateral cataract has a positive predictive value of between 83% and 100% and a negative predictive value of 26% (Table 21). In unilateral cataract, the positive predictive value is lower, at 83%, and the negative predictive value is improved, at 43%. The 4-by-4 tables from which these figures have been derived are appended (Appendix H).

With regards to the predictive power of the clinical determination of microphthalmos for axial length of less than 16mm on USS measurement, the positive predictive value is lower for both unilateral and bilateral cataract, but there are fewer false negatives for the prediction of a small eye with clinical determination, with a negative predictive value of 88% for bilateral cataract, and 100% for unilateral cataract (Table 21).

Table 21. Predictive power of clinical assessment of microphthalmos in detecting microphthalmos, ocular axial length <16mm or microcornea

	Bilateral cataract				Unilateral cataract			
	Positive predictive value		Negative predictive value		PPV		NPV	
	RE	LE	RE	LE	RE	LE	RE	LE
Microphthalmia	93.8 *(69.7-100)*	100 *(76.1-100)*	31.6 *(23.2-41.4)*	26.3 *(18.6-35.7)*	83.3 *(41.8-98.9)*	85.7 *(46.7-99.5)*	47.7 *(31.5-63.3)*	42.9 *(24.4-63.5)*
Axial length <16mm	68.8 *(44.2-86.1)*	73.3 *(47.6-89.5)*	88.8 *(80.9-93.8)*	86.9 *(78.7-92.3)*	33.3 *(9.3-70.4)*	28.6 *(7.6-64.8)*	97.1 *(83.8-100)*	100 *(81.8-100)*
Microcornea	75 *(50-90.3)*	86.7 *(60.7-97.5)*	80.3 *(69.8-87.8)*	78.5 *(68.1-86.2)*	50 *(18.8-81.2)*	50 *(18.8-81.2)*	84.6 *(65.9-94.5)*	83.3 *(60 -95)*

Horizontal corneal diameter (HCD) and microcornea

HCD measurement was undertaken in the majority of children. Amongst children with bilateral cataract, HCD was measured in 75% of children in both the IOL (43/57) and aphake groups (63/84). Amongst children with unilateral cataract HCD was also measured in a similar proportion of children: 77% of the IOL group (40/52) and in 67.4% of the aphake group (29/43).

HCD ranged from 9 to 12mm for children selected for IOL implantation, and 7 to 12mm for children selected for aphakia.

Bilateral cataract

38 of the 106 children with HCD measurements (35.8%) had microcornea. Of these, 9 children had isolated microcornea without microphthalmos (25% of all children without microphthalmos). Microcornea was a significantly less common finding amongst children who underwent IOL implantation (Table 18).

Severe microcornea or HCD <9.5mm affected 11 of the 38 children with microcornea (10.4% of all 106 children). No child with severe microcornea underwent primary IOL implantation.

Unilateral cataract

16 of the 69 children with HCD measurement had microcornea (23.2%), and 2 of these 16 children (2.9% of all children) had severe microcornea. Again, no child with severe microcornea was selected for IOL implantation. Isolated microcornea (without microphthalmos) affected 2 of 29 children who underwent IOL implantation (6.9%) compared to 6 out of 18 children who were selected for aphakia (33.3%), a significant difference (Table 19).

Persistent fetal vasculature (PFV)

56 children had persistent fetal vasculature (23.7%): 44 of the children with unilateral cataract (46.3%), and significantly fewer children with bilateral cataract (12 children, 8.5%, p<0.0001, 95% CI DIP 29.7% - 51%). In comparison to children with unilateral PFV, a higher proportion of children with bilateral PFV associated cataract had iris / pupil / anterior capsular vascular remnants (75% versus 11%, p=0.01, 95% CI DIP 20.6% - 71.2%) as shown in Figure 14.

Amongst the children with bilateral cataract similar proportions of children in the IOL (4/57, 7%) and aphake (8/84, 9.5%) groups were affected by PFV. Amongst unilaterally affected children significantly more aphake group children (65.1%) had PFV than in the IOL group (30.8%, p<0.001, 95% CI 14.2% - 50.9%). More children within both the unilateral cataract and bilateral cataract aphake groups had anterior PFV or complex PFV than children within the IOL group (Table 22) but these differences were not statistically significant.

Table 22.Proportion of children with the differing classifications of persistent fetal vasculature

		Bilateral		Unilateral		
		IOL	Aphake	IOL	Aphake	Total
None		53	76	36	15	180
Persistent fetal vasculature		4 7%	8 10%	16 31%	28 65%	56 23.7%
	Isolated retrolental	1 2%	1 1%	6 12%	12 28%	20 8.5%
	Anterior PFV	0 0%	4 5%	1 2%	2 5%	7 3%
	Complex PFV	3 5%	3 4%	9 17%	14 33%	29 12.3%
Total		**57**	**84**	**52**	**43**	**236**

Figure 14. Manifestations of persistent fetal vasculature in individual children with bilateral cataract
RL: retrolental vascularisation; IR: iris / pupil / anterior capsule vascular remnants; CP: ciliary process traction; PA: persistent hyaloid artery; ONH: optic nerve head or retinal features

Bilateral IOL
4 children

	RL	IR	CP	PA	ONH
Child 1	+	+			
2	+	+			
3	+	+			
4	+				
Total	4	3	0	0	0
%	***100***	***75***	***0***	***0***	***0***

Bilateral Aphake
8 children

	RL	IR	CP	PA	ONH
Child 1	+			+	
2		+			
3	+				
4	+	+		+	+
5		+			
6	+	+		+	
7		+			
8		+			
Total	4	6	0	3	1
%	***50***	***75***	***0***	***38***	***13***

Figure 15. Manifestations of persistent fetal vasculature in individual children with unilateral cataract

RL: retrolental vascularisation; IR: iris / pupil / anterior capsule vascular remnants; CP: ciliary process traction; PA: persistent hyaloid artery; ONH: optic nerve head or retinal features

Unilateral IOL
16 children

	RL	IR	CP	PA	ONH
Child 1	+				
2	+				
3	+	+		+	
4		+			
5	+				
6	+			+	
7	+			+	
8	+				
9	+			+	
10	+				+
11	+			+	+
12	+				
13	+			+	+
14	+				
15	+			+	
16	+				
Total	15	2	0	7	3
%	***94***	***13***	***0***	***44***	***19***

Unilateral Aphake
26 children

	RL	*IR*	*CP*	*PA*	*ONH*
1	+				
2	+	+			
3	+				
4	+				
5	+				
6	+	+	+	+	
7	+	+		+	+
8	+				
9		+			
10	+			+	
11	+	+	+	+	
12	+		+		
13	+				
14	+			+	
15	+		+		
16	+				
17	+				
18	+	+		+	
19	+			+	
20	+		+	+	
21	+			+	+
22	+				
23	+	+	+	+	
24	+				
25	+				
26	+			+	
27		+	+		
28	+		+	+	
Total	*26*	*8*	*8*	*12*	*2*
%	***92***	***29***	***29***	***43***	***7***

Anterior and posterior segment abnormalities

Higher proportions of children in the aphake group had anterior and posterior segment abnormalities when compared to the IOL group. The details of the abnormalities found in children are shown in Table 23. A significantly higher proportion of unilateral aphake children had anterior segment abnormalities (44% versus 12% of the unilateral IOL group, p=0.0004, 95% CI DIP 14.8% - 48.6%). The four children with pre-operative glaucoma have been excluded from the analyses of glaucoma as an adverse post-operative outcome.

Table 23. Details of anterior segment disorders

	Bilateral		Unilateral	
	IOL	**Aphake**	**IOL**	**Aphake**
None	53 (92.9%)	68 (80.9%)	46 (88.5%)	24 (55.8%)
Corneal	1	9	1	4
Embryotoxon	*0*	*6*	*0*	*2*
Haze	*1*	*2*	*1*	*1*
Keratolenticular touch	*0*	*0*	*0*	*1*
Flat cornea	*0*	*1*	*0*	*0*
Shallow Ant Chamber	0	8	0	1
Iris / Pupil / Ant capsule	4	12	5	5
Persistent pupil membrane	*1*	*2*	*1*	*0*
Other ant manifestation PFV	*2*	*6*	*1*	*2*
Hypoplastic iris	*0*	*2*	*3*	*2*
Ectopia pupillae	*1*	*0*	*0*	*1*
Iridocorneal touch	*0*	*1*	*0*	*0*
Iris coloboma	*0*	*1*	*0*	*0*
Lens	0	1	0	2
Microspherophakia	*0*	*1*	*0*	*1*
Ectopia lentis	*0*	*0*	*0*	*1*
Pre-operative glaucoma	0	3	0	1
Total	**57**	**84**	**52**	**43**

5.5.b.iv. Aetiology of cataract

In 160 children (68% overall and 89% of all children with unilateral cataract), the aetiology of cataract was unknown. 6% of children had an identified hereditary systemic disorder, 7 children had Trisomy 21 (2 with unilateral cataract, 5 with bilateral cataract). There were no statistically significant differences in the aetiology of cataract in children who did and children who did not undergo IOL implantation.

Table 24. Aetiology of cataract
with p values for statistical tests of difference in proportion between the IOL and aphake group
*Congenital toxoplasma
**Neonatal acquired hypercalcaemia

	Bilateral		Unilateral		
	IOL	**Aphake**	**IOL**	**Aphake**	**Total**
Idiopathic	27 47.4%	48 57.1% *p=0.3*	46 88.5%	39 90.7% *p=0.99*	160 68%
Hereditary ocular	25 43.9%	25 29.8% *p=0.11*	1 1.9%	2 4.7% *p=0.6*	50 21%
Hereditary Systemic	3 5.3%	10 11.9% *p=0.24*	1 1.9%	1 2.3% *p=0.99*	15 6%
Non hereditary genetic / chromosomal	2 3.5%	3 3.6% *p=0.99*	4 7.7%	0 *p=0.12*	9 4%
Other	0	1* 1.2% *p=0.99*	0	1 ** 2.3% *p=0.45*	2 1%
Total	**57**	**84**	**52**	**43**	**236**

5.5.b.v. Systemic disorders and impairments

54 of the 236 included children (23%) had a systemic abnormality, with a significantly higher proportion of disorders amongst the children with bilateral cataract: 43 of the 141 children (30.8%) versus 11 of the 95 (11.6%) children with unilateral cataract ($p<0.001$, 95% CI DIP 8.3 – 28.4%). 15 children had some form of impairment: hearing impairment in 3 children, all of whom also had bilateral cataract, and global developmental delay in 12 children. There was no statistically significant difference between the proportion of children in the IOL and aphake groups with a significant systemic disorder (Table 25).

Table 25. Systemic disorders and developmental impairments

	Bilateral		Unilateral		Total
	IOL	Aphake	IOL	Aphake	
Other systemic disorder	15 27.8%	28 33.3	8 27.8%	3 7%	54 22.9%
Impairment	6 10.5%	6 7.1	2 3.9%	1 2.4%	15 *6.4%*
Significant systemic disorder or developmental impairment	13 22.8%	20 23.8% *p=0.99*	6 11.5%	2 4.7% *p=0.29*	41 17.3%
Total	**57**	**84**	**52**	**43**	**236**

For 24 of the 54 children with a systemic abnormality, there was a known association between congenital or infantile cataract and the co-existent systemic disorder (Table 26). For the remaining 30 children, aetiology of cataract was unknown and the nature of any association with the co-existent systemic disorder was similarly unknown (Table 27).

Table 26. The identified systemic disorders associated with cataract

Children with cataract of **hereditary systemic** aetiology	Number of children (Bilateral:Unilateral)
Cockayne Syndrome	*3 (2:1)*
Oculorenal syndrome of Lowe	*2 (2:0)*
Congenital lactic acidosis	*1 (1:0)*
Galactosaemia	*1 (1:0)*
Hereditary hyperferritinaemia	*1 (1:0)*
Incontinentia Pigmenti	*1 (0:1)*
Rhizomelic chondrodysplasia punctata	*1 (1:0)*
Muscle-Eye-Brain disease	*1 (1:0)*
Congenital haemophagocytosis	*1 (1:0)*
Other (unidentified hereditary disorders)	*3 (3:0)*
Children with cataract of **non-hereditary genetic / chromosomal** aetiology	
Trisomy 21	*7 (4:3)*
Wilms tumour-aniridia complex (WAGR)	*2 (1:1)*
Other aetiology	
Secondary neonatal hypercalcaemia due to traumatic fat necrosis	*1 (1:0)*

Table 27. Systemic disorders noted in children still awaiting a diagnosis

BILATERAL CATARACT	**UNILATERAL CATARACT**
Metabolic disorders	
Adrenal insufficiency, hypertension	Conjugated hyperbilirubinaemia
Severe idiopathic metabolic disorder (2)	
Neurological	
Cerebral atrophy, wrist drop	
Frontal lobe infarct	
Hypoxic ischaemic encephalopathy	
Posterior fossa cyst	
Rt facial palsy, hypotonia	
Schizencephaly	
Seizure disorder	
Vascular	
Congenital heart defect (2)	Congenital heart defect
Congenital heart defect and microcephaly	
Congenital heart defect, pulmonary hypertension	
Other	
Haemangioma on face	Haemangioma on scalp
Dysmorphic facial features (2)	Haemangioma on trunk
Failure to thrive, hypospadias, dysmorphia	Ovarian cyst
Ureter dilation, dysmorphia	Imperforate anus
Polydactyly	Haemophilia
Exomphalos	

5.5.b.vi. Pre-operative visual function

Pre-operative vision was assessed in 112 of the 236 children. Given the age of the children in the cohort (which will be described in section 5.5.c, page 186) it is unsurprising that the most common assessment was qualitative: whether the child could perceive light (undertaken in 10 children), could fix and follow light stimuli (58 children) or maintain a central, steady maintained gaze (14 children). The preoperative visual assessments undertaken in children are detailed in Appendix I.

All but one child within this cohort were able to at least perceive light prior to cataract surgery. Surgery was undertaken in 1 child with no perception of light (this child had a pre-operative retinal detachment, and surgery was undertaken to prevent pupil block glaucoma). This child has been excluded from the analyses on visual outcome.

Formal quantitative visual acuity assessment was undertaken in 28 children (24 in the IOL group, 4 in the aphake group): the best achieved preoperative acuity was 0.9 LogMAR (achieved by only 2 children, one with bilateral, and one with unilateral cataract, both in the IOL group).

Pre-operative nystagmus and strabismus

There were no missing data within the cohort on the presence or absence of nystagmus and strabismus preoperatively.

Overall, 36/236 children (15.2%) were noted to have pre-operative manifest nystagmus. Specifically, 31/141 children with bilateral cataract had nystagmus (22%). This constituted 15/84 in the aphake group (17.9%) and a larger proportion of children in the IOL group, 16/57 or 28.1% (a difference which was not statistically significant, p=0.21). Nystagmus was significantly less prevalent (p<0.001) amongst the children with unilateral cataract (5/95, 5.3%, 95% CI DIP 7.9 – 24.8%), and was found in a similar proportion of unilaterally affected children in the aphake (3/43, 6.9%) and the IOL (2/52, 3.9%) groups.

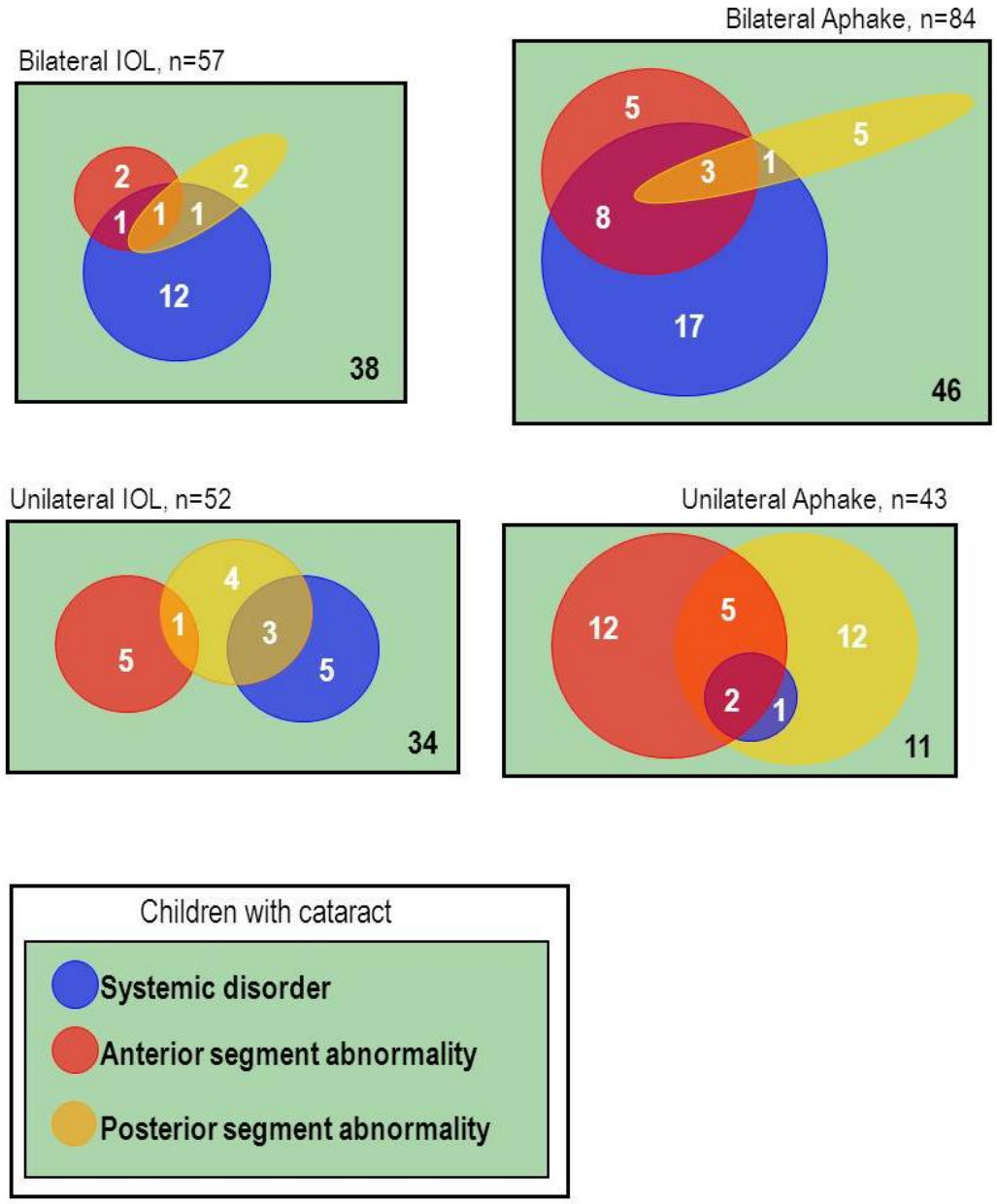
A constant divergent or convergent strabismus was noted pre-operatively in a significantly higher proportion of children undergoing surgery for unilateral cataract (18/95, 19%, versus 6/141, 4.3%, p<0.0001, 95% CI DIP 6.6% - 24%), and in a higher proportion of the children who underwent IOL implantation (19/109, 17.4% versus 5/127, 3.9%, p<0.001, 95% CI DIP 5.7% - 22).

5.5.b.vii. Summary

A similar proportion of children in the IOL and aphake groups were affected by other systemic disorders. However, a significantly lower proportion of children who were selected for primary IOL implantation had other ocular abnormalities overall (Figure 16, overleaf), and a lower proportion had severe manifestations of the most common abnormalities, microphthalmos, microcornea and persistent fetal vasculature.

Conversely, pre-operative strabismus was a more common finding in children who underwent IOL implantation.

Figure 16. Venn diagrammatic scale representation of distribution of systemic disorders and ocular abnormalities

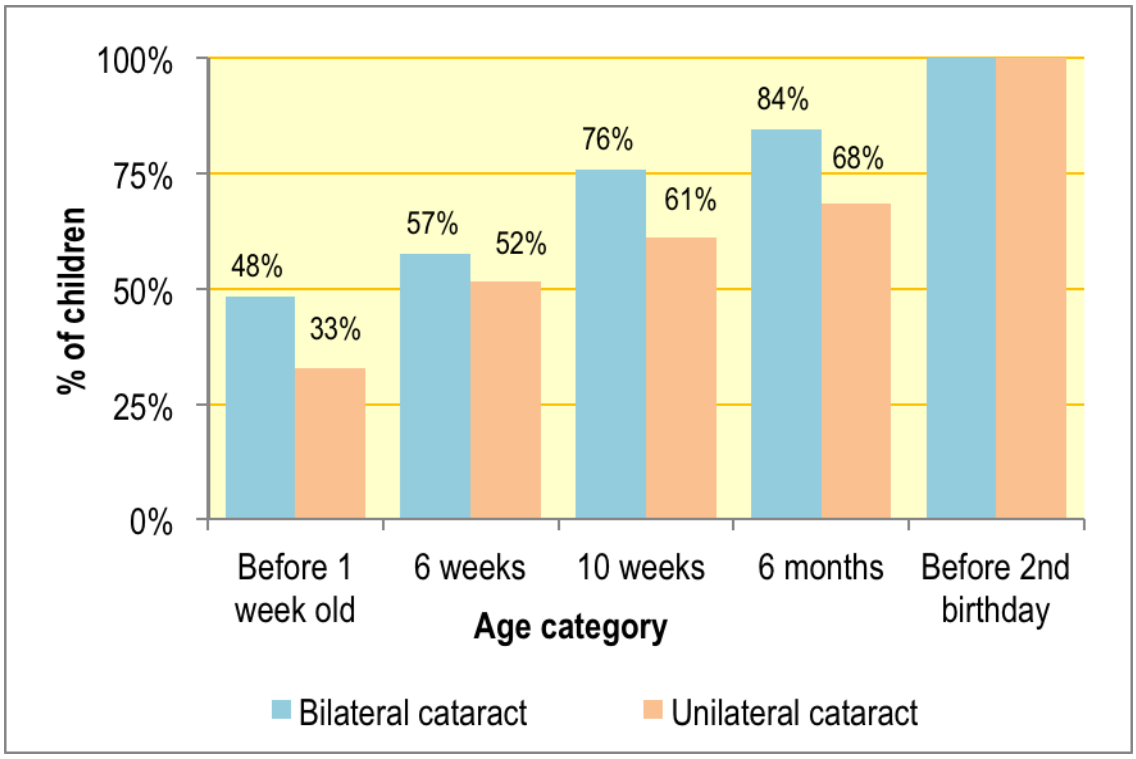


5.5.c. Age at diagnosis of cataract

The age at diagnosis of cataract was missing in 32 children: 10 children in the bilateral IOL group (17.5%), 9 children in the bilateral aphake group (10.7%), 11 children in the unilateral IOL group (21.2%) and 2 children in the unilateral aphake group (4.7%).

For these 32 children, the age at referral for cataract was used as a proxy for age at diagnosis of cataract. The age at detection of a visual problem was known for all of these children, as was the age at referral for diagnosed cataract. For 27 of these 32 children detection of a visual problem and referral for cataract occurred within two weeks of each other, and for 16 they occurred at the same age.

Figure 17. Age at diagnosis of bilateral and unilateral cataract: cumulative proportion graph with age categorised into clinically relevant groups



50% of all children were less than 2 weeks old at the time of diagnosis of cataract (median age 13 days, range 0 – 679 days / 22.4 months). A higher proportion of children with bilateral cataract were diagnosed within the first week of life: 48% of children with bilateral cataract compared to 33% of those with unilateral disease (p=0.02, 95% CI DIP 2.5% - 26.6%). Figure 17 shows the proportion of children diagnosed by clinically relevant milestones: the first week of life, which would include children diagnosed by the neonatal check, diagnosis prior to the 6 week health check, diagnosis between 6 -10 weeks of age, which would include children diagnosed by the 6 - 8week health check, diagnoses up to 6 months of age, after which cataract is more likely to be infantile rather than congenital, unless there is delayed diagnosis.

For children with bilateral cataract, median age at diagnosis of cataract was 4 days old, ranging from 0 – 507 days (16.8 months) for those in the aphake group. Children were older at diagnosis in the IOL group with a median age at diagnosis of 51 (1.7 months) days, ranging from 0 – 679 days (22.4 months).

Similarly, for children with unilateral cataract, median age at diagnosis was older in the IOL group (median 153 days, 5.1 months, ranging from 0 – 671 days, 22.2 months) than the aphake group (median 9 days, range 0 – 464 days, 15.3 months).

5.5.d. **Age at surgery**

For children with bilateral cataract, median age at surgery in the aphake group was 50 days / 1.7 months, ranging from 0.4 – 16.8 months. Children were older at surgery in the IOL group: a median age 142 days / 5 months, ranging from 0.9 – 23.8 months.

For children with unilateral cataract, median age at cataract surgery in the aphake group was 48 days / 1.6 months, ranging from 0.5 – 23.8 months. Children were again older at surgery in the IOL group, with a median age of 261 days / 8.6 months, ranging from 0.9 – 19.4 months.

Of all children aged under 1 month old at surgery, 27% of children with bilateral cataract were selected for IOL implantation, whilst 50% of children with unilateral disease were selected. Amongst the group of children who were aged over 1 year old at surgery, a higher proportion of children were selected for IOL implantation: 63% of children with bilateral and 80% of children with unilateral cataract (Table 28).

Table 28. Proportion of children undergoing IOL implantation by age at surgery

	Bilateral cataract	Unilateral cataract
Under 1 month *(95% CI)*	27.1% *(9 - 57%)*	50% *(23.7 - 76.3%)*
1 - 6 months	30.2% *(21.9 - 40%)*	34% *(23.7 - 47.9%)*
6 - 12 months	61.1% *(38.5 - 79.7%)*	93.3% *(68.1 - 99.9%)*
12 - 24 months	62.7% *(87.5 - 97.7%)*	80% *(57.8 - 92.5%)*

However, as the figure overleaf shows, with regards to the distribution of age at surgery within the subgroups, surgery was undertaken in the first month of life in similar proportions of children across the four treatment groups:

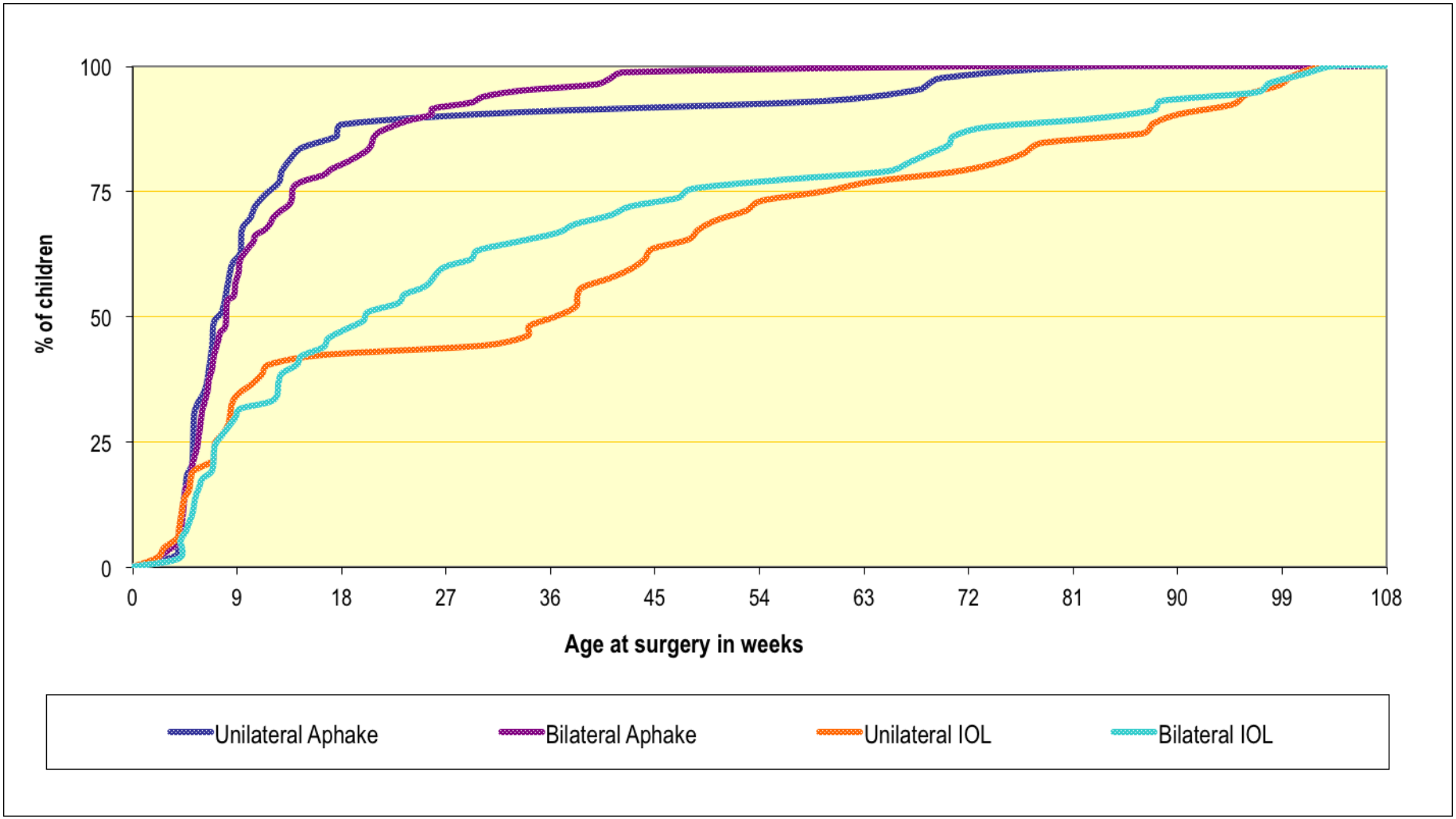
10/84, 11.9% (95% CI 6.4– 20.7%) of children in the bilateral aphake group

3/57, 8.8% (95% CI 3.4 – 19.4%) of children in the bilateral IOL group

5/43 11.6% (95% CI 4.6 – 24.9%) of children in the unilateral aphake group

6/52, 11.5% (95% CI 5.0 – 23.3%) of children in the unilateral IOL group.

Figure 18. Cummulative graph of age at surgery (age at first eye surgery if bilateral cataract)



Time to second eye surgery in bilateral cataract

Within both the IOL and aphake groups, 50% of children underwent second eye surgery within a week (median time, 7 days in both groups), and 75% of children in both groups had surgery within 14 days (upper limit of interquartile range 8 days in the aphake group, 14 days the IOL group).

5.5.d.i. Summary

Within each of the four groups (bilateral aphake, bilateral IOL, unilateral aphake, unilateral IOL) a similar proportion of children underwent surgery in the first month of life. However, within this cohort, the children who were selected for IOL implantation were significantly older at diagnosis and at surgery than the children underwent surgery without IOLs.

5.5.e. **Cited exclusion criteria for primary IOL implantation**

127 children did not undergo primary IOL implantation. In 46 children (36%), the young age of the child was the reason cited by the managing ophthalmologist, although the age threshold varied from 1 month of age to 2 years old (Table 29).

As also shown in Table 29, the other common reasons for non-implantation of an IOL included short axial length (29, 23%) and short horizontal corneal diameter (50, 39%).

Table 29. Exclusion criteria for IOL implantation as cited by managing ophthalmologists

		Freq.	Percent of 121 children in aphake group
Age		**46**	**36.1%**
	Age <1m	5	3.9%
	Age <6m	16	12.6%
	Age <1y	20	15.7%
	Age <2y	5	3.9%
Microphthalmos / Axial length		**29**	**22.8%**
	Microphthalmos, not defined	5	3.9%
	Axial Length <16	18	14.2%
	AxL <18	5	3.9%
	AxL <19	1	0.8%
Microcornea / HCD		**50**	**22.1%**
	Microcornea, not defined	2	1.6%
	Horizontal Corneal Diameter <10	11	8.7%
	Microcornea HCD <9	15	11.8%
PFV		**22**	**17.3%**
Anterior segment abnormalities		**8**	**6.3%**
	Anterior segment developmental anomaly	1	0.8%
	Glaucoma	2	1.6%
	Zonule instability	3	2.4%
	Microspherophakia	1	0.8%
	Shallow anterior chamber	1	0.8%
Other		15	11.8%
	IOL power unavailable	5	3.9%
	Parental choice	2	1.6%
	Poor visual potential	2	1.6%
	Lowe oculorenal syndrome	2	1.6%
	Haemophilia	1	0.8%
	Anaesthetic risk	2	1.6%
	Asymmetric biometry	1	0.8%

5.5.f. **Surgical management**

95 eyes of the 95 children with unilateral cataract and 278 eyes of the 141 children with bilateral cataract underwent surgery during the study period and are described within this section. 4 children with asymmetric disease underwent cataract surgery in only one eye. In 2 children, first eye surgery had been undertaken prior to the start of the study period.

208 eyes underwent cataract surgery without IOL implantation: 43 eyes of children with unilateral cataract, 165 eyes of the 84 bilaterally affected children.

165 eyes underwent primary IOL implantation: 52 eyes of children with unilateral cataract, 113 eyes of 57 bilaterally affected children.

5.5.f.i. Biometry and refractive planning for IOL implantation

Power calculation formula

As described earlier, axial length, anterior chamber depth and the corneal curvature are required in order to undertake accurate IOL power calculation. Corneal curvature was recorded for 100/109 children undergoing IOL implantation (91.7%), whilst anterior depth was recorded for 50/59 children (84.7%, details given in Appendix J).

For all but 11 children, biometry took place on the same day as cataract surgery, and for all children biometry took place within a week of surgery.

In 91 of the 109 children in the IOL group, lens power was determined using one of 5 recognised power calculation formulae. In the remaining 18 children, no calculation formula was used, with surgeons reporting that they had instead either used the highest power IOL available (30 dioptre lens, in 7 children) or used paediatric ocular axial length and departmental consensually determined guidelines to estimate the required implant power (11 children).

The most commonly used formula was the Sanders Retzlaff Kraff third generation (or SRK/T) formula. In 31 of the 59 children for whom IOL power was calculated using the SRK/T formula, the formula was further individualised using the surgeon specific 'A-constant' adjustment (52.5%), whilst in 14 of the 21 children for whom the Hoffer Q formula was used, the formula was further individualised using the child's anterior chamber depth (66.7%).

Table 30. Choice of biometric formula for implant power calculation

	Bilateral cataract (n=57) N, %, (95%CI)	Unilateral cataract (n=52)	Total (n=109)
None	9, 15.8%	9, 17.3%	18, 16.5% (10.6 - 24.7)
SRK/T			
Individualised	*15, 26.3%*	*16, 30.1%*	*31, 28.4% (20.8 - 37.6)*
Not individualised	*16, 28.1%*	*12, 23.1%*	*26, 23.9% (16.8 - 32.7)*
Total	31, 54.4	28, 53.8%	**59, 54.1%** (44.8 - 63.2)
Hoffer Q			
Individualised	*6, 10.5%*	*8, 15.4%*	*14, 12.8% (7.7 - 20.5)*
Not individualised	*6, 10.5%*	*1, 1.9%*	*7, 6.4% 2.9 - 12.9)*
Total	12, 21.5%	9, 17.5%	**21, 19.3%** (12.9 - 27.7)
SRK II	2, 3.5%	3, 5.8%	5, 4.6% (1.7 - 10.6)
Holladay	2, 3.5%	3, 5.8%	5, 4.6% (1.7 - 10.6)
Theoretic-T	1, 1.8%	0	1, 0.9% (0 - 8.3)

The Hoffer Q formula was used in 9/31 children with bilateral cataract and ocular axial lengths <20mm (29%) and 11/45 children with unilateral disease (24.4%).

Planned refractive outcome

The intended post-operative refraction for children with unilateral cataract ranged from 0 to +13 dioptres post operatively, and from +0.4 to +18 dioptres in children who underwent IOL implantation for bilateral cataract.

For both bilateral and unilateral cataract, the intended post-operative refractive outcome with IOL implantation was more hypermetropic for the younger children. Figure 19 and Figure 20 show that the trend was more apparent for children who underwent bilateral IOL implantation, and both figures also show that there was a wide range of intended outcome within the age groupings.

Figure 19. Intended refractive outcome following IOL implantation for children with bilateral cataract by age category at biometry
Median aimed outcome marked with red squares

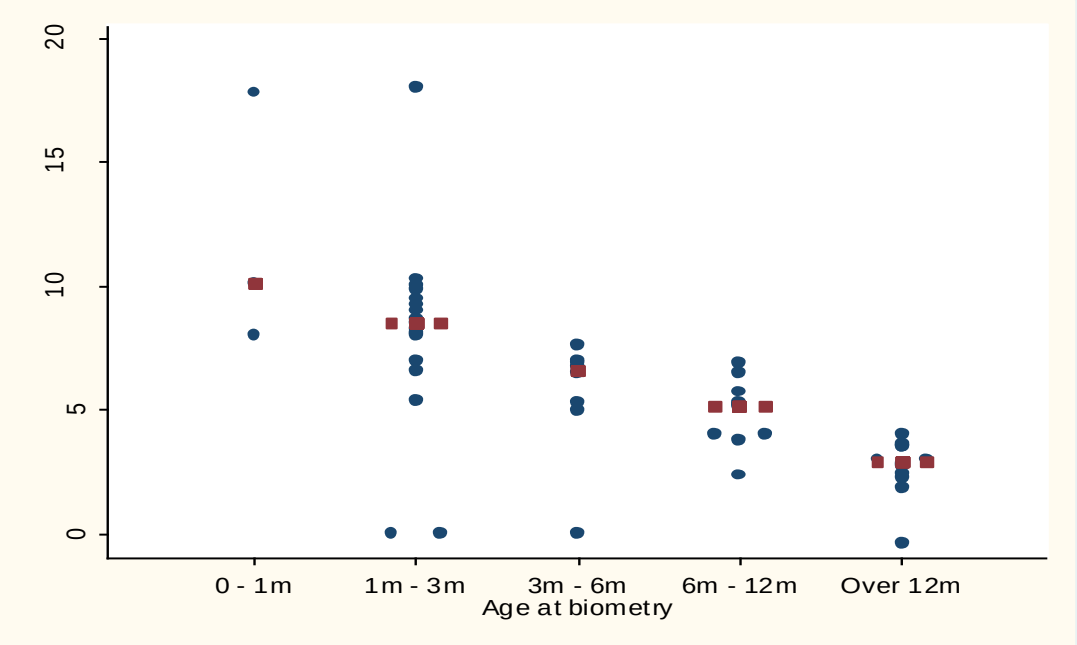
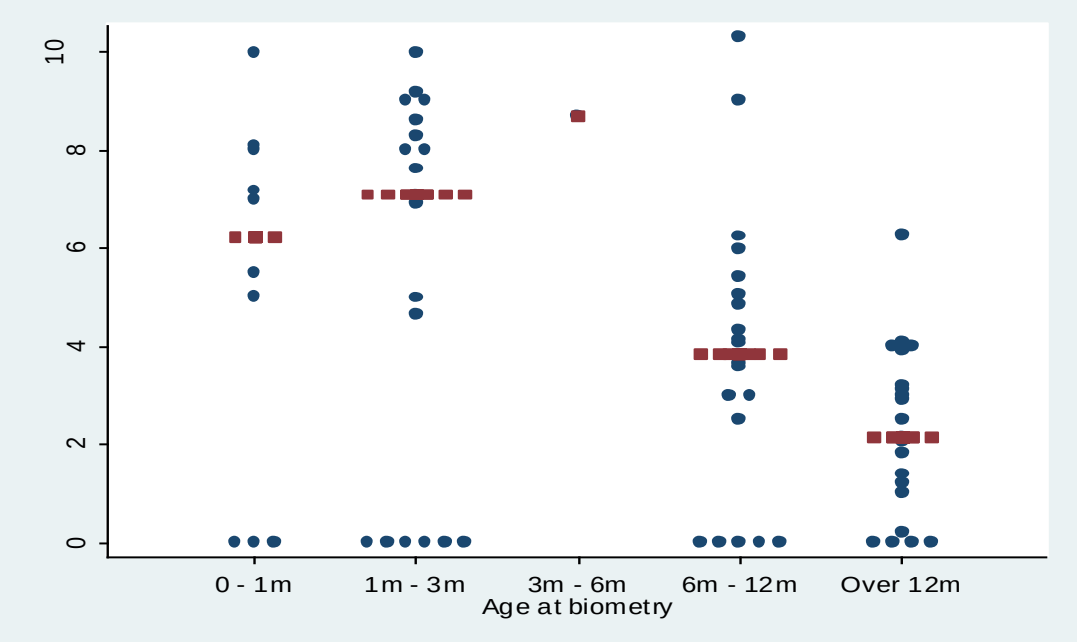


Figure 20. Intended refractive outcome for children with unilateral cataract by age category at biometry



5.5.f.ii. IOL models used

All but 1 of the implanted IOLs were hydrophobic acrylic type IOLs, with 105 of 109 children undergoing implantation with an Acrysof® model IOL (Table 31). Three piece IOLs were most commonly used: 71 of the 109 children in the IOL group, 65.8%, 95% CI around proportion 56.5 – 74%).

Table 31. Implanted IOL type, by model
*2 children had MA60 lenses implanted into one eye and MA30 lenses implanted into the second
∞Rayner C-flex is a hydrophilic acrylic lens: all other lenses are hydrophobic acrylic IOLs

	Optic diameter	Haptic diameter	Bilateral cataract n=57	Unilateral cataract n=52	Total n=109
3 piece IOL					
Acrysof MA60	6mm	13mm	27*	21	48
Acrysof MA30	5mm	12.5mm	14*	8	22
AMO Sensar	6mm	13mm	1	0	1
Hoya AF	6mm	12.5mm	0	2	2
Total number of children			40*	31	71 65.8% (56.5 - 74)
Single piece IOL					
Acrysof SN60IQ	6mm	13mm	7	13	16
Acrysof SA60	6mm	13mm	8	8	20
AMO Technis	6mm	13mm	1	0	1
Rayner C-flex∞	5.7mm	12mm	1	0	1
Total number of children			17	21	38 34.2% (26.1 - 43.5)
Missing	-	-	0	0	0

5.5.f.iii. Techniques used in surgery with and without IOL implantation

The techniques used in surgical practice are described at an eye level rather than a child level as the two eyes of individual children have in some children undergone differing surgical procedures, and have been operated upon by different ophthalmic surgeons.

Standard surgery

The appended flow charts (Appendix K) indicate how many eyes underwent which surgical algorithm with regards to surgical wound creation and capsule and vitreous management, but the important clinical details are summarised here:

120/165 operated eyes (72.7%) in the IOL group underwent 'standard' surgery (corneal/limbal wound + manual capsulorhexis + primary posterior capsulotomy and anterior vitrectomy) but significantly fewer eyes, 69/208 or 33.2%, in the aphake group underwent the same 'standard' surgery' ($p<0.0001$, 95% CI DIP 29.7% - 48.2%).

Manual capsulorhexis was undertaken in 133 IOL eyes (80.6%) and 71 aphake eyes (34.1%, again a significant difference, $p<0.0001$). The vitrectomy hand piece was most commonly used to create a capsulotomy in aphake eyes (102 eyes, 49%) The method of capsulotomy used is the surgical step which differs most between the IOL and aphake groups: if the definition of 'standard' surgery is changed to include any form of capsulotomy,150 IOL eyes (90.9%) and 194 aphake eyes (93.3%) have undergone 'standard' surgery.

Primary posterior capsulotomy and vitrectomy was undertaken in all of the eyes in the IOL group and in the majority of eyes in the aphake group (155, 94%).

5.5.f.iv. Adjunctive medical therapies

Antibiotics

206 of the 208 aphake group eyes (99%) and 149 of the 165 IOL group eyes (95%) received intraocular or subconjunctival antibiotics upon completion of primary surgery.

Corticosteroids

As shown in Table 32, the majority of eyes of included children within both the IOL (92%) and aphake (94%) groups received corticosteroids via either intraocular, subconjunctival, or other periorbital route upon completion of primary surgery. A larger proportion of eyes in the IOL group received corticosteroids via all three ocular routes (21.2% versus 0.5% of aphake eyes, p<0.0001, 95% CI DIP 14.8 – 27.6%).

Table 32. Post-operative corticosteroids after primary surgery

	IOL group eyes	**Aphake group eyes**
None	13 7.9% (95% CI 4.6 - 13.1)	13 6.3% (3.6 - 10.5)
Intraocular **OR** subconjunctival **OR** other periorbital	88 53.3% (45.7 - 60.8)	147 70.7% (64.1 - 76.5)
Intraocular **AND** either subconjunctival **OR** other periorbital	29 17.6% (12.5 - 24.2)	47 22.6% (17.4 - 28.8)
Intraocular **AND** subconjunctival **AND** other periorbital	35 21.2% (15.6 - 28.1)	1 0.5% (0 - 3.0)
Total	**165**	**208**

5.5.f.v. Post-operative medical therapies

Corticosteroids

Intensive post-operative steroid therapy, systemic corticosteroid and topical mydriatic drops were prescribed to similar proportions of eyes and children in the IOL and aphake groups (Table 33).

Table 33. Post-operative medication for operated eyes

	IOL eyes, n=165	Aphake eyes, n=208
Intense topical corticosteroid	7 43% *(95% CI 35.7 - 50.7%)*	77 37% *(30.7 - 43.8%)*
Systemic corticosteroid	21 12.7% *(8.4 - 18.7%)*	16 7.7% *(4.7 - 12.2%)*
Topical mydriatic agents	157 95.2% *(90.6 - 97.7%)*	189 90.9% *(86.1 - 94.1%)*

Amongst the children undergoing bilateral cataract surgery, 7 children in the IOL group and 6 children in the aphake group received two separate courses of oral corticosteroids (3 – 7 day courses following both first and second eye surgery for bilateral cataract).

5.5.f.vi. Summary

Variation exists within the recruitment network with regards to the refractive planning undertaken for primary IOL implantation in the children described in this study: a wide variety of power calculation formulae are used, and there also exists a wide range of planned refractive outcome.

Similar surgical techniques have been undertaken by recruiting paediatric ophthalmologists, although manual capsulorhexis was more commonly undertaken in eyes of children who underwent primary IOL implantation.

5.5.g. **Per operative events**

5.5.g.i. Planned iris trauma

Iris manipulation or planned iris trauma during surgery was more commonly undertaken in eyes of children who did not undergo IOL implantation (6 IOL group eyes, 3.6% versus 62 aphake group eyes, 29.8%, p<0.0001, 95% CI DIP 19.1 – 33%). As shown in Table 34, the most commonly undertaken procedures were. iridectomy (undertaken to prevent pupil block post-operative events) and pupil stretch (to allow greater per operative access to the lens.

Table 34. Per operative planned iris trauma

	IOL	Aphake	Total
None	159 96.4% (92.1 - 98.5%)	146 70.2% (63.7 – 76%)	304
Iridectomy	3 1.8%	22 10.6%	25
Pupilloplasty	0	2 1%	2
Stretch/hooks	2 1.2%	32 15.4%	34
Stretch/hooks + iridectectomy	1 0.6%	6 2.9%	7
Total	165	208	372

5.5.g.ii. Per-operative complications

Sight threatening per operative complications occurred in 38 of the 373 operated eyes (10.2%) and more than one complication occurred in 2 eyes (0.5%).

As shown in table, a higher proportion of IOL eyes experienced complicated surgery: 26 eyes in the IOL group, 16% versus 12 eyes in the aphake group, 6% (p=0.002, 95% CI DIP 3.7 – 16.8%). The most commonly occurring complication for all eyes was iris prolapse (18 eyes, or 4.8%). Iris prolapse did not occur in any child aged more than 100 days at surgery, and all eyes which experienced iris prolapse measured less than 19mm at biometry.

Table 35. Per operative complications

	IOL, n=165	**Aphake, n=208**
None	**139 84.2% (77.9 - 89.1%)**	**196 94.2% (90.1 - 96.8%)**
Iris prolapse	**15 9.1% (5.5 - 14.6%)**	**3 1.4% (0.5 - 3.7%)**
IOL explant	5 3%	-
IOL exchange	1 0.6%	-
IOL through PC & dialled back	3 1.8%	-
AC Tear past equator	1 0.6%	0
PC rupture during IOL implantation	1 0.6%	-
Unintentional iris trauma	0	5 2.4%
Vitreous haemorrhage	0	3 1.4%
Hyphaema	0	1 0.5%

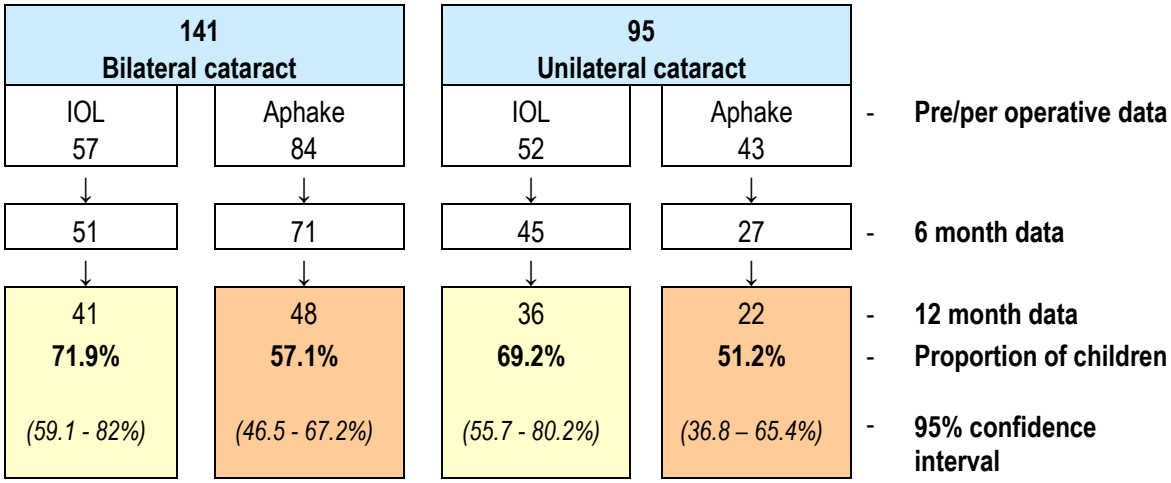
5.5.g.iii. Summary

Within the described cohort, per operative complications, specifically iris prolapse, were more common during surgery involving IOL implantation. However, iris manipulation was more common during surgery which did not involve IOL implantation.

5.6. Completeness of post-operative data collection

As of August 2011, data have been collected for 194 children who had reached their 6 month post-operative milestone, and 147 children who had reached their 12 month postoperative milestone (Figure 21). The difference between the proportion of bilaterally affected children with 12 month follow up data in the IOL and aphake groups did not reach statistical significance (p=0.08); however significantly more children in the unilateral IOL group than in the unilateral aphake group had twelve month follow up data (p=0.03, 95% CI DIP 3% - 39.7%).

Figure 21. Data collection flowchart



The 147 with 1 year follow up data thus compromise the study sample for the analyses on visual outcome and adverse events at 1 year following surgery. The 77 children in the IOL group forming the study sample for analyses on refractive changes in pseudophakic eyes.

5.7. Visual rehabilitation following cataract surgery

Data on non-surgical post-operative management of included children are available for 316 eyes of 194 children.

5.7.a. **Refractive correction**

Refractive correction was prescribed to the majority of children, with 208 of the 316 eyes receiving glasses, contact lenses or both within the first six post-operative months.

Time to commencement of correction

For those children who were prescribed refractive correction, correction was started within 2 weeks of surgery for 53 / 147 eyes of children within the IOL group (36.1%), and 120 / 168 (71%) of children within the aphake group (Table 36) .

Table 36. Commencement of refractive correction (contact lenses or glasses)

	No correction	Total wearing correction	Date of commencement missing	Corrected commenced within 2 weeks
Bilateral cataract				
IOL = 102 eyes, 51 children	14	88	8	36 eyes 45% (34.6 - 55.9%)
Aphake = 141 eyes, 71 children	6	136	0	100 eyes 73.5% (65.5 - 80.2%)
Unilateral cataract				
IOL = 45 eyes/children	8	37	0	17 46% (31 - 61.1%)
Aphake = 27 eyes/children	0	27	0	20 74.1% (58.1 - 87.1%)

Type of correction

At 12 months following surgery, with data available for 147 children as described in Table 37, 13% of children who had undergone surgery without IOL implantation were not wearing refractive correction (which was in some cases due to either poor compliance or poor visual potential consequent to pre-operative ocular or systemic disorders or post-operative glaucoma).

Table 37. Refractive correction worn
one year following surgery for a) bilateral and b) unilateral cataract

Table 37a. Bilateral cataract							
IOL, n=41 children				**Aphake, n=48 children**			
Contact lenses (CL)	Glasses	CL + Glasses	No correction	CL	Glasses	CL + Glasses	No correction
1 2.4%	34 82.9%	1 2.4%	5 12.2%	17 35.4%	19 39.6%	7 14.6%	5 10.4%

Table 37b. Unilateral cataract							
IOL, n=36				**Aphake, n=22**			
CL	Glasses	CL + Glasses	No correction	CL	Glasses	CL + Glasses	No correction
3 8.3%	22 61.1%	1 2.8%	10 27.8%	11 30.7%	4 18.2%	3 13.6%	4 18.2%

Concordance with correction

Data on concordance are available for all but 1 of the 123 children wearing contact lenses or glasses at 12 months post operatively.

Amongst children who had undergone surgery for bilateral cataract, poor compliance with refractive correction was noted in 5 of the 36 children in the IOL group (13.9%) and 2/42 in the aphake group (4.8%, difference not statistically significant, p=0.24).

Amongst children with unilateral cataract, poor compliance was noted in 7 of the 26 children in the IOL group (26.9%) and 2/18 in the aphake group (11.1%, difference not statistically significant).

Adverse events with contact lens wear

Amongst the 102 included children who wore contact lens correction during the first post-operative year, adverse events or problems with use were reported by 6/18 (33.3%) families of children in the contact lens group and 27/83 families of children in the aphake group (32.5%). The most common problem was difficulty with inserting and removing the lens (Table 38).

Specific ocular complications were noted in 6 children, all of whom were in the aphake group.

Table 38. Adverse events / problems with contact lens use amongst included children

	IOL group: 18 contact lens wearers	Aphake group: - 83 contact lens wearers
None	12 66.7%	56 67.5%
Difficulty inserting & removing	3 16.7%	15 18.1%
Frequent fall out	1 5.5%	4 4.8%
Intolerance	2 11%	2 2.4%
Recurrent conjunctivitis	0	3, 3.6%
Corneal ulcer	0	2, 2.4%
Corneal abrasion	0	2*, 2.4%

*totals >100% as one child was affected by more than one complication

Occlusion and other visual penalisation

83 / 197, 42% of children (67 who had undergone surgery for unilateral cataract, 16 bilateral cataract) underwent occlusion therapy within the first six post-operative months.

At the 12 month post-operative milestone, 63/147 children (43%) were undergoing occlusion therapy. The majority, 47, of these children had undergone surgery for unilateral cataract.

Type of visual penalisation

Of the 47 children undergoing occlusion therapy at 1 year following surgery, 31 were in the IOL group, and 16 were in the aphake group, with no statistically significant difference in the proportion of children receiving occlusion therapy in the two groups.

Table 39. Occlusion therapy at the 12 month post-operative milestone

	IOL, n=36	Aphake, n=22
Missing	0	0
No occlusion	5 13.9%	6, 27.3%
Patch fellow eye	29	14
Atropine instillation fellow eye	2	0
Occlusive contact lens fellow eye	0	2

Time to commencement following surgery for unilateral cataract

Similar proportions of children in the IOL and aphake groups started occlusion within two weeks of surgery: 20 children in the IOL group (69%) and 10 in the aphake group (62.5%).

Concordance with penalisation

As shown in Table 40, similar proportions of families of children in the IOL and aphake groups achieved good or very good concordance with prescribed occlusion. A higher proportion of children in the IOL group had poor concordance with penalisation, but this difference did not reach statistical significance (p=0.49).

Table 40. Concordance with occlusion therapy

	IOL, n=31	Aphake, n=16
Missing	0	0
Very good concordance	17 54.8%	10 62.5%
Good concordance	4 12.9%	3 18.8%
Poor concordance	10 32.2%	3 18.8%

5.7.b. **Summary**

Concordance with occlusion and refractive correction was similar within included children within the IOL and aphake groups, with similar time of commencement of occlusion for children with unilateral aphakia and pseudophakia.

5.8. Visual outcomes at one year following surgery

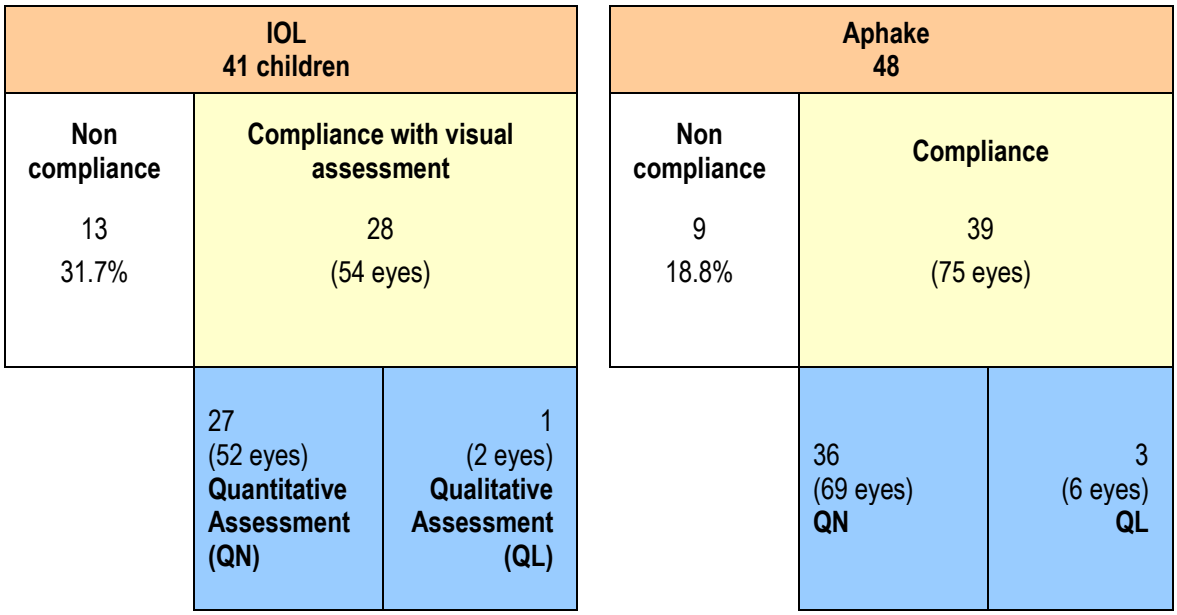
5.8.a. **Outcomes following surgery for bilateral cataract**

5.8.a.i. Compliance with visual assessment

Amongst children with bilateral cataract, a higher proportion of children in the aphake group were able to comply with uniocular vision assessment (68% versus 81%, Figure 22). Failure to comply with visual testing may have a unifactorial or multifactorial cause. Poor vision, a degree of developmental impairment, or a result of the difficulty in keeping the attention of young children may lead to noncompliance with visual assessment. In comparison to the children within the aphake group, the children within the IOL group were older at visual assessment (median age 47 months versus 37 months old, Mann-Whitney U test of difference z score -4.4, $p<0.001$) with a similar proportion of children affected by significant systemic or developmental impairment (18% in the IOL group versus 20% in the aphake group, chi2 test of correlation $p=0.69$). Thus, poor visual outcome is a possible cause of the lower compliance within the IOL group. The difference between the two groups, however, did not reach statistical significance ($p=0.2$, 95% CI of difference in proportions -5% to 30.5%).

Similarly, a smaller proportion of children in the IOL group were able to comply with quantitative acuity assessments (52 eyes of 28 children, 68% of children in the IOL group, compared to 68 eyes of 36 children in the aphake group, 75% of children), although again this difference was not statistically significant.

Figure 22. Visual assessment undertaken at 1 year following primary surgery for bilateral cataract (89 children)



5.8.a.ii. Visual outcome

At 1 year after surgery 28 of the 67 children who had complied with acuity assessments achieved binocular or 'both eyes open' vision within the age related normal range at 1 year after surgery (48%), with a higher proportion of children within the IOL group achieving the best levels of vision (Table 41, below).

Table 41. Level of vision achieved at 1 year following surgery for bilateral cataract

	IOL	Aphake
Missing outcome data due to noncompliance with formal assessment	13 32% *(95% CI 19-47%)*	9 19% *(10-32.2%)*
Form perception	28 68% *(53-81%)*	39 81% *(68-90%)*
Within normal range	19 46% *(32-61%)*	9 19% *(10-32%)*
Better than mean acuity level for age	13 32% *(19-47%)*	4 8% *(3-20%)*
Total	**41 children**	**48 children**

Better uniocular acuity outcomes were also achieved within the IOL group. 32 IOL group eyes (61.5%) and 14 aphake eyes (20.6%, 10.8 to 30.4%) achieved a uniocular vision level within the age reported normal range: a significantly higher proportion ($p<0.0001$, 95% CI DIP 23.4% to 55.3%).

All children who underwent surgery for bilateral cataract and who were able to comply with uniocular acuity assessment achieved a level of vision which allowed them to at least fix on visual stimuli. In addition, all children in the IOL group were able to demonstrate a degree of form perception. Over half of the children in the IOL group also exhibited vision which was better than the lower limit of the age reported normal range. In a third of children who had undergone IOL implantation, the visual outcome at 1 year following surgery was an acuity level which was better than the reported age-dependent mean (as shown in

Table 42), whilst only 7% of children who had undergone surgery without IOL implantation exhibited this level of vision at 1 year.

Table 42. Level of uniocular vision achieved at 1 year following surgery for bilateral cataract

	IOL	Aphake
0 – Nil Perception of Light (NPL)	0	0
1 – Light perception (PL)	0	0
2 – Able to fix on visual stimuli	0	1 1.3% (0 - 4.0%)
3 – Form perception but worse than lower limit for age	22 40.7% (95% CI 27.3 - 54.1%)	60 80% (70.8 - 89.2%)
4 – Within normal range but worse than mean acuity	11, 20.4% (9.4 - 31.3%)	9 12% (4.5 - 19.5%)
5 - Better than mean acuity level for age	21 38.9% (25.6 - 52.1%)	5 6.7% (0.9 - 12.4%)
Total	**54 eyes (28 children)**	**75 eyes (39 children)**

5.8.a.iii. Strabismus and nystagmus

15% of children with bilateral cataract had a constant strabismus at 1 year following surgery, with 20.2% having an intermittent or alternating strabismus.

Excluding the children with pre-operative strabismus, 18.9% of children in the IOL group (7/37) and 10.4% children in the aphake group (5/48) (difference not statistically significant, p=0.4) had a post-operative constant strabismus.

Post operatively, 38% of children (34/89) had manifest nystagmus, and 9% (8/89) were found to have latent nystagmus. Nystagmus was reversed (no longer present post-operatively) in 4 children with pre-operative manifest nystagmus.

Excluding the children with pre-operative manifest nystagmus, there was a statistically significant association between the absence of nystagmus at one year and primary IOL implantation (Table 43) at a univariate level.

Table 43. Nystagmus at one year following surgery

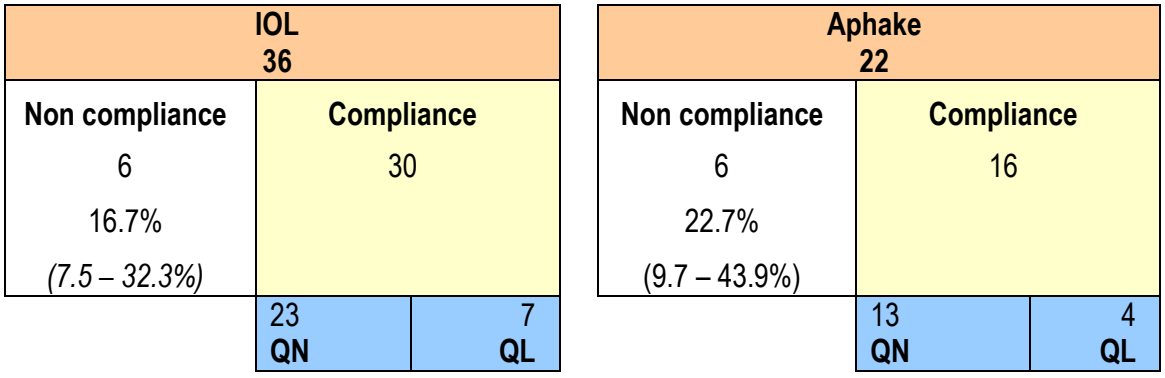
	Aphake n=40 children	IOL n=31 children	p	95% CI DIP
Manifest nystagmus	19 children 47.5%	4 children 13.3%	0.01	12.3% - 51.2%
Latent nystagmus	3 children 7.5%	3 children 10%	0.4	-

5.8.b. **Outcomes following surgery for unilateral cataract**

5.8.b.i. Compliance with visual assessment

23 children in the IOL group and 13 children in the aphake group were able to comply with quantitative uniocular acuity assessments of the aphakic or pseudophakic eye, with 9 IOL group eyes (39%) and 3 aphake eyes (23%) achieving a vision level within the age reported normal range. There was no significant difference between the proportions of children who were able to comply with visual assessment, which may be a reflection of the relatively small sample sizes.

Figure 23. Visual assessment undertaken at 1 year following primary surgery for unilateral cataract
QN: quantitative assessment of visual acuity, QL: qualitative test of visual function



As described in Table 44 (overleaf), all children in the IOL group attained vision of at least perception of light post operatively. Similar proportions of children in the IOL and aphakic group attained good or very good levels of vision at 1 year.

Table 44. Achieved visual level in pseudophakic or aphakic eye at 1 year following surgery for unilateral cataract
with numbers, proportions of children and 95% confidence intervals of proportions

	IOL	Aphake
0 – Nil Perception of Light (NPL)	0	0
1 – Light perception (PL)	2 6.7% (95% CI 0 – 16%)	1 5.9% (0 - 17%)
2 – Able to fix on visual stimuli	3 10% (0 - 21.1%)	0
3 – Form perception but worse than lower limit for age	18 60% (41.7 - 78.3%)	12 70.6% (47.6 - 93.5%)
4 – Within normal range but worse than mean acuity	4 13.3% (0.6 - 26.0%)	1 5.9% (0 - 17%)
5 - Better than mean acuity level for age	3 10% (0 - 21.1%)	2 11.8% (0 - 28%)
Total	**30 eyes**	**16 eyes**

5.8.b.ii. Strabismus and nystagmus

At one year following surgery, 26 of the 58 children (44.8%) had a constant strabismus, and 12 (20.7%) had an intermittent strabismus.

8 of the 58 children (13.8%) had a manifest nystagmus, and 4 (13.8%) exhibited a latent nystagmus.

Excluding the children with pre-operative manifestations, there were no statistically significant differences between the proportions of children with post-operative manifest nystagmus (15.6% in the aphake group versus 8.8% in the IOL group, p=0.35) or constant strabismus (52.6% in the aphake group versus 35.7% in the IOL group, p=0.44), although there were higher proportions within the aphake group of affected children with these indicators of impaired visual function.

5.8.c. **Factors associated with visual outcome**

5.8.c.i. Bilateral cataract

The results of the assessment of correlation between the factors of interest in relation to visual acuity of children with bilateral cataract (as described in section 4.10.a) are shown in Table 45 overleaf.

The details of the potential predictive factors are appended (Appendix L), as are the values of the tests for correlations between the factors (Appendix M).

Table 45. Correlations between factors of interest with regards to visual outcome for children with bilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age diagn	Time diagn	Age surg	Gest age	AL	HCD	Microphthal	IO AL	Ocl abn	Med disorder	Strab	Nystag	Standard surgery	Perop comp	Exp. Surg	Compl correctn	VAO	Glauc	Any comp	Sec procedures	Cataract asymm	Time btwn	Right eye	IMD
IOL implant	**	*	**	**	***	**	***		***		**		**			*					*			**
Age at diagnosis		***	***	****	****	**		***			*	**									*			
Time from diagnosis to surg			**	**							**					*								
Age at surgery				-	****	***	****		****	*	***	*			*			*			**	*		
Gest age surgery					****	****	**		****	*	***							*			**	*		
Axial length						****	-		-		**										***	**		*
HCD							-		-															
Microphthalmos									-		**										*		*	
IO AL difference													***		***		*			*				
Significant ocular abnormality										*								*						
Medical disorder																	*			*		*		
Pre op strabismus												****				*					****			
Pre op nystagmus																***				*				
Standard surgery														*	****									
Peroperative complication																								
Exp. Surgeon																						**		**
Good compliance correction																				*		*		
Post operative VAO																			-	-				
Post op Glaucoma																			-	-				
Any post op complication																				-	*			
Secondary procedures																						*	*	
Cataract asymmetry																						*		
Time between surgeries																								*
Right eye																								

The children within this study sample who underwent IOL implantation were significantly older at diagnosis ($p<0.01$) and at surgery ($p<0.01$), were less likely to have a significant co-existent ocular anomaly ($p<0.003$).

As would be expected, axial length and horizontal corneal diameter were strongly associated with each other ($p<0.001$) and both were associated with age at surgery ($p<0.001$). Correlations were also found between age at surgery ($p<0.001$) and the duration between diagnosis and surgery, with children diagnosed at a younger age having surgery sooner following diagnosis ($p<0.05$). Children who were diagnosed earlier were more likely to have a significant ocular anomaly ($p=0.05$) but were less likely to have pre-operative nystagmus ($p=0.08$, $p=0.04$). This suggests that within this study population pre-operative nystagmus may have been a sequelae of late diagnosis of early life cataract. Older age at surgery was associated with the presence of a significant medical disorder or developmental impairment ($p<0.001$). As there was no association with age at diagnosis, the relationship may be have been due to concerns regarding the effect of anaesthetic in young infants with another systemic disorder.

The age at visual assessment undertaken one year after surgery correlated significantly (as would be expected) with factors which had correlated with the age at surgery, including IOL implantation, axial length and horizontal corneal diameter and presence of a significant ocular abnormality.

The level of experience of the operating surgeon was associated with the undertaking of a ‘standard’ operating technique. This statistical correlation exists because the experienced surgeons operated on more eyes, and the most commonly used surgical steps were used to create the variable of ‘standard surgery’. However, higher surgeon experience level was also associated with a shorter duration between first and second eye surgery ($p=0.03$).

Overleaf (Table 46) are the results of the univariate regression analysis of factors related to visual outcome.

As described in Table 46, on univariate logistic regression analysis, IOL implantation, increasing age at diagnosis, surgery and at visual assessment, increasing axial length and horizontal corneal diameter (and thus the absence of microphthalmos) and the absence of a significant ocular abnormality were associated with increased odds of a better visual outcome at one year following surgery.

In order to further examine the relationship between age at surgery and the odds of better vision, age at surgery was categorised into quartiles, the cut off points for which also correlated with clinically relevant milestones (5.9 weeks, 9.5 weeks and 6.2 months). In comparison to age at surgery of less than 6 weeks, on univariate regression analysis age of greater than 6 months of age at surgery was associated with a greater odds of better visual outcome. This may have been due to a subset of children with infantile rather than congenital cataract who developed lens opacity outside the sensitive developmental window for amblyopia.

A multivariate model was then constructed, as described in section 4.10.a.

Table 46. Univariate multilevel (adjusted for within child relationships) ordinal logistic regression of uniocular visual outcome in eyes of children with bilateral cataract

	Relative odds of better vision	95% CI	p
IOL implantation undertaken	**7.57**	2.65 - 21.66	**<0.001**
Increasing age at diagnosis (weeks)	**1.03**	1.01 – 1.05	**0.008**
Increasing time from diagnosis to surgery (days)	0.99	0.99 - 1.003	0.7
Increasing age at surgery (weeks)	**1.02**	**1.00 – 1.04**	**0.013**
Increasing age at surgery corrected for gestational age (weeks)	**1.02**	**1.00 - 1.04**	**0.013**
Log age surgery	**1.8**	**1.1 – 3.0**	**0.02**
Increasing age at surgery categorised			
Baseline (0- 5.9 weeks), n=38	1	-	-
6 - 9.9 weeks, n=28	1.87	0.34 - 10.13	0.47
10 - 26 weeks, n=34	1.93	0.42 - 8.79	0.4
Over 26 weeks (6 months), n=33	**7.68**	1.55 - 38.03	**0.012**
Increasing axial length (mm)	**1.31**	**1.02 - 1.69**	**0.033**
Log axial length	**190**	**0.9 - 12955**	**0.03**
Increasing horizontal corneal diameter (mm)	**2.24**	**1.34 - 3.74**	**0.002**
Log horizontal corneal diameter	**8.4**	**3 – 13.9**	**0.002**
Microphthalmos	**0.26**	**0.09 - 0.73**	**0.011**
Interocular axial length difference (mm)	0.89	0.71 - 1.11	0.29
Significant ocular anomaly	**0.12**	**0.03 - 0.44**	**0.001**
Medical disorder / impairment	0.77	0.23 - 2.59	0.68
Pre-operative strabismus	0.73	0.1 – 5.5	0.76
Pre-operative nystagmus	0.61	0.15 - 2.38	0.48
Standard surgery	1.19	0.49 - 2.83	0.7
Per operative complication	1.12	0.43 - 2.94	0.82
More experienced surgeon	0.79	0.32 - 1.98	0.63
Good concordance with refractive correction	0.77	0.13 - 4.48	0.78
Post-operative visual axis opacity	1.78	0.75 - 4.24	0.19
Post-operative glaucoma	0.36	0.08 - 1.58	0.17
Any post-operative complication	0.96	0.45 - 2.05	0.92
Secondary intraocular procedures	1.39	0.64 - 3.05	0.41
Cataract asymmetry	0.92	0.22 - 3.77	0.91
Increasing time to second eye surgery (days)	0.99	0.99 - 1.00	0.56
Right eye	1.02	0.98 - 1.07	0.32
IMD Deprivation score	1.1	0.9 – 1.5	0.4
Increasing age at visual assessment (weeks)	**1.02**	**1.01 – 1.05**	**0.01**

Table 47. Multivariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery

	Relative odds of better vision	95% CI	p
IOL implantation	**4.7**	**1.3 – 16.4**	**0.01**
Significant ocular anomaly	**0.22**	**0.05 – 0.96**	**<0.05**
Increasing age at surgery (weeks)	1.01	0.98 – 1.02	0.94

On multivariate analysis, IOL implantation was associated with a 4.7 times higher odds of better visual outcome at one year following surgery.

As an association between worse post-operative visual outcomes and increasing age at surgery has been reported by many previous investigators, the absence of a significant association between age at surgery and visual outcome was explored using interaction terms.

Table 48. Multivariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery with interaction term (age and IOL implantation)

	Relative odds of better vision	95% CI	p
IOL implantation	**9.2**	**1.8 – 48.7**	**0.009**
Increasing age at surgery in children who HAVE undergone IOL implantation (in weeks)	0.97	0.9 – 1.0	0.06
Increasing age at surgery in children who have NOT undergone IOL implantation	1.03	1.0 – 1.06	0.051
Significant ocular anomaly	0.24	0.05 – 1.1	0.07

The associations found between age at surgery and visual outcome approached but did not reach statistical significance, and were in different directions for children who had and who had not undergone IOL implantation.

Sensitivity analysis of the impact of missing data on the analysis of visual outcome was undertaken. In model 1, missing data were imputed with data derived from regression analysis of the other clinical features (STATA multiple imputation method).

As data which were missing due to noncompliance may reflect poor visual performance, in model 2, missing visual assessment data were imputed as vision worse than form perception (that is, visual outcome at the worse extreme)

Table 49. Multivariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery, imputation Model 1

Missing at random – multiple imputation model	Relative odds of better vision	95% CI	p
IOL implantation	**3.6**	**1.71 – 7.58**	**0.001**
Increasing age at surgery (in weeks)	0.99	0.98 – 1.02	0.9
Significant ocular abnormality	0.35	0.16 – 0.68	0.004

Table 50. Multivariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery, imputation Model 2

Missing data due to poor visual performance model	Relative odds of better vision	95% CI	p
IOL implantation	**0.7**	**0.2 – 3.4**	**0.009**
Increasing age at surgery (in weeks)	1.01	0.98 – 1.1	0.39
Significant ocular abnormality	0.63	0.3 – 1.4	0.26

In model 1, as maybe expected in a model which computes missing data using regression paradigms drawing on the relationships between the missing variable and the other variables, the associations found using the real dataset remained. However, in model 2, testing the effect of the assumption that missing data was due to poor visual outcome, the positive association between IOL implantation and visual outcome

was no longer present. This reversal of effect direction may be in part due to the association between missing visual outcome data and IOL implantation (although this association had not reached statistical significance, as described in section 5.8.a.i, page 214).

As the presence of significant ocular anomaly may have been a confounder which was not adequately dealt with within the multivariable model, this population of children were excluded from dataset analysis in a further model. The results of univariate and multivariate analyses are shown overleaf. On multivariate analysis, within the subgroup of children who had cataract without another significant ocular anomaly, IOL implantation was still associated with higher odds of better visual outcome, as was younger age at surgery.

In order to investigate the timing of surgery for, in particular, children diagnosed in the first month of life and who are thus candidates for early life surgery (surgery in the first month of life) the analyses was then limited to this group. Within this group, younger age at surgery was again associated with better odds of better visual outcome but there was no evidence of significantly improved visual outcomes for children who underwent surgery in the first six weeks of life, whilst surgery after 6 months of age was significantly associated with poorer outcome. However, the study subgroup sample size used for this analysis is small.

Table 51. Univariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery in children without significant ocular co-morbidity

	Relative odds of better vision	95% CI	p
IOL implantation undertaken	**5.2**	1.5 – 17.9	**0.009**
Increasing age at diagnosis (weeks)	**1.01**	1.0 – 1.01	**0.07**
Increasing time from diagnosis to surgery (days)	0.99	0.99 – 1.0	0.4
Increasing age at surgery (weeks)	1.01	0.99 – 1.02	0.2
Increasing age at surgery corrected for gestational age (weeks)	1.01	0.99 – 1.02	0.2
Log age surgery	1.4	0.8 – 2.4	0.2
Increasing age at surgery categorised			
Baseline (0- 5.9 weeks), n=17			
6 - 9.9 weeks, n=14	2.1	0.2 – 19.3	0.5
10 - 26 weeks, n=12	0.9	0.1 – 7.4	0.9
Over 26 weeks (6 months), n=9	3.9	0.5 – 29.6	0.2
Increasing axial length (mm)	1.2	0.9 – 1.7	0.2
Log axial length	69.1	0.1 – 45976	0.2
Increasing horizontal corneal diameter (mm)	1.4	0.7 – 3.2	0.3
Log horizontal corneal diameter	91	0.03 – 301815	0.3
Microphthalmos	0.4	0.1 – 1.4	0.14
Interocular axial length difference (mm)	0.8	0.5 – 1.4	0.5
Medical disorder / impairment	1.4	0.2 – 12.8	0.7
Pre-operative strabismus	0.9	0.1 – 9.1	0.9
Pre-operative nystagmus	0.8	0.2 – 4.0	0.8
Standard surgery	2	0.7 – 5.9	0.2
Per operative complication	1.4	0.4 – 4.4	0.6
More experienced surgeon	1.0	0.4 – 2.9	0.9
Good concordance with refractive correction	0.6	0.1 – 3.9	0.6
Post-operative visual axis opacity	2.1	0.8 – 5.5	0.1
Post-operative glaucoma	1.1	0.3 – 3.9	0.8
Any post-operative complication	1.2	0.5 - 3	0.7
Secondary intraocular procedures	1.2	0.5 – 2.7	0.7
Cataract asymmetry	0.7	0.2 – 3.3	0.7
Increasing time to second eye surgery (days)	1.0	0.99 – 1.0	0.6
Right eye	1.04	0.9 – 1.2	0.6
IMD Deprivation score	1.09	0.8 – 1.5	0.6
Increasing age at visual assessment (weeks)	1.01	0.99 – 1.01	0.1

Table 52. Multivariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery in children without significant ocular co-morbidity

	Relative odds of better vision	95% CI	p
IOL implantation	**6.7**	**1.8 – 24.9**	**0.005**
Increasing age at surgery (weeks)	**0.95**	**0.91 – 0.99**	**0.03**
Increasing age at visual assessment (weeks)	**1.01**	**1.0 – 1.01**	**0.03**

Table 53. Multivariate multilevel logistic regression analysis of uniocular visual outcome following bilateral cataract surgery in children without significant ocular co-morbidity and diagnosed in first month of life

	Relative odds of better vision	95% CI	p
Age as a categorical variable			
IOL implantation	**25.2**	**1.7 – 369**	**0.02**
Increasing age at surgery categorised			
Baseline (0- 5.9 weeks), n=17	-		
6 - 9.9 weeks, n=14	1.6	0.04 – 10.1	0.7
10 - 26 weeks, n=12	0.1	0.01 – 1.2	0.07
Over 26 weeks (6 months), n=9	**0.02**	**0.01 – 1.1**	**0.05**
Increasing age at visual assessment (weeks)	1.0	0.9 – 1.1	0.2
Age as a continuous variable			
Excluding significant ocular abnormality, diagnosed in first month of life	**Relative odds of better vision**	**95% CI**	**p**
IOL implantation	**14.5**	**1.6 – 130**	**0.02**
Increasing age at surgery (weeks)	**0.94**	**0.9 – 0.99**	**0.03**
Increasing age at visual assessment (weeks)	**1.1**	**1 – 1.1**	**0.04**

5.8.c.ii. Unilateral cataract

Correlations between the factors of interest in relation to visual acuity in the operated eye following surgery for unilateral cataract were assessed as shown in Table 54.

As with bilateral cataract, there are significant correlations between age at surgery, age at diagnosis and ocular axial length and corneal diameter. The associations between IOL implantation and age at diagnosis, age at surgery, axial length, corneal diameter, and 'standard' surgical procedure are similar in direction, size and strength. Pre-operative strabismus was strongly associated with older age at diagnosis and surgery. The presence of a medical disorder, a less common finding amongst children with unilateral cataract, is significantly correlated with the presence of pre-operative nystagmus.

Table 54. Correlations between factors of interest with regards to visual outcome for children with unilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age diagn	Time diagn	Age surg	Gest age	AL	HCD	Microphth	IO ALD	Ocular abnorm	Med disorder	Strab	Nystag	Stand surgery	Per-op comp	Exp. Surg	Compl occlusn	Compl correctn	VAO	Glaucoma	Any comp	Sec proc	Right eye	IMD
IOL implant	**		*			**			**			*	***					*					
Age at diagnosis			****	****	****	**	**	***			**		**			*		**			*		
Time from diagnosis to surgery			***	***	**	*		*							*	**	*	**		***	**		
Age at surgery				-	****	**	**	**			**		***		**	**		***			***		
Gestational age at surgery					****	**	***	*			***		***		**	**		***			***		
Axial length						***	-	****	-		***		*		**			**	**	*	***		
HCD							-	**	-				**						*		*		
Microphthalmos								**	-				*		**			*			**		
Interocular axial length difference												*						*			**		
Significant ocular abnormality															*							**	
Medical disorder / impairment													*						*				
Pre operative strabismus													**	*		*	*	*			**		
Pre operative nystagmus																	**	*					
Standard surgery															*								
Per operative complication															*				*				
Experienced Surgeon																		**		**	**		
Good concordance occlusion																	**			*			
Good concordance correction																							
Post operative VAO																				-	-		
Post op Glaucoma																				-	-		
Any post op complication																					-		
Secondary intraocular procedures																							**
Right eye																							

The results of univariate regression analysis of visual outcome in the operated eye are shown in Table 55 below.

Table 55. Univariate ordinal regression analysis of visual outcome in the operated eye in children with unilateral cataract

	Relative odds of better vision	95% CI	p
IOL implantation	2.22	0.67 - 7.30	0.19
Increasing age at diagnosis (weeks)	1.03	1.0 - 1.06	0.08
Increasing time from diagnosis to surgery (days)	**1.02**	**1.00 - 1.03**	**0.03**
Increasing age at surgery (weeks)	**1.02**	**1.00 - 1.05**	**0.02**
Increasing age at surgery corrected for gestational age (weeks)	**1.03**	**1.00 - 1.04**	**0.02**
Increasing age at surgery (categorised)			
Baseline (0- 5.9 weeks), n=11	1	-	-
6 - 9.9 weeks, n=12	5.9	0.95 - 36.90	0.06
10 - 26 weeks, n=5	1.33	0.16 - 10.9	0.79
Over 26 weeks (6 months), n=16	**15.03**	**2.42 - 93.2**	**0.004**
Increasing axial length	**1.52**	**1.09 - 2.14**	**0.02**
Increasing horizontal corneal diameter	1.87	0.79 - 4.43	0.16
Microphthalmos	**0.27**	**0.07 - 1.01**	**0.05**
Interocular axial length difference	1.37	0.76 - 2.48	0.3
Significant ocular abnormality	**0.29**	**0.08 - 0.95**	**0.04**
Medical disorder / impairment	0.32	0.04 - 2.6	0.29
Pre operative strabismus	-	-	-
Pre operative nystagmus	1.6	0.22 - 12.2	0.63
Standard surgery	1.7	0.53 - 5.43	0.37
Per operative complication	0.26	0.06 - 1.06	0.06
More experienced surgeon	0.33	0.1 - 1.1	0.07
Good concordance with refractive correction	0.61	0.12 - 3.02	0.54
Good concordance with occlusion therapy	0.61	0.15 - 2.47	0.49
Post operative visual axis opacity	0.46	0.14 - 1.52	0.2
Post operative glaucoma	0.14	0.02 - 1.1	0.06
Any post operative complication	0.5	0.15 - 1.7	0.27
Secondary intraocular procedures	0.41	0.13 - 1.36	0.15
Right eye	0.64	0.21 - 1.99	0.44
Age at visual assessment	**1.02**	**1.00 – 1.04**	**0.02**

The factors which were found to be significantly associated with better or worse odds for visual outcome were used to build a multivariate model. Children aged between 6 and 10 weeks at surgery had the highest odds of better visual outcome: however, the wide confidence intervals shown in Table 56 are a reflection of the small number of children within the sample for this analysis. There was no statistically significant evidence of an association between IOL implantation and an increased odds of better vision at one year following surgery for unilateral cataract.

Table 56. Multivariate ordinal regression analysis of visual outcome in the operated eye in children with unilateral cataract

	Relative odds of better vision	95% CI	p
Increasing age at surgery (categorised)			
Baseline (0- 5.9 weeks), n=8	-		
6 - 9.9 weeks, n=9	**18.7**	**2 – 176**	**0.01**
10 - 26 weeks, n=8	4.8	0.5 – 51	0.2
Over 26 weeks (6 months), n=11	1.91	0.1 – 67	0.7
Increasing axial length	**1.7**	**1.1 – 2.9**	**0.03**
Age at visual assessment	1.01	0.8 – 1.1	0.6

5.9. Adverse per operative events

As described in section 5.5.g.ii, page 204, iris prolapse was the most common adverse event, affecting 18 eyes: 14 eyes of children with bilateral cataract (5%), and 4 eyes of children with unilateral cataract (4.2%).

Statistical analysis of potential predictors of iris prolapse was undertaken. Initially, correlations between the factors of interest were assessed as shown in Table 57.

5.9.a. **Bilateral cataract**

With regards to the relationships between the potential predictors of iris prolapse (as shown in Table 57 overleaf), in addition to previously described correlations, for children with bilateral cataract there was an association between IOL implantation and the viscosity of the oculoviscous device used. A more viscous OVD was used in a higher proportion of pseudophakic eyes (p=0.01 and these OVDS (Healon GV and Healon 5) were also less commonly used in microphthalmic eyes.

Table 57. Correlations between factors of interest with regards to per operative iris prolapse in children with bilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age at surgery	Gest age at surg	Signif ocular abnorm	PFV	Axial length	HCD	AxL <16mm	HCD <9.5mm	Microphthal	IO AL diff	Microcornea	Exp. surg	Viscous OVD	Right eye
IOL implantation	****	****	****		****	****	****	***	****		**	*	**	
Age at surgery		-	****	**	****	****	****	**	****		****			
Gestational age at surgery			****		****	****	****	**	****		**			
Significant ocular abnormality				-	-	-	-	-	-		-			
Persistent fetal vasculature													**	
Axial length						***	-	-	-		-			
Horizontal corneal diameter							-	-	-	*	-			
Axial length <16mm								-	-	*	-			
HCD <9.5mm									-	**	-			
Microphthalmos											-		****	**
Intercocular axial length difference														
Microcornea														
Experienced surgeon														
Viscous oculoviscous device														

As Table 58 below shows, on univariate analysis, IOL implantation and decreasing axial length were significantly associated with increased odds of per operative iris prolapse.

Table 58. Univariate multilevel logistic regression analysis of iris prolapse in eyes of children with bilateral cataract

	Relative odds of iris prolapse	95% CI	p
IOL implantation	**5.82**	**1.44 - 23.53**	**0.013**
Age at surgery unadjusted (weeks)	0.88	0.76 – 1.02	0.08
Age at surgery adjusted for gestational age (weeks)	0.88	0.76 - 1.01	0.06
Significant ocular abnormality	0.55	0.14 - 2.22	0.41
Axial length in mm	**0.73**	**0.57 - 0.94**	**0.016**
Horizontal corneal diameter in mm	0.97	0.56 - 1.47	0.69
Axial length<16mm	1.18	0.27 - 4.32	0.91
Microphthalmos	4.72	0.58 - 38.14	0.15
Interocular axial length difference in mm	0.79	0.56 - 1.13	0.21
Microcornea	0.84	0.19 - 3.78	0.82
More experienced surgeon	3.87	0.73 - 20.38	0.11
Viscous oculoviscous device	-		
Right eye	1.02	0.49 - 2.10	0.97

A multivariate model was constructed using the significantly associated factors. The decision was made to also include horizontal corneal diameter and age of child at surgery within the construction of a multivariate model, to examine the effect of including these biologically important factors which are both strongly correlated with ocular axial length. The factors which were included in the model of best fit are shown in the table overleaf.

Table 59. Multivariate multilevel logistic regression analysis of iris prolapse in eyes of children with bilateral cataract

	Relative odds of iris prolapse	95% CI	p
Increasing axial length in mm	0.44	0.28 - 0.69	<0.0001
IOL implantation	25.02	4.16 - 150.6	<0.0001

IOL implantation is independently associated with a 25 times higher odds of per-operative iris prolapse in children with bilateral cataract, and a longer axial length is also associated with a reduction in the risk of iris prolapse. In addition, rather than IOL implantation having a weaker association with iris prolapse once the effect of axial length is taken into consideration, IOL implantation is associated with a higher odds of iris prolapse (although the wide confidence intervals reflect the small sample size for analysis).

5.9.b. **Unilateral cataract**

The correlations between the potential predictors of per operative iris prolapse in children undergoing unilateral cataract surgery are shown in Table 60 overleaf. In addition to previously described correlations, for children with unilateral cataract there was an association between the experience of the operating surgeon and the viscosity of the oculoviscous device used, with a more viscous OVD (specifically, Healon GV) used by a significantly higher proportion of experienced surgeons eyes (p=0.03). This may be due to the perceived effectiveness of this form of OVD, or may reflect the shared training history of the more experienced surgeons within this cohort.

Table 60. Correlations between factors of interest with regards to per operative iris prolapse in children with unilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age at surgery	Gest age at surg	Signif ocular abnorm	PFV	Axial length	HCD	AxL <16mm	HCD <9.5mm	Microphthalmos	IO AL diff	Microcornea	Exp. surgeon	Viscous OVD	Right eye
IOL implantation	***	****	****	***	****	****	*	-	*	***		*	*	
Age at surgery		-			****	****			***					
Gestational age at surgery					****	****			****				*	
Significant ocular abnormality				-	-	-	-	-	-		-			
Persistent fetal vasculature														
Axial length						****	-	-	-	****	-			
Horizontal corneal diameter							-	-	-		-		*	
AxL <16mm								-	-	***	-			
HCD <9.5mm									-	*	-			
Microphthalmos										****	-	*		
Interocular axial length difference														*
Microcornea													*	
Experienced surgeon													**	*
Viscous OVD														

Table 61. Univariate logistic regression analysis of per operative iris prolapse in children with unilateral cataract

	Relative odds of iris prolapse	95% CI	p
IOL implantation	-		
Age at surgery unadjusted (weeks)	0.97	0.9 - 1.04	0.33
Age at surgery adjusted for gestational age (weeks)	0.97	0.9 – 1.04	0.33
Significant ocular abnormality	0.49	0.05 - 4.86	0.54
Increasing axial length in mm	0.63	0.32 - 1.24	0.18
Horizontal corneal diameter	0.68	0.19 - 2.52	0.57
Axial length<16mm	4.67	0.41 - 53.4	0.22
Microphthalmos	2.32	0.22 - 22.5	0.5
Interocular axial length difference	0.46	0.06 - 3.75	0.47
Microcornea	1.73	0.15 - 20.5	0.66
More experienced surgeon	-		
Oculoviscous device	-		
Right eye	1.07	0.14 - 7.91	0.95

As all 4 eyes which experienced iris prolapse were eyes of children in the IOL group, and were eyes which had been operated on by experienced surgeons, and had undergone surgery with the same type of OVD device (Healon GV), it was not possible to estimate a univariate relative odds of iris prolapse with these factors . On univariate analysis none of the considered factors reached statistical significance. This may be due to the small number of episodes of iris prolapse within this group.

5.10. Adverse outcomes at one year following surgery

5.10.a. **Glaucoma**

At present, 12 month data is not available for any of the 4 children who had pre-operative glaucoma. These children will be excluded from future analyses of post-operative glaucoma within the study group.

5.10.a.i. Bilateral cataract

Glaucoma (without an acute or pupil block event) affected 9.6% of eyes (17/177) and 15.7% of children (14/89) during the first post-operative year.

Glaucoma and ocular hypertension were diagnosed in a higher proportion of children who had undergone surgery without IOL implantation, as shown in Table 62 overleaf.

Table 62. Occurrence of ocular hypertension related events in the first year following surgery for bilateral cataract

	IOL group 81 eyes of 41 children	Aphake group 96 eyes of 48 children	p	95% CI of difference in proportions
No IOP related complications	75 92.2%	71 73.5%	0.001	7.6% - 29%
Glaucoma	4 4.9% (3 children, 4%)	13 13.7% (11 children, 22.9%)	0.07 0.04	7% - 32.8% 6.8% - 39.5%
Ocular hypertension	2 2.9%	9 9.4%	0.002	-0.6% - 15.6%
Transient IOP rise	0	2 2.1%	0.5	
Pupil block event	0	1 1%	0.99	

2 of the 4 pseudophakic eyes (2 children) and 4 of the 13 aphakic eyes (3 children) required surgical therapy to manage their glaucoma.

5.10.a.ii. Unilateral cataract

In the first post-operative year, glaucoma had been diagnosed in 8% of children in the IOL group, and 9% of children in the aphake group.

Table 63. Occurrence of ocular hypertension related events in the first year following surgery for unilateral cataract

	IOL - 36 children	Aphake - 22 children	P
No IOP related complications	26 72.2%	15 68.2%	0.48
Glaucoma	3 8.3%	2 9.1%	0.63
Ocular hypertension	5 13.9%	4 18.2%	0.6
Transient IOP rise	1 2.8%	1 4.5%	0.99
Pupil block event	1 2.8%	0	0.99

2 of the 3 pseudophakic eyes and 1 of the two aphakic eyes required surgical treatment for glaucoma.

5.10.a.iii. Factors associated with post-operative glaucoma

Bilateral cataract

The correlations between the factors assessed for an association with the occurrence of glaucoma in the first post-operative year are shown in Table 64 overleaf.

In addition to the previously described correlations, the occurrence of per-operative planned or unintended iris manipulation or trauma was positively correlated with the presence of severe microphthalmos (p=0.01) microcornea (p=0.03), and younger age at surgery (p=0.01). As the role of primary iridectomy is to prevent angle closure glaucoma in small eyes, and pupil stretch is only required for small pupils, these associations were expected. There was strong evidence of an association between IOL implantation and post-operative inflammation (p=0.002). The association between inflammation and younger age at surgery (p=0.02) may reflect either the pro-inflammatory state of early infancy, or the sequelae of the per-operative iris trauma which was undertaken in a higher proportion of younger eyes (the occurrence of post-operative inflammation will be described in more detail in section 5.10.b).

The surgical management undertaken by ophthalmologists correlated with child specific factors: the viscosity of the oculoviscous device used per operatively positively correlated with the occurrence of persistent fetal vasculature whilst negatively correlating with the presence of microphthalmos (although there was no correlation with axial length). Different aspects of surgical management were also inter-correlated: the use of intensive post-operative topical steroid regimens and the higher experience level of the operating surgeon.

Table 64. Correlations between factors of interest with regards to occurrence of post-operative glaucoma in children with bilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age at surgery	Gest age	Oc abnorm	PFV	Axial length	HCD	AxL <16mm	HCD <9.5mm	Microphthalm	IO AL diff	Microcornea	Exp. Surg	Viscous OVD	Post caps'my	Iris trauma	IOL explant	Intensive steroid	System steroids	Post op inflamm	Sec proc	Right eye
IOL implantation	****	***	****		****	****	****	****	****		****			*		-	*		**	**	
Age at surgery		-	***		****	****	****	*	****		***			*					**		
Gestational age at surgery			**		****	****	****	*	***		**			*	**				*		
Significant ocular abnormality				-	-	-	-	-	-		-				*						
Persistent fetal vasculature						**		**				*									
Axial length						****	-	-	-		-				***						
Horizontal corneal diameter							-	-	-		-		*	**	**				*		
Axial length <16mm								-	-		-				**	**					
HCD <9.5mm									-	**	-				**	-					
Microphthalmos											-		*		***						*
Interocular axial length difference																					*
Microcornea															*					*	
Experienced surgeon															**		**	*			
Viscous OVD														*				*			
Posterior capsulotomy																			*		
Per op iris trauma																					
Per op IOL explant																					
Post op intensive steroid																		*			
Post op systemic steroid																				**	
Post op inflammation																				****	*
Secondary procedures																					

Table 65. Univariate multilevel logistic regression analysis of post-operative open angle glaucoma in eyes of children with bilateral cataract

	Relative odds of post-operative glaucoma	95% CI	P
IOL implantation	0.33	0.1 - 1.1	0.07
Increasing age at surgery (weeks)	**0.93**	**0.89 - 0.97**	**0.002**
Adjusted age at surgery (weeks)	**0.94**	**0.9 - 0.98**	**0.003**
Baseline (0- 5.9 weeks), n=50	1		
6 - 9.9 weeks, n=34	1.5	0.5 - 5	0.52
10 - 26 weeks, n=50	0.9	0.3 - 3.0	0.86
Over 26 weeks (6 months), n=43	-	-	-
Significant ocular abnormality	1.72	0.7 - 4.4	0.26
Persistent fetal vasculature	0.43	0.06 - 3.3	0.42
Increasing axial length	0.88	0.7 - 1.0	0.14
Horizontal corneal diameter	0.9	0.5 - 1.4	0.54
Axial length <16mm	1.2	0.4 - 3.2	0.78
HCD <9.5mm	1.32	0.4 - 4.7	0.69
Microphthalmos	0.89	0.3 - 3.1	0.85
Interocular axial length difference	1.4	0.7 - 2.8	0.39
Microcornea	**3**	**1.0 - 8.8**	**0.05**
Experienced surgeon	1.4	0.6 - 3.6	0.49
Viscous OVD	1.5	0.2 - 11.2	0.72
Posterior capsulotomy	-		
Per operative iris trauma	1.6	0.6 - 4.1	0.37
Per operative IOL explant	-		
Post-operative intensive steroid regimen	1.2	0.5 - 3.2	0.67
Post-operative systemic steroids	0.85	0.1 - 7.1	0.88
Post-operative inflammation	-		

Microcornea and younger age at surgery were the only factors associated with higher odds of glaucoma at 1 year. As shown in the table above, due to insufficient sub sample sizes (insufficient numbers of children who underwent bilateral cataract surgery were affected by IOL explantation, post-operative inflammation, or had or intact posterior capsules at primary surgery) regression analysis was not possible for these three potential predictors of outcome.

In addition, as none of the children who underwent surgery aged over 6 months developed glaucoma in the first year, it was not possible to determine a meaningful odds ratio for the relative odds of glaucoma at 1 year for this age group.

Only age at surgery was associated with a higher odds of glaucoma following surgery on multivariate analysis (Table 66).

Table 66. Multivariate multilevel regression analysis of post-operative glaucoma in eyes of children in the first year following surgery for bilateral cataract

	Relative odds of post-operative glaucoma	95% CI	p
Increasing age at surgery (weeks)	**0.94**	**0.98 – 0.99**	**0.03**
Microcornea	2.2	0.69 – 7.1	0.18

Unilateral cataract

The correlations found within the cohort of children undergoing surgery for unilateral disease are shown in Table 67 overleaf.

As with the bilateral cataract group, there are correlations between different aspects of surgical practice: an intensive post-operative steroid regimens were used by higher proportions of the more experienced operating surgeons, and these surgeons were also less likely to use systemic steroids for their children post operatively ($p<0.01$).

Table 67. Correlations between factors of interest with regards to post-operative glaucoma in children with unilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age at surgery	Gest age	Ocular abnorm	PFV	Axial length	HCD	AxL <16mm	HCD <9.5mm	Microphthalm	IO ALD	Microcornea	Exp. Surg	Viscous OVD	Iris trauma	IOL explant	Intensive steroid	System steroids	Post op inflamm	Sec proc	Right eye
IOL implantation	*	*	****	***	*	***	*	-			***		*	**	-					
Age at surgery		-			****	**			**	*		*							****	
Gest age at surgery					****	*			**	*		*							****	
Significant ocular abnormality				-	-	-	-	-	-		-			**						
Persistent fetal vasculature						*									*					
Axial length						****	-	-	-	****	-	***		*		*	**		***	
Horizontal corneal diameter							-	-	-		-									
Axial length <16mm								-	-	***	-	*		**					**	
HCD <9.5mm									-	*	-			*	-					
Microphthalmos										****	-					**	**		*	
IOALD														*					**	*
Microcornea													*							
Exp. Surgeon													*	*		**	***	*	**	**
Viscous OVD																				*
Per op iris trauma																***				
Per op IOL explant																*				
Post op intensive steroid																				
Post op systemic steroids																				
Post op inflammation																			**	*
Secndary procedures																				

Figure 24. Univariate logistic regression analysis of glaucoma in the operated eye following unilateral cataract surgery

	Relative odds of glaucoma	95% CI	p
IOL implantation	0.96	0.15	0.97
Increasing age at surgery (weeks)	0.97	0.92 – 1.02	0.31
Increasing adjusted age at surgery (weeks)	0.97	0.92 – 1.03	0.29
Age at surgery (categorised)			
Baseline (0- 5.9 weeks), n=14	1		
6 - 9.9 weeks, n-16	2.4	0.2 - 28.7	0.5
10 - 26 weeks, n=7	2.4	0.1 - 42.8	0.56
Over 26 weeks (6 months), n=21	0.7	0.04 - 12.4	0.83
Significant ocular abnormality	6.2	0.7 - 58.7	0.11
Persistent fetal vasculature	0.7	0.12 - 4.9	0.78
Increasing axial length	**0.3**	**0.08 - 0.94**	**0.04**
Increasing horizontal corneal diameter	0.3	0.08 - 0.9	0.06
Axial length <16mm	**28**	**2.5 - 313.2**	**0.007**
HCD <9.5mm	17	0.84 - 343.7	0.07
Microphthalmos	-		
Interocular axial length difference	0.04	0.002 - 1	0.05
Microcornea	3	0.4 - 23.5	0.3
More experienced surgeon	2.9	0.3 - 28	0.34
Viscous OVD	0.4	0.04 - 4.8	0.5
Posterior capsulotomy	-		
Per op iris trauma	2.9	0.43 - 19	0.27
Per op IOL explant	-		
Post op intensive steroid	1.5	0.24 - 9.8	0.66
Post op systemic steroids	-		
Post op inflammation	5.3	0.81 - 34.7	0.08

On univariate analysis, although the size and direction of association for factors such as age at surgery and corneal size were similar to the associations found for glaucoma following bilateral surgery, the only factor which reached a statistically significant association was pre-operative axial length, with eyes measuring less than 16mm having a 28 times higher odds (with a wide confidence interval) of developing glaucoma in the first post-operative year.

Again, no child who was aged over 6 months old at surgery had developed glaucoma by the end of the first post-operative year.

Overall, amongst the 19 children who had developed glaucoma (14 following bilateral cataract surgery, 5 following unilateral cataract surgery) almost half (9/19 or 47%) of these children were aged under 6 weeks old at surgery.

5.10.b. **Visual axis opacity**

5.10.b.i. Bilateral cataract

During the first post-operative year, visual axis opacity necessitating surgical repair affected 42 of the 177 eyes of children who had undergone surgery for bilateral cataract (24%).

Visual axis opacity in the form of pearls or fibrosis occurred in a significantly higher proportion of eyes of children in the IOL group. The difference between the proportions of eyes affected by membranous visual axis opacity did not reach statistical significance (Table 68).

3 eyes (3%) of children in the aphake group, and 4 eyes (6%) of children in the IOL group underwent 2 or more procedures in the first post-operative year.

Table 68. Occurrence of visual axis opacity in children with bilateral cataract in the first post-operative year

	IOL group 81 eyes of 41 children	Aphake group 96 eyes of 48 children	p	95% CI of difference in proportions
Visual axis opacity involving pearls / fibrosis	19 23.5% (14 children, 34.2%)	7 7.3% (6 children, 12.5%)	0.003 0.02	5.6% - 27.1% 4.1% - 38.2%
Membranous visual axis opacity	11 13.6% (8 children, 19.5%)	5 5.2% (5 children, 10.4%)	0.053 0.25	-0.3% to 18% -5.9% - 24.8%

5.10.b.ii. Unilateral cataract

27 of the 58 eyes of children with unilateral cataract underwent surgery for visual axis opacity in the first post-operative year (46.6%).

A higher proportion of eyes which underwent IOL implantation were affected by visual axis opacity in the first post-operative year, and there was again a significant difference between the two groups in the proportion of children affected by proliferative VAO (pearls / fibrosis) (Table 69).

Table 69. Occurrence of visual axis opacity in children with unilateral cataract in the first post-operative year

	IOL, n=36 eyes	Aphake, n=22 eyes	p
Visual axis opacity involving pearls / fibrosis	17 47.2%	4 18.2%	0.047
Membranous visual axis opacity	7 19.4%	4 18.2%	0.99

4 children (18.2%) in the aphake group, and 8 children (22.2%) in the IOL group underwent 2 or more procedures in the first post-operative year.

5.10.b.iii. Factors associated with VAO

Bilateral cataract

The variables assessed in the analysis of visual axis opacity included previously considered factors (Table 70) and the undertaking of a manual anterior capsulotomy, use of intraocular heparin, fixation of the implant, and use of a single piece rather than three piece implant.

There were several correlations between the different aspects of surgical management: the use of manual capsulorhexis correlated with the use of a single piece IOL implant and intensive post-operative steroid regimens, as well as the experience level of the surgeon. The undertaking of a manual anterior capsulorhexis, a more controlled method of capsule manipulation also correlated with the undertaking of IOL implantation, which is to be expected as capsule integrity is essential if an implant is to be used. Accordingly, manual capsulorhexis correlated with axial length and horizontal corneal diameter.

The use of intraocular heparin did not correlate with any other clinical factor.

Table 70. Correlations between factors of interest with regards to occurrence of visual axis opacity in children with bilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Manual anterior capsulotomy	Single piece IOL	IOL in bag	Per operative heparin
IOL implantation	****	-	-	
Gestational age at surgery				
Age at surgery	*			
Persistent fetal vasculature			**	
Axial length	**			
Horizontal corneal diameter	**	*	**	
Experienced surgeon	***		***	
Viscous OVD	**	**		****
Posterior capsulotomy				-
Single piece IOL	****			
IOL fixed within the bag		*		
Per operative heparin				
Per operative iris trauma				
Per operative IOL explant		-	-	
Post-operative intensive steroid	**			*
Post-operative systemic steroids		*		
Post-operative inflammation				
Right eye				

The results of regression analysis of the occurrence of proliferative visual axis opacity (pearls, fibrosis or anterior capsular contraction) at 1 year following surgery are shown below.

Table 71. Univariate multilevel regression analysis of proliferative visual axis opacity in eyes of children at one year following surgery for bilateral cataract

	Relative odds of visual axis opacity	95% CI	p
IOL implantation	**3.9**	**1.4 – 11.1**	**0.01**
Age at surgery unadjusted (weeks)	0.98	0.96 – 1	0.15
Age at surgery adjusted for gestational age (weeks)	0.98	0.96 - 1	0.16
Increasing category of age at surgery			
Baseline (0 - 5.9 weeks), n=50	-	-	-
6 - 9.9 weeks, n=34	1.6	0.4 – 5.9	0.72
10 - 26 weeks, n=50	0.85	0.2 – 3	0.81
Over 26 weeks (6 months), n=43	0.39	0.1 – 1.6	0.19
Persistent fetal vasculature	2.1	0.4 – 11.5	0.41
Axial length	0.84	0.7 – 1	0.06
Horizontal corneal diameter	1.2	0.8 – 1.8	0.3
Experienced surgeon	1.3	0.5 – 3.6	0.6
Manual anterior capsulorhexis	2.2	0.7 – 6.4	0.14
Viscosity of OVD	-		
Posterior capsulotomy	-		
Single piece IOL	**4.3**	**1.1 – 15.9**	**0.03**
Increasing IOL power	**1.2**	**1.1 – 1.5**	**0.008**
Bag fixation	1.2	0.2 – 16.3	0.85
Per-operative heparin	0.9	0.3 – 3.1	0.88
Per-operative iris trauma	0.8	0.2 – 2.7	0.74
IOL explantation	-		
Intense post op steroids	**2.8**	**1.02 – 7.4**	**0.04**
Systemic steroids	1.1	0.2 – 5.8	0.91

As Table 71 shows IOL implantation, single piece implants, IOL power and intensive post-operative steroid regimens are associated with higher odds of visual axis opacity. Due to the interaction between all these factors and age at surgery, and the biological importance of age at surgery, this variable was also included in the construction of the multivariable model of best fit.

Table 72. Multivariate multilevel regression analysis of proliferative visual axis opacity following surgery for bilateral cataract

	Relative odds of VAO	95% CI	p
IOL implantation	**7.1**	**2.4 – 21.5**	**0.001**
Increasing age at surgery (weeks)	**0.96**	**0.93 – 0.99**	**0.03**

Primary IOLs were associated with a 7 times higher odds of proliferative visual axis opacity, whilst increasing age at surgery by one week reduced the odds of proliferative VAO by 4%.

The relationship between single piece IOL implants and the risk of visual axis opacity was explored by undertaking analysis on those children who had undergone IOL implantation. The results of the multivariate analysis are shown in Table 73 below.

Table 73. Multivariate multilevel regression analysis of proliferative visual axis opacity following surgery with IOL implantation for bilateral cataract in eyes

	Relative odds of VAO	95% CI	p
Single piece IOL	**4.1**	**1.0 – 17.3**	**<0.05**
Increasing age at surgery (weeks)	**0.96**	**0.94 – 0.99**	**0.008**
Increasing IOL power	1.2	0.96 – 1.4	0.1

Amongst children undergoing IOL implantation, single piece intraocular lens implantation was independently associated with a 4 times higher odds of proliferative visual axis opacity.

The results of regression analysis of the occurrence of membranous visual axis opacity at 1 year following surgery are shown below. No factors reached significance on univariate analysis.

Table 74. Univariate multilevel regression analysis of membranous visual axis opacity in eyes of children at one year following surgery for bilateral cataract

	Relative odds of visual axis opacity	95% CI	p
IOL implantation	2.9	0.9 – 9.2	0.08
Age at surgery unadjusted (weeks)	1	0.98 – 1.02	0.83
Age at surgery adjusted for gestational age (weeks)	1	0.98 – 1.02	0.81
Increasing category of age at surgery			
Baseline (0- 5.9 weeks)	1		
6 - 9.9 weeks	0.2	0.02 – 1.1	0.07
10 - 26 weeks	-		
Over 26 weeks (6 months)	0.7	0.2 – 2.4	0.6
Persistent fetal vasculature	-		
Axial length	0.89	0.7 – 1.1	0.37
Horizontal corneal diameter	1.5	0.9 – 2.6	0.14
Experienced surgeon	0.91	0.3 – 2.9	0.89
Manual anterior capsulorhexis	1.1	0.4 – 3.3	0.8
OVD	0.3	0.04 – 1.7	0.18
Posterior capsulotomy	0.1	0.0 – 1.6	0.1
Single piece IOL	3.8	0.8 - 18.5	0.11
Increasing IOL power	1	0.9 – 1.1	0.3
Bag fixation	-		
Per-operative heparin	1.7	0.5 – 6.3	0.43
Per-operative iris trauma	1.7	0.5 – 6.3	0.43
IOL explantation	-		
Intense post op steroids	1.04	0.3 – 3.5	0.95
Systemic steroids	2.1	0.4 – 11.3	0.39

Unilateral cataract

The pattern of correlation between factors of interest again matched the patterns found amongst predictors of interest in the analysis of bilateral cataract outcomes. A newly found correlation (Table 75) was that between the use of intraocular heparin and the use of an intensive post-operative intensive steroid: this was due to practice within one hospital (which contributed the third largest single-site group of children to the study sample).

Table 75. Correlations between factors of interest with regards to occurrence of visual axis opacity in children with unilateral cataract

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Manual anterior capsulotomy	Single piece IOL	IOL in bag	Per operative heparin
IOL implantation	***	-	-	
Gest age at surgery	**	**		
Age at surgery	**	**		
Persistent fetal vasculature			*	
Axial length	*	***		
Horizontal corneal diameter	**	**		
Experienced surgeon	*			
Viscous OVD	**		*	
Single piece IOL				
IOL fixed within the bag				
Per operative heparin				
Per op iris trauma	*			
Per op IOL explant		-	-	
Post-operative intensive steroid			*	*
Post-operative systemic steroids			**	
Post-operative inflammation				
Right eye		*	*	

On univariate analysis and then on multivariate analysis, IOL implantation was independently associated with increased odds of visual axis opacity, as was younger age at surgery.

Table 76. Univariate regression analysis of proliferative visual axis opacity following surgery for unilateral cataract

	Relative odds of VAO	95% CI	p
IOL implantation	**4.0**	**1.1 – 1.4**	**0.03**
Age at surgery unadjusted, (weeks)	**0.97**	**0.95 – 0.99**	**0.03**
Age at surgery adjusted for gestational age, (weeks)	**0.97**	**0.95 – 0.99**	**0.03**
Increasing category of age at surgery			
Baseline (0- 5.9 weeks), n=14	1		
6 - 9.9 weeks, n=16	0.6	0.1 – 2.5	0.47
10 - 26 weeks, n=7	0.3	0.0 – 2.1	0.23
Over 26 weeks (6 months) , n=21	**0.2**	**0.04 – 0.8**	**0.03**
Persistent fetal vasculature	0.4	0.2 – 1.2	0.1
Axial length	0.7	0.5 – 1.0	0.06
Horizontal corneal diameter	1.1	0.5 – 2.7	0.76
Experienced surgeon	1.4	0.5 – 4.4	0.53
Manual anterior capsulorhexis	1.4	0.4 – 4.2	0.59
OVD	-		
Posterior capsulotomy	-		
Single piece IOL	**6.2**	**1.4 – 27.1**	**0.01**
Increasing IOL power	1.1	0.99 – 1.2	0.09
Bag fixation	0.5	0.1 – 3.2	0.54
Per-operative heparin	0.6	0.1 – 5.8	0.63
Per-operative iris trauma	0.5	0.1 – 2.2	0.4
IOL explantation	-		
Intense post op steroids	**0.2**	**0.1 – 0.98**	**0.05**
Systemic steroids	0.9	0.1 – 5.2	0.8

Table 77. Multivariate regression analysis of proliferative visual axis opacity following surgery for unilateral cataract

	Relative odds of VAO	95% CI	p
IOL implantation	**6.3**	**2.7 – 19.0**	**<0.0001**
Increasing age at surgery unadjusted (weeks)	**0.96**	**0.94 – 0.99**	**0.008**

The relationship between single piece IOL implants and the risk of visual axis opacity was again explored for children with unilateral cataract. The results of the multivariate analysis are shown in Table 73 below. Although the association between IOL power and visual axis opacity did not reach statistical significance on univariate analysis, it was included within the multivariate model because of its significance in outcomes following bilateral cataract surgery.

Table 78. Multivariate regression analysis of proliferative visual axis opacity following IOL implantation for unilateral cataract

	Relative odds of VAO	95% CI	p
Single piece IOLs	7.4	0.6 – 98.9	0.1
Increasing age at surgery unadjusted (weeks)	**0.93**	**0.88 – 0.99**	**0.02**
Increasing axial length	1.5	0.7 – 13.3	0.3
Increasing IOL power	1.0	0.8 – 1.4	0.8

For children undergoing IOL implantation during primary surgery for unilateral cataract, the association between single piece IOL implantation and occurrence of proliferative visual axis opacity did not reach statistical significance. However, the direction and size of the effect (with higher odds of proliferative visual axis with single piece implants) was similar to that found for children with bilateral cataract).

The results of regression analysis of the occurrence of membranous visual axis opacity at 1 year following surgery for unilateral cataract are shown below.

Table 79. Univariate regression analysis of membranous visual axis opacity following surgery for unilateral cataract

	Relative odds of VAO	95% CI	p
IOL implantation	1.08	0.3 – 4.2	0.91
Age at surgery unadjusted	0.94	0.88 – 1.01	0.08
Age at surgery adjusted for gestational age	0.94	0.89 – 1.01	0.08
Increasing category of age at surgery			
Baseline (0- 5.9 weeks)	1		
6 - 9.9 weeks	0.6	0.1 – 2.9	0.52
10 - 26 weeks	0.3	0.03 – 3.2	0.32
Over 26 weeks (6 months)	**0.09**	**0.01 – 0.9**	**0.04**
Persistent fetal vasculature	1.1	0.3 – 4.2	0.86
Axial length	**0.6**	**0.4 – 1.0**	**0.05**
Horizontal corneal diameter	0.6	0.2 – 1.8	0.36
Experienced surgeon	**8.4**	**0.99 – 71.1**	**0.05**
Manual anterior capsulorhexis	1.1	0.3 – 4.2	0.91
OVD	0.6	0.1 – 6.4	0.64
Single piece IOL	7.1	0.7 – 68.6	0.09
Increasing IOL power	1.1	0.9 – 1.2	0.5
Bag fixation	0.3	0.04 – 2.2	0.23
Per-operative heparin	-		
Per-operative iris trauma	2.8	0.7 – 11.8	0.17
IOL explantation	-		
Intense post op steroids	2.2	0.6 – 8.3	0.26
Systemic steroids	-		

There was no evidence of an (independent) relationship between IOL implantation, axial length or age at surgery with the odds of membranous visual axis opacity on multivariate analysis.

5.10.c. **Other adverse events**

5.10.c.i. Bilateral cataract

Fibrinous uveitis was three times more common in IOL eyes following surgery, affecting 11.1% (9/81) IOL eyes (8 children) and 3.1% (3/96) aphake eyes (3 children) but this difference did not reach statistical significance (p=0.07, 95% CI difference in proportions -0.6% to 7.4%)

In total, significant (requiring additional intervention) post-operative inflammation events or sequelae indicative of significant inflammation (membranous visual axis opacity and pupil synechiae) affected a significantly higher proportion of eyes of children in the IOL group: 19.8% (16/81) IOL eyes and 7.3% (7/96) aphake eyes (p=0.02, 95% CI DIP 2.4 – 23.1%).

Pupil irregularities were noted in 4 IOL eyes (4.9%) and 4 aphake eyes (4.2%).

The other adverse events were vitreous haemorrhage (in 3 aphake group eyes and 2 IOL eyes), iris incarceration within the wound requiring surgical repair (1 IOL eye, 1 aphake eye), retained cortical matter requiring surgical removal (1 IOL eye), wound opening requiring surgical repair (1 aphake eye), and retinal detachment, which affected a child in the aphake group in association with bilateral persistent fetal vasculature.

No child was affected by endophthalmitis following primary surgery: however, one child developed endophthalmitis following surgical intervention for aphakic glaucoma.

One child in the aphake group was hospitalised with bacterial pneumonia acquired whilst on systemic steroid treatment following primary cataract surgery.

5.10.c.ii. Unilateral cataract

There was no significant difference in the proportion of eyes in the IOL or aphake group affected by fibrinous uveitis (4/36, 11.1% of IOL children and 4/22, 18.1% of aphake group children, p=0.46).

Significant post-operative inflammation affected almost twice as many children who had undergone IOL implantation (12/36, 33.3%) than aphake eyes (4/22, 18.2%) but this difference did not reach statistical significance (p=0.08).

Pupil irregularities were noted in 3 IOL eyes (8.3%) but did not affect any children in the aphake group.

The other adverse events were vitreous haemorrhage (in 2 aphake group children), wound opening requiring surgical repair (1 IOL child, 1 aphake child), and partial retinal detachment, which affected one child in the IOL group.

No child was affected by post-operative endophthalmitis.

5.11. Refractive outcomes following primary IOL implantation

5.11.a. **Prediction error**

Planned refractive outcome and actual refractive outcome data are available for 70 of the 96 eyes in children with bilateral pseudophakia, and 36 of the 42 children with unilateral pseudophakia. Refractive outcome as measured in the first post-operative month was within a dioptre of planned outcome in fewer than half of operated eyes, 44% (47/106), and the prediction error was greater than 2 dioptres in 29% of eyes (31/106). The occurrence of significant prediction error was similar in unilateral and bilateral pseudophakia (Table 80).

Table 80. Prediction error

		Bilateral pseudophakia	Unilateral pseudophakia
Planned refractive outcome missing		12	6
Post-operative refractive outcome missing		14	2
Total with data on prediction error		**70**	**36**
Prediction error within 1 dioptre		30 43%	17 47%
Prediction error with more myopic result:			
	>1 dioptre error	12 17%	6 16.7%
	>2 dioptre error	2 2.9%	5 13.9%
Prediction error with more hyperopic result:			
	>1 dioptre error	28 40%	11 30.6%
	>2 dioptre error	20 28.6%	6 16.7%

5.11.a.i. Factors associated with prediction error

The results of the assessment of correlation between the factors of interest in relation to prediction error of children with bilateral and unilateral cataract are shown in the tables overleaf.

There then follows the results of the univariate analyses of prediction error following primary IOL implantation in children with unilateral and bilateral cataract (Table 83 and Table 84).

Table 81. Correlations between factors of interest with regards to prediction error in bilateral pseudophakia

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age at surg	K	K astig	Axial length	HCD	AxL <16 mm	AxL <20 mm	HCD <9.5 mm	IO AL diff	ACD	Forml	IOL power	Ant seg abnorm	Visc OVD	Post. caps	Ant vitrect	Wnd sutured	Exp. Surg	Single piece	IOL in bag	Right eye
Gestational age at surgery	-	****		****	****	****	****	**		*		**									
Age at surgery		****		****	****	****	****	**		*		**									
Corneal curvature (K)				****	****	****	****	**				-									
Corneal astigmatism						*	*								*				*		
Axial length					****	-	-	-				-									
HCD						-	-	-	*				-								
Axial length <16mm							-	-				-	**								
Axial length <20mm								-		*	****	-									
HCD <9.5mm									**		-	-	-						-	-	
Interocular axial length difference																					
Anterior chamber depth												-	**								
Power calculation formula															-	***		**			
IOL power																	**		**		
Anterior segment abnormality																					
Viscous OVD															****					*	
Posterior capsulotomy																***					*
Anterior vitrectomy																					
Wound sutured																					
Experienced Surgeon																					
Single piece IOL																					
IOL fixation within capsular bag																					*

Table 82. Correlations between factors of interest with regards to prediction error in unilateral pseudophakia

Peach squares indicate a positive correlation. Blue squares indicate a negative correlation. *p value<0.1; **p value<0.05; ***p value<0.01; ****p value<0.001. Full details in Appendix M (0)

	Age at surg	K	K astig	Axial length	HCD	AxL <16mm	AxL <20mm	HCD <9.5mm	IO AL diff	ACD	Forml	IOL power	Ant seg abnorm	Visc OVD	Ant vitrectomy	Wnd sutured	Exp Surg	Single piece	IOL in bag	Right eye
Gestational age at surgery	-	****		****	****		****			**	*	****	***	*		**				
Age at surgery		****		****	****		****			**	*	****	***	*		**				
Corneal curvature (K)				****	****		****			**	**	-	***				*			
Corneal astigmatism																				
Axial length					****	-	-	-	****	****		-						**		
HCD						-	-	-		****		***	-	*						
Axial length <16mm							-	-	****	**		-								
Axial length <20mm								-	****	***		-						**		
HCD <9.5mm									*		-	-	-					-	-	
Interocular axial length difference												****						*		**
Anterior chamber depth												-					*			
Power calculation formula																				
IOL power																		***		
Anterior segment abnormality														**						
Viscous OVD															****		**			
Anterior vitrectomy																			****	*
Wound sutured																				
Experienced Surgeon																				*
Single piece IOL																				*
IOL fixation within capsular bag																				*

Table 83. Univariate multilevel regression analysis on prediction error in bilateral pseudophakia

	Correlation with myopic error	95% CI	p	Correlation with hyperopic error	95% CI	p
Age at surgery (in weeks)	-0.01	-0.01 to 0.01	0.5	**-0.02**	**-0.04 to -0.01**	**0.007**
Log age surgery	-0.05	-0.3 to 0.2	0.7	**-0.8**	**-1.4 to -0.3**	**0.005**
Corneal curvature (K)	0.3	-0.2 to 0.8	0.3	0.6	-1.2 to 2.3	0.5
Log corneal curvature	2.1	-1.7 to 5.9	0.3	3.9	-8.9 to 16.6	0.5
Corneal astigmatism	0.5	-0.7 to 1.7	0.4	0.5	-1.4 to 2.3	0.6
Axial length	0.01	-0.2 – 0.2	0.9	**-0.4**	**-0.6 - -0.1**	**0.01**
Log axial length	0.2	-2.9 to 3.3	0.9	**-7.1**	**-12.3 to -1.8**	**0.009**
Horizontal corneal diameter	-0.1	-0.8 – 0.6	0.8	-0.4	-1.6 – 0.8	0.5
Log HCD	-1.1	-8.5 to 6.3	0.8	-4.1	-17.4 to 9.1	0.5
Axial length <16mm	**-0.4**	**-0.7 to -0.1**	**0.02**	**4.9**	**4.2 to 5.6**	**<0.001**
Axial length <20mm	-0.04	-0.7 to 0.7	0.9	**1.4**	**0.3 to 2.4**	**0.01**
Interocular axial length difference	**0.6**	**0.05 to 1.2**	**0.03**	-0.2	-1.1 to 0.8	0.8
Anterior chamber depth	-0.2	-0.5 to 0.2	0.3	**-1**	**-1.9 to -0.1**	**0.03**
Power calculation formula – Hoffer Q	0.2	-0.4 to 0.9	0.5	0.9	-0.8 to 2.7	0.3
Power calculation formula – Holladay 1	**-0.4**	**-0.8t o -0.05**	**0.03**	1.0	-0.9 to 2.9	0.3
Power calculation formula – SRK II	-	-	-	**1.9**	**1.1 to 2.8**	**<0.001**
Power calculation formula – SRK/T	0.5	-0.09 to 1.1	0.09	1.2	-0.2 to 0.4	0.08
IOL power	-0.01	-0.1 to 0.1	0.6	**0.2**	**0.01 to 0.3**	**<0.001**
Anterior segment abnormality	**-0.4**	**-0.7 to -0.1**	**0.02**	**0.9**	**0.1 to 1.6**	**0.02**
Viscous OVD	0.3	-0.3 to 0.8	0.3	0.1	-2.9 to 3.10	0.9
Anterior vitrectomy	0.3	-0.3 to 0.9	0.4	-0.07	-1.6 to 1.5	0.9
Experienced Surgeon	-0.04	-0.8 to 0.7	0.9	-1.1	-2.5 to 0.3	0.1
Single piece IOL	**0.9**	**0.4 to 1.5**	**0.001**	1.4	-0.4 to 3.2	0.12
IOL fixation within capsular bag	**0.4**	**0.08 to 0.7**	**0.02**	0.7	-1.6 to 0.13	0.09
Right eye	-0.5	-1 to 0.03	0.06	-0.6	-1.7 to 0.4	0.2

Table 84. Univariate regression analysis on prediction error in unilateral pseudophakia

	Correlation with myopic error	95% CI	p	Correlation with hyperopic error	95% CI	p
Age at surgery (in weeks)	-0.01	-0.04 to 0.02	0.6	0.01	-0.01 to 0.02	0.4
Log age surgery	-0.04	-0.9 to 0.9	0.9	0.1	-0.3 to 0.6	0.5
Corneal curvature (K)	-0.6	-2.9 to 1.6	0.5	-0.2	-1.2 to 0.8	0.7
Log corneal curvature	-4.4	-20.9 to 11.9	0.6	-1.2	-8.5 to 6.3	0.7
Corneal astigmatism	-0.4	-2.2 to 1.3	0.6	-0.4	-3.0 to 2.3	0.8
Axial length	0.01	-4.5 to 0.5	0.9	-0.07	-0.3 to 0.2	0.6
Log axial length	0.06	-9 to 9	0.9	-1.4	-5.9 to 3.1	0.5
Horizontal corneal diameter	-1.1	-2.6 to 0.4	0.1	**-0.5**	**-0.9 to -0.04**	**0.03**
Log HCD	-12.6	-29.2 to 4.0	0.1	**-5.6**	**-10.8 to 0.5**	**0.04**
Axial length <16mm	-			2.2	-0.4 to 4.8	0.1
Axial length <20mm	-0.04	-1.8 to 1.7	0.9	0.09	-0.9 to 1.2	0.9
Interocular axial length difference	-0.2	-1.3 to 0.8	0.6	0.01	-0.3 to 0.3	0.9
Anterior chamber depth	1.5	-5.4 to 8.3	0.6	-0.4	-1.1 to 0.4	0.3
Power calculation formula – Hoffer Q	-			1.1	-1.9 to 4.1	0.5
Power calculation formula – Holladay 1	0.7	-2.7 to 4.1	0.6	0.5	-2.9 to 3.9	0.7
Power calculation formula – SRK II	-0.7	-3.5 to 2.0	0.6	-0.01	-3.5 to 3.4	0.9
Power calculation formula – SRK/T	0.7	-1.3 to 2.9	0.4	1.2	-1.8 to 4.1	0.4
IOL power	0.02	-0.2 to 0.2	0.8	0.03	-0.05 to 0.1	0.4
Anterior segment abnormality	-0.5	-3.1 to 2.1	0.7	-0.5	-2.5 to 1.5	0.6
Viscous OVD	0.3	-2.4 to 3.0	0.8	1.3	-2 to 4.6	0.4
Anterior vitrectomy	0.9	-1.0 to 3.9	0.4	-1.3	-4 to 1.4	0.3
Experienced Surgeon	0.5	-1.5 to 2.4	0.6	0.3	-0.8 to 1.5	0.6
Single piece IOL	0.5	-9.2 to 1.8	0.5	-0.1	-1.3 to 1.1	0.9
IOL fixation within capsular bag	0.7	-2.3 to 3.8	0.6	**-2**	**-3.2 to -0.9**	**0.002**
Right eye	1.9	0.3 to 3.6	0.05	0.9	-0.04 to 1.9	0.06

On univariate analysis, in bilateral pseudophakia a myopic prediction discrepancy was associated with increasing intraocular axial length asymmetry, the absence of an anterior segment anomaly, use of a single piece implant, use of a power formula which is not the Holladay 1 formula, and fixation of the IOL within the capsular bag. A hyperopic discrepancy was associated with younger age at surgery, shorter axial length, increasing IOL power, the presence of an anterior segment anomaly and use of the SRK II power formula.

In unilateral pseudophakia a hyperopic discrepancy was associated with shorter horizontal corneal diameters, and fixation of the IOL within the capsular bag. As Table 81 and Table 82 show, relationships exist between age at surgery, ocular size, the presence of an anterior segment anomaly, power formula selection and IOL power. Multivariate regression analysis models were built for myopic and hyperopic refractive discrepancy following IOL implantation in bilateral cataract surgery, and hyperopic refractive discrepancy following IOL implantation in unilateral cataract surgery.

Table 85. Multivariate multilevel regression analysis of myopic prediction error in bilateral pseudophakia

	Correlation with myopic prediction error	95% CI	p
Increasing interocular axial length difference	**0.6**	**0.06 to 1.2**	**0.03**
Anterior segment anomaly	-0.3	-0.7 to 0.05	0.08
Single piece IOL implantation	**0.96**	**0.4 to 1.6**	**0.03**

Table 86. Multivariate multilevel regression analysis of hyperopic prediction error in bilateral pseudophakia

	Correlation with hyperopic prediction error	95% CI	p
Axial length less than 16mm	**5.1**	**3.4 to 6.8**	**<0.001**
IOL power	**0.3**	**0.05 to 0.5**	**0.02**
Anterior segment anomaly	**2.9**	**0.4 to 5.4**	**0.02**
Power calculation formula – Hoffer Q	1.9	-0.4 to 4.3	0.1
Power calculation formula – Holladay 1	**2.1**	**0.4 to 3.9**	**0.02**
Power calculation formula – SRK II	**2.9**	**1.8 to 3.9**	**<0.001**
Power calculation formula – SRK/T	**2.8**	**0.7 to 4.9**	**0.01**

Table 87. Multivariate multilevel regression analysis of hyperopic prediction error in unilateral pseudophakia

	Correlation with hyperopic prediction error	95% CI	p
Increasing horizontal corneal diameter in mm	-0.5	-0.9 to 0.05	0.07
Bag fixation of IOL	-0.8	-1.8 to 0.1	0.07

On multivariate analysis, for bilateral pseudophakia, increasing interocular axial length difference and the use of a single piece IOL were associated with a more myopic discrepancy, whilst an axial length of less than 16mm, higher IOL power, and use of the SRK II, Holladay 1 or SRK/T formulae were independently associated with a more hyperopic discrepancy.

In unilateral pseudophakia, shorter axial length was again associated with a more hyperopic refractive outcome, as was fixation of the IOL in a position other than the capsular bag.

6. DISCUSSION

6.1. Summary of key findings

This thesis describes an inception cohort of infants and young children undergoing surgery for congenital and infantile cataract at a time when primary IOLs have been adopted for this age group despite unanswered questions regarding best practice, visual benefits and adverse outcomes.

Active surveillance through the BCCIG has resulted in a nationally representative cohort of children aged ≤2 years undergoing surgery with IOL implantation and surgery without IOLs. More cases have been ascertained than were reported by NHS trusts to the central databases of hospital activity.

Within this cohort of children, ocular anomalies co-existent with cataract were a common finding. Severe microphthalmos affected 1 in 5 of all children with (bilateral or unilateral) cataract and microcornea affected 1 in 10. Persistent fetal vasculature occurred more frequently than had been anticipated, with signs of PFV noted in half of all children undergoing surgery for unilateral cataract,.

As would be expected for children aged ≤2 years old at surgery, cataract was diagnosed early in life. Almost a half of bilateral cataract and a third of unilateral cataract was diagnosed in the first week of life, presumably through the routine new-born physical examination (NIPE). Over 75% of the cohort underwent surgery aged 6 months or younger, and 1 in 10 underwent surgery in the first month of life.

IOL implantation was undertaken in the majority of children over 6 months of age at surgery, but aphakia was the preferred option for the majority of younger children, due to the presence of other ocular anomalies as well as concerns regarding outcomes in young eyes.

In children for whom pseudophakia is the selected management, there was considerable variation in the refractive planning undertaken by surgeons with regards to IOL power calculation formulae and refractive outcome.

During the first post-operative year, 80% of pseudophakic children required additional refractive correction (glasses or contact lenses). Contact lens related adverse events or complications occurred in similar proportions of aphakic and pseudophakic children.

Among children who were able to comply with visual assessment testing, at one year following surgery for both unilateral and bilateral cataract, 60% of children in the IOL group and 20% of children in the aphake group achieved vision within the age related normal ranges.

In children undergoing unilateral cataract surgery, there was an association between younger age at surgery and higher odds of better vision, but no association was found between primary IOL implantation and visual outcome.

In children undergoing bilateral cataract surgery, IOL implantation was associated with higher odds of better vision on multivariate analysis, whilst the presence of a significant ocular abnormality was a predictor of a poorer visual outcome. On analysis of outcome for children with bilateral cataract without other significant ocular morbidity, younger age at surgery was associated with a higher odds of better visual acuity.

There was no evidence of a threshold effect for children undergoing cataract surgery in the first six weeks of life when compared to surgery later in infancy. This was true for children undergoing unilateral and bilateral cataract surgery, and the subgroup of children with bilateral cataract without ocular co-morbidity, and for the subgroup of children with bilateral cataract diagnosed in the first month of life.

Glaucoma had been diagnosed in 10% of all eyes and 16% of all children by the end of the first postoperative year, affecting a higher proportion of children with bilateral than unilateral cataract. Age at surgery was the most significant factor for children with bilateral cataract, with a 6% reduction in the odds of glaucoma for every 7 days increase in age at surgery. No child undergoing surgery aged 7 months or older developed glaucoma, and 47% of children who developed glaucoma were under 6 weeks old at surgery. Greater axial length and horizontal corneal diameter, the other indicators of ocular growth, were associated with reduced odds of glaucoma.

24% of children underwent secondary surgical procedures within the first postoperative year for visual axis opacity. Increasing age at surgery was again protective against the development of VAO. IOL implantation was associated with significantly higher odds of proliferative visual axis opacity in children with bilateral and unilateral cataract. Single piece IOLs were associated with higher odds of developing proliferative VAO, specifically the ‘pearl’ form of postoperative proliferation.

The predictability of refractive outcome for children undergoing IOL implantation in the first 2 years of life is poor. A hyperopic discrepancy of greater than 2 dioptres occurred in 29% of bilateral cataract eyes, 17% unilateral cataract eyes. A myopic discrepancy of greater than 2 dioptres occurred in 3% of bilateral cataract eyes, and 14% of unilateral cataract eyes. The use of the SRKII power formula, steeper corneal curvatures and shorter axial lengths were associated with hyperopic discrepancy.

These findings are discussed in turn in greater detail in the following sections of this chapter.

6.2. Ascertainment of children undergoing cataract surgery in the first two years of life

In comparison to the national databases of activity, a good to excellent level of ascertainment of cases of cataract surgery in children aged 2 years or under (in the UK) has been achieved by the active surveillance programme undertaken through the British Isles Congenital Cataract Interest Group.

The surveillance network also enabled high levels of completeness of study data. The findings reported here are thus generalisable to the population at risk, that is, all children undergoing cataract surgery in the first two years of life in the UK, and by extrapolation in the British Isles.

6.2.a. **Incidence of surgery for congenital and infantile cataract surgery for children ≤2 years old in the UK**

310 children underwent surgery aged 2 years or under in the UK between 1st Jan 2009 and 31st December 2010. Using the number of live births between 2007 and 2010 minus child mortality in the first year of life in 2007 as a denominator, the estimated annual incidence of surgery for congenital or infantile cataract in children aged under or equal to 2 years in the UK is 1 per 10,000 children (95% CI 0.9 – 1.13). The birth figure data may not be a fully robust denominator for all children alive and at risk during the study period, but it is the only available measure of the number of children at risk during this period.

This overall incidence rate cannot be adjusted for ascertainment as there is no alternative independent source of cases that would allow capture-recapture analysis to be undertaken.

The annual incidence of disease per se (congenital or infantile cataract) was 2.29 per 10,000 in first year of life and 2.93 per 10,000 for children aged 0 – 5 years in 1995-96.[293] A contemporaneous disease incidence rate is unavailable, and it is possible that the incidence of congenital and infantile cataract in the first year of life has fallen due to wider pre-natal screening for congenital anomalies or reproductive counselling for families affected by hereditary cataract. There is, for example, evidence that wider screening for Trisomy 21 led to a reduction in the number of children born with Downs Syndrome between 1989 and 2008, due to more women opting for planned terminations.[299] The proportion of the children with hereditary or chromosomal disease in this cohort of operated cases is lower than has been reported for the cohort of all children diagnosed with cataract. Systemic disease may be preclude early life surgery for congenital cataract due to the risk of general anaesthetic. Thus, whilst this study is able to provide an estimate unadjusted incidence of cataract surgery, it is difficult to place it this estimate into the overall context of the incidence of congenital and infantile cataract.

Nevertheless, cataract surgery in the first few years of life is an uncommon procedure, and research into outcomes requires an approach which is able to recruit a large and representative cohort, as achieved in this study

6.2.b. **The role of active surveillance in the ascertainment of rare ophthalmic disorders**

The labour intensive active surveillance methodology used within this study is likely to have provided a more complete ascertainment than that possible through passive surveillance, enabling the confirmation of the absence as well as presence of cases. The regular contact and feedback system across an established national network of involved specialists was not overly onerous for reporting clinicians. The system is ideal for rare disease with limited numbers of specialists treating the disorder, although this requires the creation of a network and regular expansion attempts to ensure a comprehensive recruitment pool.

The high response rates achieved by the methods used was due to in part to the initial survey of practice, which resulted in the recruitment of new consultants to the interest group as well as stimulating continued engagement by existing group members. This continued engagement was, importantly, underpinned by the prior investment of time and effort into research by members of BCCIG, and the outcomes of prior research.

The creation and maintenance of large networks of specialists for the investigation of rare diseases is particularly important for ophthalmic research, and paediatric ophthalmic research. Rare diseases affect 5% of the UK population and as such are an important health care issue.[284]

The value of 'alliances between networks of specialists' in the investigation of rare disorders has been recognised both by the UK's Chief Medical Officer and by the European Union Scientific board.[284;300] These alliances enable the creation of large cohorts of individuals with disorders of interest, reducing random error in subsequent investigations, and enable consensual standardisation of disease definition and standardised data collection, reducing systematic error.

Ophthalmologists have a significant role to play in the investigation of rare diseases: 16% of ‘rare’ diseases registered on Orphanet (the peer-reviewed European database) have associated ophthalmic or vision related signs and symptoms. Although there are continued obstacles to multicentre research despite recent improvements in research governance bureaucracy, the BCCIG remains a replicable and desirable model for future research into rare (ophthalmic) disorders.

The modern clinical research environment also calls for approaches involving groups of doctors rather than specialists working in isolation. Modern medicine has rightly prioritised evidence based practice and the patient journey, the quantification of the latter being dependent on patient centred research. This is true for all medical disorders, common and uncommon, and with regards to rare diseases, this evidence base is unattainable without multicentre studies.

6.3. Prospective studies of disease management - the measurement effect

Clinical research may lead to changes in practice through the dissemination of study findings, but also through the undertaking of the research itself. The practice of cataract surgery in children aged under 2 years by the clinicians involved in this study has changed during the study period, arguably as a result of their involvement in the research.

6.3.a. **Standardisation of clinical records in response to the study**

Standardised data collection is necessary to reduce systematic error in clinical research, but it also improves patient care through the prevention of the omission of clinically significant investigations (for example, pre-operative horizontal corneal diameter).

Clinical record standardisation through the use of proforma derived from the data collection instruments occurred at 3 hospitals as a result of involvement in this study, with clinicians showing willingness to use study document to the mutual benefit of the research and clinical team.

The work undertaken in this thesis thus provides evidence of the feasibility of future observational or interventional multicentre (paediatric ophthalmic) research.

6.3.b. **Standardisation of clinical practice in response to the study**

There is direct evidence from the largest patient identification centre (Great Ormond Street Hospital) of standardisation of clinical practice: pre-operative assessments and post-operative steroid regimen for children undergoing cataract surgery were standardised as a discussion of results around study methodology.

The standardisation of clinical practice, preferably underpinned by an evidence base, improves patient care through the reduction of clinical risk, but also assists investigations of outcome through the reduction of the number of possible confounders, and enables clinical audit and the maintenance of achieved standards. The consistent exposure of junior medical staff to best practice also supports medical education.

There may also have been changes at other centres following the publication of the findings of the national survey prior to start of the recruitment period. A number of consultants undertook procedures different to those they had described in response to the national survey. In all cases, the direction of change was towards practices undertaken by the majority of respondents. Of 38 surgeons who responded to the national survey and who recruited children to the study of outcomes:

- 1 of the 4 who stated that they used a non-'AcrySof' lenses in children aged ≤2 years did in fact implant AcrySof IOLs during the study
- 2 of the 5 who stated that they used Holladay formula in practice used the SRKT formula
- 4 of the 8 who stated that they did not routinely undertake vitrectomy did undertake vitrectomy in all recruited children

This constitutes a movement towards a form of implicitly consensually agreed practice, although not underpinned by a debate on evidence base, in part due to the absence of robust evidence.

6.4. Ocular co-morbidity in children undergoing cataract surgery aged ≤2 years in the British Isles

6.4.a. **Microphthalmos and microcornea**

6.4.a.i. Main findings

73% of children were affected by microphthalmos or microcornea.

64% of children had axial lengths shorter than the age reported normal range or were diagnosed with microphthalmos by their managing consultant, and 24% of children had severe microphthalmos. Both microphthalmos and severe microphthalmos were more common findings in bilateral than unilateral cataract.

25% of children without microphthalmos were affected by microcornea.

6.4.a.ii. Sources of bias

Missing data

Axial length measurements were missing in 16/95 (17%) and 23/141 (16%) children affected by unilateral and bilateral cataract respectively. These data may not be missing at random, with fewer children selected for aphakia and fewer of those who were diagnosed with 'clinical microphthalmos' undergoing axial length measurements. This may reflect a perceived lower risk of microphthalmos in these children, and thus the figures above may be an overestimation of the true proportion of children with congenital or infantile cataract who have microphthalmos.

Quality of data

The identity of the clinician undertaking axial length measurement was not requested. The contact method of axial length measurement was used in 96% of cases, and the interobserver differences in the measurement of axial length through contact methods can be as large as 0.5mm, with potential technician dependent systematic inaccuracies in measurement due to differing placements of the ultrasound probe. Immersion axial length methods provide improved accuracy and repeatability, and are now described as 'gold standard' for adults.[301;302]

Clinicians were asked to determine presence of 'clinical microphthalmos', which was particularly important for classifying children in whom axial length measurement was not undertaken. This study identifies the poor negative predictive power of clinical assessment of microphthalmos for age related abnormally short axial length in the first two years of life. This either represents a failure by clinicians to diagnose children who are potentially at risk of poorer outcome, or the inadequacy of the study definition of microphthalmos. The negative predictive power is, as expected, better for unilateral cataract, and is also better for eyes with axial lengths of <16mm. This reflects a higher rate of identification by clinicians of children at risk of poor outcome due to severe microphthalmos.

6.4.a.iii. Interpretation of findings

If data on axial length are not missing at random, that is if eyes in which ultrasound measurement was not undertaken and clinical microphthalmos was not diagnosed are in fact 'normal', the estimated frequency of microphthalmos is 64% in children with bilateral cataract (91/141) and 34% in children with unilateral cataract (32/95).

This is a higher frequency than previously reported. Rahi et al reported a frequency for isolated microphthalmos of 6% in bilateral cataract and 7% in unilateral disease, with ocular anomalies found in 14% of cataractous eyes of children aged 0 – 15 years at diagnosis.[63] The cohort described in this thesis constitutes a study population which differs by age and inclusion criteria, and there is evidence from this cohort that children with ocular anomalies present earlier in life.

Nevertheless, this finding that a majority of children with congenital and infantile cataract undergoing surgery in the first few years of life are also affected by microphthalmia should be interpreted in the light of the limited literature on the normative values of axial length in children under 2 years old.

Microphthalmos is an indicator of the failure of global development, and of an insult to the eye at an early stage of development. It can impact on a child's final visual outcome following surgery both directly due to poor ocular development and indirectly through the higher incidence of post-operative glaucoma. It is thus important to be able to classify microphthalmos in order to stratify the risk of poorer outcome in children with cataract. Diagnosing an abnormal biometric value using a 'cut off point', even an age adjusted cut off point, risks classifying normal values as abnormal and vice versa. Large data sources are needed in order to define normality in this way. For example, the determination of a cut off value for 'normality' for body mass index in children necessitated a sample of almost 200,000 children[303]

Such normative data are not currently available for axial length in children aged under 2 years. Obtaining these data is challenging, as examination under sedation or anaesthesia is needed for accurate measurement. However, measurement is a non-interventional procedure with no risk to the child. Thus large scale longitudinal studies of axial length involving children undergoing sedation or anaesthesia for other procedures are feasible.

Until these normative data are available, it is important that clinicians are able to diagnose children at risk of poor outcomes due to **severe** microphthalmos, so that they can provide some level of prognostic counselling to parents. The findings of this study indicate that will only be possible if clinicians undertake pre-operative ocular ultrasound, as clinical assessment alone has an insufficiently strong predictive power. This currently under-utilised modality should be a mandatory pre-operative assessment, as it also enables the future diagnosis and management of glaucoma.

The existing evidence supports that in the absence of other structural anomalies, diagnosis in children aged under 2 years with congenital and infantile cataract should be limited to:

severe microphthalmos: an axial length of less than 16mm in children aged over 1 month (gestational age)

and **possible** microphthalmos, using the classification used within this study (section 2.3.d.i, box 2), with confirmation of diagnosis on repeated axial length measurement once the child has reached 2 years old with an axial length of less than 20mm .

6.4.b. **Persistent fetal vasculature**

6.4.b.i. Main findings

Persistent fetal vasculature affected almost half (46%) of all children with unilateral cataract and 9% of children with bilateral cataract.

6.4.b.ii. Sources of bias

As the older definition of persistent hyperplastic primary vitreous (PHPV) is less inclusive than the newer classification scheme for persistent fetal vasculature (PFV), information on the form of persistent vasculature noted was collected using the study data instrument. Thus this study is able to determine where the children with PFV would fit within the description of PHPV, allowing comparison with previous studies.

6.4.b.iii. Interpretation of findings

The proportion of children who underwent surgery for unilateral cataract who have associated PFV is significantly higher than previously reported. As children with unilateral persistent fetal vasculature may not undergo surgery due to either the absence of an associated visually significant lens opacity or the preclusion of surgical intervention due to poor prognostic features (such as retinal detachment) the overall incidence of persistent fetal vasculature may be even higher. Rather than reflecting a 'true' increase in the incidence of PFV (which would require a dramatic biological influence), the findings of this study suggest that there is improved identification of the signs of persistent fetal vasculature. Rahi et al reported that 22% of children aged 0 -15 years diagnosed with unilateral cataract were affected by PFV,[63] whilst investigators in Toronto reported the frequency to be 11%,[304] but as touched on earlier, these study

populations differ from the population described within this thesis. Some features of PFV may only be visible during removal of the cataractous lens, and children with persistent fetal vasculature may present earlier in life. Thus a study which recruits children undergoing surgery in early life may report a higher frequency of affected children. An Austrian study which prospectively recruited 31 children aged 0 – 15 years old with unilateral cataract reported that all of these children were affected by some feature of persistent vasculature.[93]

The aetiology of PFV is poorly understood, but animal models have identified a role for the failure of both the macrophage orchestrated extrinsic apoptotic pathway[305] and the tumour suppressor gene intrinsic apoptotic pathway[306] in the pathogenesis of the persistence of the nutrient fetal vasculature. One gene complex implicated in the failure of ocular fetal vasculature apoptosis via the intrinsic pathway is *frizzled/wnt*[307], which codes for a transmembrane protein. This protein is also implicated in the allelic congenital human retinal vascular development disorders of Norrie disease and familial exudative vitreoretinopathy, with the latter being described clinically as a 'hereditary form of retinopathy of prematurity (ROP)'. It has also been suggested that PFV is a result of failure of apoptosis due to reduced exposure to VEGF. This pathway has been supported by the changing patterns of VEGF receptors on mammalian fetal intraocular vasculature,[308] and is a pathway of current clinical interest due to the emerging use of VEGF inhibitors as treatment for ROP.

Primary prevention of unilateral cataract is of particular importance as visual outcomes remain poor, and understanding the aetiology of PFV may also increase the understanding of the vascularisation of the fetal retina and possibly of the entire fetal cerebral system. PFV is thus a worthy candidate for future genetic research: careful description of morphology with pre-operative clinical images would be required to clarify phenotype ahead of investigation into genetic markers of the disorder.

6.5. Practice of IOL implantation in children aged <2yrs

6.5.a. **Main findings**

Intraocular lens implantation is undertaken at primary surgery for the majority of children aged over 6 months with congenital and infantile cataract (90% of children with unilateral cataract, 80% of children with bilateral cataract)

Amongst children who underwent surgery in the first 3 months of life and excluding those children with other ocular abnormalities, primary IOL implantation was undertaken in 40% of children (20/50) with bilateral cataract and 44% of children (37/84).

However, the proportion of children undergoing cataract surgery in the first month of life is similar across the four 'treatment groups' (that is, unilateral cataract surgery with and without IOL implantation and bilateral cataract surgery with and without IOL implantation).

6.5.b. **Sources of bias**

There are no missing data on the ages of the children undergoing cataract surgery ensuring a robust data source for the analysis of the practice of IOL implantation across different age groups within the first two years of life.

In addition, the recruitment base underpinning this multicentre study is sufficiently wide to support the argument that this is a true picture of national practice. However, it is possible that practitioners who chose not to undertake primary IOL implantation also chose not to collaborate with the study as a member of the BCCIG. As the ascertainment achieved by this study is better than national records of activity (cataract

surgery in children under 2 episodes recorded through national databases) this is unlikely to have had a significant impact on the findings.

6.5.c. **Interpretation of findings**

The paediatric ophthalmic community appears to be beyond the point of equipoise with regards to IOL implantation in children aged over 6 months, despite the existing uncertainties surrounding refractive planning and the impact of adverse events such as visual axis opacity.

It has been suggested that the adoption of any new technology, or the adaptation of an existing technology, proceeds along an 'S' shaped curve.[278] The 'hawks', 'innovators' or 'mavericks' (the terminology used being dependent on the position of the observer) within the community are the first to take up the new technology. The more cautious practitioners wait until either sufficient anecdotal evidence has been gathered or until more robust evidence on safety and efficacy is available before they take up the new technology. During this process of diffusion there may come a 'tipping point' at between 20% and 30% adoption, following which there is more rapid adoption of the practice by the community.[278] This rapid adoption can occur in the absence of a robust evidence base supporting the new intervention: a significant precedent for this is the adoption of modern adult cataract surgery techniques. The first randomised trials comparing modern phacoemulsification cataract surgery (where the lens is broken up with ultrasound waves prior to removal and currently the most commonly performed operation in the NHS) and the long established extracapsular extraction method took place in the 1990s, at least a decade following the wide adoption of the newer practice in high income countries[309-311] We appear, in the UK, to be at the tipping point with regards to primary IOLs in children undergoing cataract surgery aged 3 months or

younger (these are the children diagnosed with congenital cataract either through neonatal screening or the six to eight week infant screening programme).

6.6. Comparison of ascertainment through central NHS databases and through active surveillance

6.6.a. **Main findings**

More cases of cataract surgery in children aged ≤2 years old were ascertained through the active surveillance undertaken in this study than were ascertained through the NHS databases.

There is under reporting of cataract surgery (undertaken in these children) by hospitals in England, Scotland and Northern Ireland, and under reporting of primary IOL implantation by hospitals in England

The inaccuracies created by this under-reporting are compounded by the use of multiple codes across different hospitals for paediatric cataract surgery, and this is despite all recruited children undergoing the same form of surgery: lens aspiration with (or, less commonly, without) vitrectomy.

6.6.b. **Sources of bias**

Patient identity linked data were not available, therefore it was not possible to compare directly the NHS databases and the IOLu2 study samples at an individual level. Nor is it possible to undertake capture-recapture analysis, which would allow us to report an ascertainment adjusted incidence rate for cataract surgery in these children.

6.6.c. **Interpretation of findings**

The under reporting by hospitals of paediatric cataract surgery is consistent with previous reports of poor levels of completeness of centralised NHS ‘returned’ data for other specialities such as paediatric cardiothoracic surgery and adult oncology.

The NHS is currently facing significant re-organisation and financial constraints. Accurate coding of hospital activity is vital for primary care trust payment for activities undertaken and for efficient planning of hospital services. These findings suggest that NHS ophthalmic departments may be losing money by failing to ensure that their administrative system records their true level of activity. Clinical governance is part of the duties of every doctor, and consultants must take the responsibility of ensuring that the hospital administrative staff responsible for reporting their activity to the national database have the information they need to generate accurate and complete reports.

The consultants undertaking cataract surgery in early life should also reach a consensual decision regarding which code is to be used for lens aspiration and posterior capsulotomy with or without vitrectomy, and to ensure that this decision is disseminated to coding administrators. This should be achievable using the communication pathways established by the BCCIG.

6.7. Parental willingness to participate in clinical research

Future research into children undergoing primary IOL implantation, and indeed into any paediatric (ophthalmic) intervention, will be dependent on consent from affected families.

This study necessitated the seeking of consent for enrolment at a difficult time for families, this time being soon after diagnosis of a life changing disorder which would involve surgical intervention. Despite this, 79% of families consented to their child's involvement. 3% of families refused, and as of August 2011, 18% of families were yet to reply, which may reflect lack of willingness to participate.

Thus parents are, in the majority, willing to participate in an observational study which is not of direct benefit to their child. This willingness is possibly a consequence of the perceived importance of study, although the strength of the relationship between parents and the managing clinical team is also likely to play a role.

The degree to which parents are willing to participate in paediatric interventional studies, specifically randomised control trials of IOLs, is at this time uncertain. 71% of North American parents were willing to participate in the North American Infant Aphakia Treatment Study randomised controlled trial of intraocular lens implantation versus aphakic correction (IATS). The reimbursement of travel costs, free contact lenses and glasses, and extra financial support provided to the families participating in the IATS may have influenced parents' willingness to participate in the trial. Evidence from previous studies also suggests that parents who consent to their child's participation in research are motivated not only by altruism but also by the awareness that involvement in research strengthens their relationship with their health care service providers and affords them greater involvement in their child's care. [312;313]

To inform further studies which may arise due from the findings of this present study, investigators need further information on parental attitudes towards participation into ophthalmic research, in particular randomised controlled trials. This information will allow investigators to estimate the number of parents who will need to be approached to obtain a necessary study sample size. As systematic failures to recruit sub-groups of the potential recruitment pool negatively impacts on the representativeness of the study cohort, research into the possible determinants of parental attitudes will also be needed to identify any need for, and to help design, targeted recruitment methods to ensure adequate representation of families who would otherwise not take part in research.

6.8. Visual outcomes following surgery with and without primary IOL implantation

6.8.a. **Bilateral cataract**

6.8.a.i. Main findings

For the children able to comply with formal visual testing, visual outcomes are within the age reported normal range for 19% of children in the aphake group, and 59% in the IOL group.

On multivariate multilevel analysis, primary IOL implantation is independently associated with 5 times higher odds of better visual outcome. The same size of association is seen even when analysis is limited to the dataset of children without a significant ocular abnormality. However, when missing data were imputed on the reasonable assumption that inability to comply with visual assessment reflected poor visual outcome, IOLs were associated with a reduced odds of better visual outcome on multivariate analysis.

6.8.a.ii. Sources of bias

It is possible that the data on visual outcome are not missing at random. The failure to comply with visual assessment was significantly higher in the IOL group, despite this group having a higher median age at surgery in comparison to the aphake group, and a similar proportion of children with systemic disorders or developmental abnormalities.

The difficulty of obtaining reproducible, accurate quantitative visual acuity data from preschool children is well recognised. The objective assessment of acuity in childhood is difficult due to within-child variability (discomfort / boredom / room illumination /

inattentiveness may alter a child's performance) and the variability which may exists between examiners or acuity assessment procedures. Thus, ideally studies which investigate visual outcomes should use standardised acuity assessment methodologies undertaken and at an age where children are more able to verbally respond to visual assessment. There was no standardisation of acuity assessment within methodology described for the study within this thesis, and whilst in all centres acuity measurements were undertaken by trained specialists (orthoptists) there was no formal assessment of examiner performance. It is impossible to adjust for this potential measurement bias at the analysis stage, however, the author has attempted to ground the investigation of visual outcome within clinical practice by categorising vision into wide but clinically relevant bands using the best available evidence on normative values.

6.8.a.iii. Interpretation of findings

The proportion of children achieving 'normal' vision at one year following surgery with intraocular lens implantation is 60%, falling to 40% if the assumption that failure to comply with visual assessment is an indicator of poor vision is true. This latter figure, of 40% attaining normal visual levels, is consistent with previously published data of outcome following cataract surgery (usually) without IOL implantation. Chak et al reported that 40%, and Francis et al reported that 34% of children had attained normal vision at 5 years after surgery.[39;64]

These findings suggest that a large proportion of these children will be able to attend mainstream schooling (in the absence of other disorders) with some being able to read normal print, and the majority able to read some form of print. However, early visual outcomes are not a robust indicator of final visual outcome, and further follow up studies on this cohort are needed. Within a follow up study of the IOLu2 cohort, visual outcome should be assessed at 5 years following surgery (when all children are likely

to be of school age, and when visual outcome will be a firmer indication of adult visual function) and at 10 years following surgery (when all children will be in or approaching secondary education). The proportion of aphakic children with normal vision at one year following surgery is 20%. This low proportion is a reflection of the high proportion of these children affected by other ocular abnormalities. A small proportion of the bilateral aphakes will be able to read normal print, but the majority of the children achieved form perception and thus may be able to read some form of large print as older children and adults.

It is unclear if the visual outcome is better for these children than it would have been if they had not undergone cataract surgery, particularly in the cases of children without dense, total or nuclear lens opacities. A randomised controlled trial of surgery versus conservative treatment for bilateral cataract may be able to provide the answer, although the ethical challenges inherent to the design of such a study are immense. For partial or lamellar cataract, a grading scale could be designed so that children with only a certain degree of lens opacity would be recruited to such a study.

It is possible that primary IOL implantation, in comparison to aphakia, leads to improved visual outcome in children at 1 year following surgery. The higher odds of better visual outcome are independent of the presence of ocular abnormalities and the age of the child. There are no other similar studies into the associations between IOLs and visual outcome for bilateral cataract in children under 2 years old with which to compare the findings of the present study. It could be argued that the findings presented here demonstrate a need for a multicentre randomised controlled trial of IOL in children with bilateral cataract (which would recruit children with no other ocular abnormalities, no neurological disorders, with symmetrical cataract, and children aged 3 months or under at surgery). Nevertheless, follow up studies on the IOLu2 cohort should also be able to provide robust evidence on the effect of primary IOL implantation on visual outcome for bilateral cataract in children aged ≤2 years.

6.8.b. **Unilateral cataract**

6.8.b.i. Main findings

60% of eyes in which IOL implantation was undertaken achieved normal vision at one year following surgery, whilst 20% of eyes which were not implanted achieved this level of vision. However, there was no independent association of IOL implantation with the odds of better vision, although the direction of the effect seen was similar to that seen in bilateral cataract.

Although younger age at surgery was associated with higher odds of better vision, there was no evidence of a threshold effect, that is an age at surgery prior to which visual outcome at one year was significantly better.

6.8.b.ii. Sources of bias

Again, the missing data on visual outcome may not have been missing at random, as the children who did not comply with assessment may have had poor post-operative vision. In addition the sample population of children with one year visual outcome data was small, with consequent risk of random error.

6.8.b.iii. Interpretation of findings

These study findings are consistent with the finding of the IATS that there was no association between visual outcome and 1 year following surgery and the use of IOLs in children aged 6 months or under at surgery.

Further 1 year follow up data is awaited for the children described within this study, and the longer term follow up data from this cohort should also provide further evidence on the effect of IOL implantation on visual outcome.

6.9. Glaucoma following surgery with and without primary IOL implantation

6.9.a. **Main findings**

6.9.a.i. Bilateral cataract

Although 5% of eyes (4% children) in the IOL group and 14% of eyes (23% children) in the aphake group developed glaucoma, there was no independent association between IOL implantation and the risk or hazard of post-operative open angle glaucoma during the first post-operative year.

Increasing age at surgery, axial length and horizontal corneal diameter were all protective, that is associated with reduced odds of developing post-operative glaucoma.

Glaucoma was only diagnosed in children who underwent surgery during the first 6 months of life. This may have been due to chance, but as all of the children recruited to this study were under 2 years old at surgery a threshold effect cannot be ruled out. Surgery during the first 4 weeks of life was independently associated with 75% higher odds of developing glaucoma (OR 1.75, 95% CI 1.2 – 1.9, p=0.001), suggesting that the first month is a critically sensitive period for the development of post-operative glaucoma.

6.9.a.ii. Unilateral cataract

8% of IOL eyes, and 9% of aphake eyes developed glaucoma in the first post-operative year, and there was again no association between IOL implantation and post-operative open angle glaucoma, whilst increasing axial length and horizontal corneal diameter at surgery were again protective associations.

6.9.b. **Sources of bias**

Disease misclassification prevents the investigator from robustly investigating the factors associated with the disease of interest. The data collection instruments did not request confirmation of the diagnosis of open angle glaucoma through gonioscopy, but used an established definition with presumption of gonioscopy, as surgeons were asked to classify glaucoma as ‘open angle’ rather than pupil block or closed angle. The assumption was therefore made that they were confident in this diagnosis. Nevertheless, non pupil block, apparent open angle glaucoma could in some cases be due to closed angle mechanisms such as the hydration of retained lens matter pushing the angle closed. The aetiology of such forms of glaucoma would be linked to surgical technique rather than to risk factors such as the age of the child.

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6.9.c. **Interpretation of findings**

6.9.c.i. IOL implantation and the risk of post-operative glaucoma

These study findings do not support previous reports of a protective association between IOL implantation and post-operative glaucoma, but as previously described these previous reports have lacked a robust approach.

This suggests that the aetiology of post-operative open angle glaucoma is less likely to be associated with the loss of physical support to the developing angle, or the barrier effect of an IOL against potentially damaging factors from posterior segment. The focus should now be moved to the other posited pathological mechanisms.

Over time, more cases of glaucoma will develop within this study cohort, therefore further data on IOL implantation as a predictor of post-operative glaucoma risk will be available through the longer term studies of outcome amongst the IOLu2 study cohort.

6.9.c.ii. Balancing the benefits of early intervention with the risks of post-operative glaucoma

The early age at diagnosis for many of the children in this cohort suggests that there may have been improvements within the national screening programme. However, whilst 129/171 children diagnosed in the first year of life were diagnosed in the first month of life in the 1995/6 national cohort study (75%),[293] the proportion is similar (81% or 165/204) for this cohort. Nevertheless, a significant proportion of children are being diagnosed at an early age, affording clinicians the chance of undertaking surgery at an earlier age.

It is possible that there exists a 'latent' period prior to the start of the critical period of visual sensory development during which sensory deprivation has no impact on later visual development, and that cataract surgery which is undertaken prior to the end of the latent period limits the amblyogenic impact of lens opacity. This theory drives the impetus to undertake very early cataract surgery. Evidence from a small scale study suggested that for children diagnosed prior to 4 weeks of age, for each week after 1st month of age (the possible end of the latent period), visual outcome falls due to visual deprivation during the critical window.[195] However, Chak et al reported that, for their population based cohort, whilst visual outcome following surgery worsened with increasing age at surgery, there was no threshold effect.[39]

The key interpretation of this study's findings regarding glaucoma is that although early infancy surgery (prior to 6 weeks of age) does not result in significantly better visual outcomes, surgery in the first 4 weeks of life does result in a significantly higher risk of post-operative glaucoma developing in first post-operative year

It might be possible to further investigate the impact of early life cataract surgery on the risk of glaucoma through a clinical trial with different trial arms undergoing surgery at different ages, (for example prior to four weeks versus after 4 weeks) but ethics approval for such studies would be difficult to obtain. Thus large scale 'natural experiments' such as provided by this cohort may provide the highest level of evidence possible.

6.9.c.iii. The prevalence of glaucoma following cataract surgery in children ≤2 years old

Higher proportions of children were diagnosed with glaucoma in the first post-operative year than were reported in Chak et al, presumably due to the younger age at surgery in the IOLu2 cohort.

Assuming that 5% of eyes develop glaucoma each year, by 10 years 55% of operated eyes in the present cohort will have developed glaucoma. This is a considerable proportion: it is possible that for this cohort, children are more likely than not to develop iatrogenic glaucoma following congenital cataract surgery

A greater understanding of the mechanism by which the insult of surgery causes glaucoma is urgently needed. This will require premorbid data on the angle through gonioscopy and ultrasound biomicroscopy imaging.

Normative data on the development of the anterior segment, specifically the differentiation of the angle in the first few years of life, will be difficult to obtain and would require examination under anaesthetic or sedation, but would be of great value.

6.10. Visual axis opacity following surgery with and without primary IOL implantation

6.10.a. **Main findings**

6.10.a.i. Bilateral cataract

24% of eyes (34% of children) which underwent IOL implantation developed proliferative visual axis opacity requiring surgery by the end of the first post-operative year, versus 7% of aphakic eyes. IOL implantation was independently associated with seven times higher odds of proliferative visual axis opacity (VAO) during the first post-operative year.

14% of eyes (20% of children) which underwent IOL implantation developed membranous VAO, compared to 5% of aphake eyes, with IOL implantation being independently associated with a four times higher odds of membranous VAO.

The use of systemic steroids was not significantly associated with reduced odds of developing membranous (inflammatory) VAO, or indeed any form of visual axis opacity.

Single piece IOLs were associated with higher odds of proliferative VAO, with a higher proportion of children having the ‘pearl’ form of VAO.

6.10.a.ii. Unilateral cataract

Following IOL implantation, 47% of eyes developed proliferative VAO, and 20% developed membranous VAO. 5% of children underwent more than one secondary surgical procedure (in the operated eye) for VAO in the first year. IOLs were again independently associated with higher odds of VAO.

6.10.b. **Sources of bias**

Assumptions were made regarding the frequency of follow up across different centres, and frequency following surgery with or without IOLs. Centres which more frequently undertook IOL implantation may have had shorter follow up visit intervals, which may have increased the chance of diagnosing VAO in the first post-operative year.

Also, data were collected on time at treatment for VAO rather than time at diagnosis – the assumption here being that treatment occurs soon after diagnosis.

6.10.c. **Interpretation of findings**

6.10.c.i. The impact on multiple intraocular procedures on long term development

VAO has previously been recognised as a complication of IOL implantation in early childhood.[144;166;273]

There is an apparent lack of awareness amongst the paediatric ophthalmic community regarding the emerging evidence on the association between multiple general anaesthetics in children under 2 years old and long term impairment of cognitive function.[145;314-319] Preclinical animal studies report that general anaesthetic causes significant patho-histological damage to the developing mammalian brain.[320;321] A relatively large population based cohort study (n=5357) from North America reported that the relative hazard of having a learning difficulty in late childhood was 1.59 (95% CI 1.06 – 2.36) following two or more episodes of general anaesthetic in the first 4 years of life.[322] Another large scale retrospective case controlled study (383 cases, 5050 controls) reported adjusted hazard ratios of 2.3 (95% CI 1.3, 4.1) of cognitive impairments following general anaesthetic for hernia repair in the first 3 years of life. [323]

It may be that there are as yet unidentified confounding factors contributing to these associations, but whilst there is the possibility of an association, multiple occurrences of general anaesthetic should be avoided for young children where possible. Ophthalmologists who undertake primary IOL implantation in the first two years of life must deal with the possible future ramifications of a total of four episodes of general anaesthetic for children with bilateral cataract (primary and secondary surgery for each eye) and the undertaking of multiple general anaesthetics in unilaterally affected children with no real improvement in unaided binocular vision.

6.10.c.ii. The use of systemic corticosteroids to reduce post-operative inflammation

Inflammatory membranes are the most apparent sequelae of significant post-operative inflammation, and there is no evidence that the use of systemic steroids is associated with lower odds or hazards of inflammatory visual axis opacity. The reported complications of systemic steroids in infancy include hyperglycaemia, infection, and developmental delay.[324] One child in this cohort was affected by a significant infective illness whilst treated with systemic steroids, and the use of systemic steroids may also have delayed the timing of early life vaccinations for some children in the cohort.

There is a risk of harm with systemic steroids, and no evidence of additional benefit, thus systemic corticosteroids should be used with caution in these children.

With regards to the most effective post-operative regimen of topical steroids, randomised controlled trials of peri and post-operative corticosteroid delivery may be needed. These studies would require standardised objective assessment of the degree of post-operative intraocular inflammation: the presence of fibrin or inflammatory membranes, pupil synechiae and iris vessel dilatation.

However, the cohort described in this thesis should also be able to provide the data needed (once one year follow up data collection is complete) to undertake further analyses into the associations between the different regimens of post-operative steroids and the occurrence of inflammatory sequelae necessitating surgical repair. In addition, the impact of inflammation and further surgery on the risk of glaucoma will be investigated through follow up studies of this cohort.

6.10.c.iii. Single piece IOL implantation and the risk of visual axis opacity

This is the first study to report an association between single piece IOLs and the occurrence of VAO. Previous studies have studied outcomes in older populations or have not differentiated between VAO rates following implantation of different models of IOLs.[277;325] The risk of increased rates of VAO in adults was, however, first theorized in reports from the 2003 European Society of Cataract and Refractive Surgery meeting, to be related to the 'step' between the optic / haptic junction acting as a potential focus for lens epithelial cell proliferation.[326;327]

Further research such as randomised controlled trails of single piece IOLs in childhood may be useful: such a trial is currently underway in adults, but is unlikely to provide a definitive answer as the patterns of development of VAO (termed posterior capsular opacity or PCO in adults) are different in adulthood.

The 'natural experiment' described in this thesis provides enough information to raise the issue within the paediatric ophthalmologic community.

6.11. Accuracy of refractive planning in children ≤2 yrs old

6.11.a. **Main findings**

There exists considerable variation in the use of power calculation formula, and in planned refractive power, with resultant variation in refractive outcome.

There is poor predictability of refractive outcome for children, with 53% of unilateral pseudophakes and 57% of bilateral pseudophakes having a significant prediction error. Interocular axial length difference and the use of a single piece IOL were associated with a more myopic discrepancy, whilst an axial length of less than 16mm, higher IOL power, and use of the SRK II, Holladay 1 or SRK/T formulae were associated with a more hyperopic discrepancy.

6.11.b. **Sources of bias**

It can be difficult to achieve accurate retinoscopy assessment in an awake post-operative infant, and thus the quality of the data may be in doubt.

Only a small number of consultants undertook post-operative refraction within a month of surgery: with such a small dataset it is difficult to exclude the role of random error.

6.11.c. **Interpretation of findings**

Previous studies[243;301;328] have reported the absolute error without examining the direction of the discrepancy (myopic versus hyperopic). It is possible that different factors are in action with myopic discrepancy than with hyperopic discrepancy, as indicated by the opposing effect directions in the univariate analyses.

If IOLs are to be used routinely in children, ophthalmologists will need to establish a national audit programme similar to that set up for adult cataract surgery, and it should be mandatory to undertake post-operative refraction to determine refractive discrepancy.

Follow up studies on the IOLu2 cohort should provide data on the consequences of refractive discrepancy (for example further surgery, visual outcome), particularly of high myopic errors.

6.12. Future directions of investigations into outcomes within the IOLu2 cohort

The children recruited into this study and the systematically collected and categorised data regarding their pre, per and post-operative status form a valuable and unique source of information on outcomes following cataract surgery in children under two years old. Thus, the cohort generated by the IOLu2 study should be and will be used to provide data which may be able to support or refute key clinical hypotheses around visual and refractive outcome and adverse post-operative events.

These further investigations will require ethics approval and research governance approval, as well as confirmation of informed consent from parents for the collection of further clinical data.

6.12.a. Visual outcome following bilateral cataract surgery

Hypothesis 1: In comparison to aphakia, IOL implantation in children aged under 2 years with bilateral cataract is associated with better visual outcome

Whilst the majority of children undergoing surgery for bilateral congenital or infantile cataract escape severe visual impairment almost two thirds of these children will become adults burdened by some degree of visual impairment. (Chak et al) Primary pseudophakia, with refractive correction constantly in place, may lead to better post-operative visual results.

Children within the IOLu2 cohort should form the basis of follow up studies of visual outcome. In order to limit selection bias, it will be necessary to exclude those children with ocular disorders which not only impact on visual potential but which also prevent the implantation of an IOL: axial length <16mm, HCD<10mm, significant persistent fetal vasculature and significant anterior or posterior segment pathology. It will also be necessary to exclude those children within the cohort who are unable to comply with visual assessment, and children with neurological disorders involving the visual pathways.

Ideally, visual assessment should be undertaken by a small group of travelling examiners. However considering the geographical spread of the IOLu2 cohort, a more achievable aim would be assessments by examiners with appropriate experience (as judged by a senior central 'head' examiner). Assessment should be undertaken at an age when children are able to provide a robust verbal response to optotype acuity tests, such as over five years of age, using a standardised process involving the ETDRS LogMAR acuity charts for verbal children and grating acuity charts for the small number of non-verbal children who are not limited by neurological or developmental abnormalities.

The study cohort will be able to provide data not only on the strength and direction of the association between IOL implantation and post-operative vision, but also, through multilevel multivariable ordinal logistic regression analysis of logMAR vision, on the impact of factors described earlier within this thesis such as age at surgery, socioeconomic status, and post-operative complications.

As undertaken within this thesis, as well as examination on the whole cohort, investigation of the subgroup of children diagnosed in the first month of life will also be performed (thus excluding children with infantile cataract in whom deprivation amblyopia may not be as profound).

6.12.b. Visual outcome following unilateral cataract surgery

Hypothesis 2: In comparison to aphakia, IOL implantation in children aged under 2 years with unilateral cataract is associated with better visual outcome

The most predictable outcome for children with unilateral cataract remains moderate or severe visual impairment in the operated eye. The group of children within this study cohort who have undergone surgery for unilateral cataract should and will be followed up in order to further investigate the predictors of good visual outcome.

As well as the absolute visual acuity in the operated eye, the secondary outcome measure should also be the difference in acuity between this eye and its fellow, which may usefully be employed as a marker of the child's visual potential.

Whilst the exclusion criteria and outcome assessment remain the same for unilateral cataract, visual outcome following unilateral cataract surgery is made more complex by amblyopia. Thus, visual outcome assessment should not be undertaken until the age of 8 years, when children have reached some level of visual stability and past which there is little chance of significant improvement of acuity through further visual rehabilitation. Also, the impact of concordance with amblyopia treatment will need to be assessed in a standardised manner in order to investigate the other associated factors. Concordance with occlusion should be measured using parental reports, parental diaries, or, more ideally an objective measurement such as an electronic monitoring system such as used in the PEDIG studies.[329] However, as concordance throughout the first eight post-operative years and particularly the first three years will need to be considered, the use of compliance monitoring aids throughout the study follow up period would bring a considerable expense.

6.12.c. **Refractive planning**

Hypothesis 3: An initial pseudophakic refractive outcome which matches the normal age adjusted refractive state / the refractive status of the fellow phakic eye is associated with better visual outcome following bilateral / unilateral cataract surgery

The most appropriate post-operative refractive aim for early childhood pseudophakia is unclear. It is important to investigate the impact of refractive planning on visual development and final visual outcome.

The primary outcome measure should be distance and near acuity measurements (undertaken according to a standardised study protocol as described above). Standardised data collection on the use of, compliance with and the nature of refractive correction will also be necessary, as it is possible that children who have been prescribed and are compliant with overcorrection of their residual refractive error (thus leaving them myopic and able to focus objects within their 'near' world) may have better visual development. Comparative models of refractive change as stratified by the final visual outcome can be created, and as the refractive status may differentially impact on different age groups, effects within subgroups stratified by age at surgery will also need to be investigated.

6.12.d. Ocular growth

Hypothesis 4. In comparison to aphakia, primary IOL implantation aged under 2 years is associated with a more normal rate of ocular growth

Axial myopia consequent to post-operative marked axial elongation impacts not just on visual outcome but may also lead to visually impactful sequelae of high myopia (macular degeneration, retinal detachments). Serial axial length measurements of aphakic and pseudophakic eyes of children in the IOLu2 cohort should provide data on the impact of primary IOL implantation on the post-operative pattern of eye growth.

The children from the IOLu2 cohort who will be able to contribute data to a study such as this are those who have not been diagnosed with glaucoma (which may lead to axial elongation), those who do not have trisomy 21 or any other disorder associated with musculoskeletal / collagen abnormalities, and those without a significant ocular abnormality (which may result in disordered ocular growth. The outcome measure will be ocular growth as determined by serial ultrasound measurements. In order to standardise the measurement of axial length, a study protocol will need to determine whether contact or immersion techniques will be used, and the methodology of assessment (through closed lids / open eye contact, contact gel used, machine used, number of readings taken from each child to obtain an average reading) will also need to be standardised.

A possible consequence of the dissemination of findings within this thesis may be stimulation of the discussion of the risks of general anaesthetic in early childhood to further cognitive development. As a result, fewer children may undergo examination under anaesthetic, which may lead to less available data on ocular length in the first years of life.

Multilevel multivariable longitudinal modelling should be used to investigate the impact of IOL implantation on ocular growth once known associated factors such as acuity have been taken into consideration

6.12.e. **Secondary glaucoma**

Hypothesis 5. IOL implantation is associated with a lower prevalence of secondary post-operative open angle glaucoma

Whilst the investigation of the pathogenesis of post-operative glaucoma is beyond using the IOLu2 study cohort is not possible, the cohort will be able to provide data for the investigation of the determinants of the most significant post-operative complication.

The primary outcome measure will be the presence of open angle glaucoma as confirmed by gonioscopy and as diagnosed by the eighth post-operative year (the time point at which studies of visual outcome will be undertaken). The definition of glaucoma and the potential associated factors (including the impact of topical and systemic steroids) to be investigated will the same as those described within this thesis. One addition will be the investigation of the impact of child's ethnicity (as defined by the family) on the risk of glaucoma.

Modelling on the occurrence or absence of glaucoma and the time to glaucoma (cox survival analysis modelling) will be undertaken in order to investigate the differential impact of factors on the time to onset of glaucoma.

7. CONCLUSIONS

This study is an example of the power of collaborative work, which is essential in the investigation of rare disorders. Multi-centre research involving national networks of specialist practitioners are not only feasible but are also desirable, and the BCCIG should continue to act as a model for the establishment of future (paediatric) ophthalmic collaborative groups.

Persistent fetal vasculature is significantly more common in children with cataract than previously reported, and is probably even more common if the population of unoperated cataract is considered. Despite the small numbers of children affected and the usually unilateral nature of the disease, it should be a focus for future research into the pathogenesis of unilateral cataract and the failure of vascular apoptosis in the fetal eye.

IOL implantation may lead to better visual outcome for children with bilateral cataract. Clarification of the strength and robustness of this effect will be provided by further follow up studies on outcomes in this cohort.

Post-operative glaucoma may go on to develop in the majority of children in whom cataract surgery is undertaken in the first year of life, particularly if undertaken in the first month of life. The potential magnitude of the effect of this blinding disorder within the population of aphakic and pseudophakic is considerable, and the findings of the associations with early life surgery will be disseminated to ophthalmic surgeons, as will the finding that cataract surgery in the first month of life was not associated with significantly better visual outcome, in order to encourage debate about the balance between the risk of amblyopia and the risk of glaucoma.

IOL implantation has not yet been widely adopted for the majority of children aged under 6 months old at surgery. However, the widespread use of IOL implantation in children aged over 6 months suggests that we are past the point of equipoise for investigations into outcome in this age group children, despite the potential increased risk to future cognitive development with multiple general anaesthetic episodes for secondary surgery for visual axis opacity. Nevertheless, the ophthalmic community of surgeons who undertake cataract surgery in the first few years of life will be encouraged to consider the ramifications of repeated general anaesthetics in young children.

Refractive planning for and refractive outcomes in children aged under 2 years old are overly dependent on individual practice or are unpredictable. There is a pressing need for a consensus based decision on refractive planning.

The suggested five year and 10 year post-operative follow up studies of outcome in this unique inception cohort of children, supported by the BCCIG, will provide information on visual outcome, the natural history of the development of aphakic and pseudophakic glaucoma, the refractive growth patterns in pseudophakic eyes (information which may guide refractive planning for future pseudophakic children). It will also provide information on the impact of these outcomes on their educational and personal development.

Overall, the findings presented in this thesis indicate that primary IOL implantation for children ≤2 years old conferred no visual benefit for children with unilateral cataract, but may have improved visual outcome for children with bilateral cataract, whilst increasing the risk of the need for further surgical procedures which may adversely impact on cognitive development. The time has come for a nationally shared recording system for visual, refractive and visual outcomes following early life cataract surgery with IOL implantation, similar to that which exists for adult cataract surgery.

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9. APPENDICES

Appendix A: Aphakic and pseudophakic glaucoma following paediatric cataract surgery

(Paper in press, Der Ophthalmolge, accepted September 2010)

Aphakic and pseudophakic glaucoma following paediatric cataract surgery

Introduction

Almost 1 in 7 of the world's blind children is visually impaired due to cataract.(1) Early detection and surgical intervention are essential to the prevention of blindness associated with this disorder but surgery carries the risk of blinding post-operative complications such as glaucoma. Since the 1980s, rates of post operative closed angle glaucoma following early childhood surgery have reduced following the introduction of microsurgical and vitrectomy techniques which allow safer and more thorough removal of the cataract and anterior vitreous.(2;3) Aphakic or pseudophakic open angle glaucoma is now the most common sight threatening post-operative outcome of childhood cataract surgery, accounting for a third of all secondary childhood glaucoma in industrialised countries such as the United Kingdom.(4)

Aphakic or pseudophakic glaucoma (APG) is difficult to manage, and the majority of children require multiple interventions.(5-7) It can result in severe visual impairment in almost a half of affected children.(5;6) Indeed, the outcome in APG may in some cases be worse than the outcome in un-operated cataract.(8) Individuals who have undergone cataract surgery in early childhood have a life-long increased risk of developing glaucoma(5;9;10), and the child who undergoes cataract surgery in 2010 may live until 2100. Understanding this disorder is thus a priority for ophthalmologists who specialise in glaucoma as well as paediatric ophthalmologists. We present here a brief review of the literature on the frequency of the disorder and the 'risk factors' or possible causative factors.

The limitations of the existing evidence base for aphakic and pseudophakic glaucoma

There is a considerable literature on APG, presenting evidence on the prevalence, time to onset and the possible associated factors and pathogenetic mechanisms. However, comparison and meta-analysis of the existing evidence is made difficult by the methodological limitations of the published studies. These limitations include misclassification bias (varying definitions of glaucoma), selection bias (heterogeneity of cases), confounding (failure to account for all linked risked factors), lack of statistical power to determine the role of chance and inappropriate statistical analysis methods which fail to account for the structure of ophthalmic data.

- Bias

1. Selection bias – the misclassification and varying definitions of glaucoma

The starting point for an investigation of a disorder is the definition of the phenotype. Without a definition, or if there are differing definitions, the arising misclassification of non-diseased individual as diseased (or vice versa) has a profound effect on the subsequent analysis of the frequency of disease or the associations with possible causative factors.

The definition of glaucoma is clinical change associated with elevated intra-ocular pressure; thus an appropriate definition of childhood glaucoma could be argued to be:

'the presence of a combination of clinical signs consistent with high IOP (≥21mm Hg), such as: disc cupping ≥0.3 or disc asymmetry ≥0.2, progressive disc cupping, buphthalmos, enlarged corneal diameter, corneal oedema, Descemet's membrane splits / Haab's striae, visual field defects, and progressive myopia'.(4)

Several papers neglect to provide any definition of glaucoma.(11-33) Other papers on childhood aphakic and pseudophakic glaucoma (APG) use differing definitions. For example, there are studies which define glaucoma as the presence of 'elevated pressure and signs of that elevated pressure'; however, these studies differ in their threshold of IOP, using 21mmHg,(6;8;9;34-41) 25mmHg(42-45) or not stating a threshold.(46;47) Other investigators define glaucoma as 'elevated intraocular pressure', again with varying IOP threshold (21mmHg(2;48;49) and 25mmHg(3;5;10;50-57)) or they define it as 'elevated IOP **or** signs of elevated pressure'.(58-60) These classifications allow inclusion of children with ocular hypertension but without glaucoma. Misclassification of APG is of particular significance as individuals who have undergone early childhood cataract surgery (first 5 years of life) have thicker corneas than 'normal' individuals,(61;62) which results in artificially elevated measurements of intraocular pressure. Thus, in a large number of studies, there has been a misclassification of the outcome of interest (with isolated ocular hypertension considered as glaucoma) with subsequent biased analysis of the clinical associations of APG.

2. Selection bias – the heterogeneity of study populations

Children with cataract form a varied group, and the populations investigated within the existing literature reflect this heterogeneity. Investigators have either limited study populations to children with isolated cataract (no other ocular or systemic disorder)(5;10;22;39;46;63) or to children with cataract associated with microphthalmos, microcornea or other ocular disorders,(14;34;54) or to children undergoing cataract surgery in the first year or two years of life.(42;43;64-66) Other studies have included children with traumatic cataract.(30) Included (or excluded) children may have different susceptibilities to developing APG, differences which are not always appropriately dealt with at analysis. This case mix adversely impacts on attempts to compare the findings of different studies and the generalisablity of individual study findings.

The majority of the many retrospective studies on APG fail to report how many children were lost to follow up, or on the case mix of those children.(1-46) Consequently, these studies are at risk of

ascertainment bias, a subtype of selection bias. Only one retrospective case series explicitly reports on loss to follow up rates: the authors report an attrition rate of 29%.(47) It is not possible to determine whether other studies have similar attrition rates, or how the inclusion of data from cases lost to follow up would impact on study findings.

- The power to discriminate between chance and significant associations or effects

When a disease or an outcome is uncommon, it can be a challenge to obtain the sample size needed to demonstrate an acceptable level of statistical significance for any association. Many of the published studies on APG involve fewer than 30 children,(3;6;9;12;14;15;17;22-25;48;49) and therefore unlikely to have the power to meaningfully investigate even potentially large effects.

- Statistical analyses

1. Confounding – the role of multivariable analysis

Several clinical variables which as potentially associated with the risk of glaucoma, such as age at surgery, axial length and corneal diameter are interrelated. Thus, in order to reduce the risk of confounding, the relationships between these and other variables and the risk of APG must be considered and investigated during analysis. In order to be considered, the variable needs to be well defined, and information on the variable needs to be collected in a systematic fashion. For example, microcornea is sometimes defined as a horizontal corneal diameter (HCD) of 10mm or less, but a neonate with a HCD of 9.5mm has a normal corneal diameter for age. Thus, when data on children undergoing cataract surgery is being gathered, it is necessary to consider the age of the child when determining the presence of microcornea.(42)

The most robust way of investigating the relationship between multiple, possibly interrelated clinical variables such as age, ocular findings and family history is to undertake multivariate analysis. In this way, the independent effect of one variable on the risk of APG *once other variables have been taken into account* can be ascertained, as can the direction and size of effect one variable has on another variable's association with the risk of APG. Only five of the reported studies on APG undertook multivariate analysis to explicitly examine and quantify confounding.(37;39;42;50;51)

2. Multilevel analysis

With regards to the investigation of the risk factors and possible associations of a disorder, the structure of the data should be considered so that the most appropriate analytical methods are used. Failure to do this leads to imprecise analysis, and the reporting of spurious clinical associations, often in the direction of a falsely high effect.

Ophthalmic data are inherently anchored in a multi-level structure. In a child with bilateral cataract, the outcome of the right eye is more likely to be associated to the outcome of the left eye than to the outcome of another eye in another individual. If these correlations are not taken into account, there may be resultant errors in study findings, usually in the form of small p values and narrow confidence intervals when possible clinical associations are reported. That is, there is an over-estimation of the precision and significance of the reported association.

Again, very few of the published studies deal with intra-subject correlation and the resultant impact on the analysis of the clinical associations of APG. For example, Kirwan et al analysed outcomes for only one eye of children with bilateral disease(36) and Egbert et al investigated associations at the level of children rather than eyes(52), thereby losing data from already small datasets. By contrast,

Chak et al,(50) Swamy et al(37) and Rabiah et al(42) used statistical tools to deal with the multilevel structure of the data, thereby making use of data from both eyes whilst accounting for the intra-subject relationships of those data.

- Study design

In order to report on the prevalence of APG, it is important that studies have a sufficiently long follow up period as it is recognised that glaucoma can occur many years after cataract surgery. As prospective data collection on children who undergo cataract surgery can be an expensive and labour-intensive process, many of the existing studies are retrospective case series (table 1). Although large, well designed retrospective studies can provide robust and useful clinical evidence, there are several flaws inherent in this type of study. These include incomplete or inaccurate datasets due to the absence of systematic clinical data entry in medical records, and ascertainment bias due to attrition.

Table 1. Papers on aphakic and pseudophakic glaucoma by study type

Type of study	**Number of studies** (citations)
Population based cohort study	4 studies (50;51;53;54)
Randomised controlled trial	1 study(55)
Prospective cohort study	2 (48;52)
Cross sectional study	4 (49;56-58)
Case control study	1 (59)
Prospective case series	2 (47;60)
Retrospective case series	**47** (1-47;61)
'Expert opinion'	2 (62;63)

Prospective longitudinal and cross sectional studies are able to provide information on the frequency and associations of APG more robustly, as they allow systematic data collection with reduced selection / misclassification bias and the ability to deal with confounding variables.

Despite these limitations within published studies, there exists some useful evidence regarding the frequency of glaucoma following childhood cataract surgery, and the possible risk factors.

The prevalence of secondary glaucoma following childhood cataract surgery

Following childhood cataract surgery, about 10% to 25% of aphakic and pseudophakic eyes will develop glaucoma by the 10th post operative year. (13;20;35;42;50;52;57;64) These studies report on children who have undergone surgery at different ages (from surgery in the first 6 months of life to surgery in late childhood) which may be responsible for the differences in reported prevalence of glaucoma.

Population based studies and large scale longitudinal studies of outcomes following congenital and infantile cataract surgery consistently show that the frequency of glaucoma increases with the duration of follow up (50;52;54) with approximately 5% of operated eyes developing secondary glaucoma each year.(50)

Age at cataract surgery – the key risk factor for developing secondary glaucoma?

There is robust evidence that increasing age at surgery is protective against the risk of glaucoma. A 10 fold increase in age at surgery (for example, from 3 days old to 30 days old at surgery) may be associated with a 60% reduction in the risk of developing APG. When other factors have been accounted for (using multivariate analysis) age at surgery is either the only significant or the most significant risk factor for developing glaucoma. (37;39;42;50;50;51) One recent study (29) did not find a significant association between age at surgery and the risk of developing APG. However, with only 2-3 years median follow up, there were insufficient cases of glaucoma to enable the authors to undertake robust multivariable analysis.

Figure 1. Graph showing the development of open angle glaucoma in operated eyes by age at detection (Nelson Aalen Curve). A 10 fold increase in age at detection (which was in this group closely associated with the age at surgery) was associated with a 64% reduction in the hazard ration for the development of glaucoma (95% CI, 41%–79%; *P*<0.0001). Taken from Chak et al 08(50), reproduced with permission.

It is increasingly recognised that determining the 'ideal' age at cataract surgery for an individual child requires balancing the risk of amblyopia with the risk of glaucoma, but there is no robust evidence of a 'threshold' age for early life cataract surgery, that is, an age at which the risk of developing subsequent glaucoma significantly drops. The strongest available evidence puts a threshold age well beyond the age needed for good visual results: Rabiah et al and Swamy et al used an ad hoc cut off of 9 months of age, and reported that age under 9 months conferred an increased risk of glaucoma (n=322 children, hazard ratio =7.0 [CI 3/6 – 13.7] and n=234 children, hazard ratio=2.9 [CI 1.3 – 7.7] respectively following multivariate analysis).(37;42)

Other risk factors for developing aphakic and pseudophakic glaucoma

Microphthalmos and microcornea have been reported as risk factors for glaucoma following univariate analysis.(54) However, following multivariate analysis, only microcornea has been shown to be an independent risk factor for glaucoma, with hazard ratios of 3.7[2.0 – 7.0] and 3.5[2.5-5.1]. (37;42)

Persistent fetal vasculature (PFV) has not consistently been found to be a significant risk factor for APG,(35;37) but as PFV and persistent hyperplastic primary vitreous (PHPV) are umbrella terms used to describe phenotypes as different as small plaques on the posterior capsule and dense vascularisation of the capsule with pulled ciliary processes, the case mix may be responsible for the absence of robust reported associations.

Despite initial enthusiasm, intraocular lenses (IOLs) have not been found to confer protection from the risk of secondary glaucoma,(50) and papers which have reported on a lower prevalence of glaucoma following IOL implantation have been based on children who have been carefully selected for surgery or who are older at surgery. (4;30;40) It is possible that IOL implantation in very young children is associated with a greater risk of glaucoma: Lambert et al have recently reported on the increased risk of early onset glaucoma in pseudophakic infants versus aphakic infants from a randomised study of primary IOL implantation in children under 6 months old with unilateral cataract.(55)

The pathogenesis of aphakic and pseudophakic glaucoma following early childhood surgery

Several anatomical changes have been noted within eyes which have developed secondary open angle glaucoma following surgery for congenital or infantile cataract. These changes are:

- Peripheral anterior synechiae.(23;65)
- High iris insertions or narrowing of ciliary band.(23;58;65) The angle is significantly less open on UBM imaging in children who have undergone congenital cataract surgery, with shortened ciliary processes and flattening of the pars plicata.(58)
- Membranous material over the trabecular meshwork.(23)
- Increased angle pigmentation.(23;65)

In addition to these pathological findings, aphakic and pseudophakic children with and without glaucoma have thicker corneas (1;2;25;49;59) and there also exists an association between age at surgery and corneal thickness.(2) This evidence suggests that the structure and function of the trabecular meshwork and iridocorneal angle is adversely affected by cataract surgery within a critical period of ocular development and growth.

The postulated mechanisms for this abnormal development

- Intraocular inflammation – iridocorneal angle development may be altered by iatrogenic trabeculitis and resultant microsynechiae.
- 'Chemical effects' of surgery – angle damage may be mediated by trabeculo-toxic factors released from the vitreous gel, (66) or lens epithelial cell modulation of gene expression in cells of the trabecular meshwork.(67)
- Physical / mechanical effects – per-operative barotrauma or the loss of the architecture supporting the developing angle following lens removal may adversely affect angle development.

The recent randomised controlled trial reported by Lambert et al (55) also showed that IOL implantation was associated with an increased risk of per operative iris prolapse and secondary surgery, both of which would result in further intraocular inflammation, and possibly an increased risk of developing glaucoma. Another group has recently reported an increased risk of glaucoma following due to aborted IOL implantation necessitating explantation at primary surgery. (29)

The directions for future research

To reduce the risk of glaucoma following cataract surgery, it is necessary to identify modifiable risk factors. Most important is the question of whether there is an optimal age 'window' for cataract surgery, an age at which an increased risk of amblyopia due to delayed surgery is balanced by a reduced risk of subsequent APG. The effect of primary IOL implantation also requires more robust investigation, especially as this technique becomes more widely adopted in younger children. Such future clinical research will require national or possibly even international collaborations in order to obtain the sample sizes needed for powerful statistical analysis. Longitudinal studies are needed, as they are able to provide natural history data with serial gonioscopy, IOP, corneal thickness and anterior segment UBM imaging, as well as further information on the time to the development of glaucoma (or 'survival rate'). Data collection on putative risk factors must be undertaken in a systematic, standardised fashion. Standardised case definitions and explicit inclusion and exclusion criteria will also be requires so that selection biases are kept to a minimum. Multivariable analysis using multi-level modelling should be undertaken to reduce confounding. Inevitably, these studies need adequate follow up (of at least 10 yrs).

Overall, the epidemiological principles of causality are paramount – which individual (or combination of) causes are 'sufficient' and which are 'necessary' for the development of aphakic and pseudophakic glaucoma? In this way, paediatric ophthalmologists can work to ensure that the child who undergoes cataract surgery in 2010 has the best chance of being glaucoma free until 2100.

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Appendix B: Members of the British Isles Congenital Cataract Interest Group

Mr	MN	Abdel-Khalek	Pilgrim Hospital
Mr	W	Aclimandos	Kings College Hospital
Miss	G	Adams	Moorfields Eye Hospital
Mr	SA	Aftab	Scunthorpe General Hospital
Mr	A	Aguirre Vila-Coro	Huddersfield Royal Infirmary
Mr	JR	Ainsworth	Birmingham & Midland Eye
Ms	LE	Allen	Addenbrokes Hospital
Mr	LA	Amanat	James Paget Hospital
Mr	L	Amaya	St Thomas' Hospital
Ms	S	Anwar	Leicester Royal Infirmary
Mr	S	Armstrong	Countess of Chester
Mr	A	Assaf	Milton Keynes General Hospital
Mr	N	Astbury	West Norwich Hospital
Ms	J	Ashworth	Manchester Royal Eye Hospital
Mr	J	Barry	Birmingham & Midland Eye
Mr	AC	Bates	Pembury Hospital
Mr	AB	Beckingsale	Essex County Hospital
Mr	G	Bedford	Dumfries & Galloway Infirmary
Mr	L	Benjamin	Stoke Mandeville Hospital
Miss	B	Billington	Royal Berkshire Hospital
Mr	S	Biswas	Manchester Royal Eye Hospital
Mr	AJ	Blaikie	Queen Margaret Hospital
Prof	P	Bloom	Western Eye Hospital
Mr	D	Boase	Queen Alexandra Hospital
Miss	M	Boodhoo	St Peter's Hospital
Mr	R	Bowman	Yorkhill Hospital
Ms	N	Boyle	Crosshouse Hospital
Mr	J	Bradbury	Bradford Royal Infirmary
Mr	J	Brazier	Middlesex Hospital
Prof	A	Bron	Oxford Eye Hospital
Mr	D	Brosnahan	Our Lady's Children Hospital
Mr	RD	Brown	North Staffordshire Hospital
Mr	I	Brown	Old Rectory
Mr	S	Bryan	Whipps Cross Hospital
Miss	P	Burgess	Princess Margaret Hospital
Mr	J	Burke	Royal Hallamshire Hospital
Mr	J	Butcher	Countess of Chester
Miss	L	Butler	Birmingham & Midland Eye
Mr	D	Calver	Guy's Hospital
Mr	A	Casswell	Sussex Eye Hospital
Mr	TKJ	Chan	Sheffield Children's Hospital
Mr	A	Chandna	Alder Hey Children's Hospital
Ms	J	Choi	Sheffield Children's Hospital
Ms	AJ	Churchill	Bristol Eye Hospital
Mr	J	Clarke	James Cook University Hospital
Mr	M	Clarke	Royal Victoria Infirmary
Mr		Coffey	Rep Ireland
Mr	M	Cole	Torbay Hospital
Mr	J	Innes	Hull Royal Infirmary
Mr	I	Jalili	66 Roman Bank
Dr	E	Johnson	Gloucestershire Royal Hospital
Mr	DH	Jones	Royal Cornwall Hospital
Ms	A	Joseph	North Staffordshire Hospital
Mr	N	Kaushik	Wrexham Maelor Hospital
Mr	N	Kayali	Whipps Cross Hospital
Mr	SJ	Keightley	North Hampshire Hospital
Prof	P	Khaw	Moorfields Eye Hospital
Mr	P	Kinnear	Charing Cross Hospital
Mr	A	Kostakis	Doncaster Royal Infirmary
Mr	S	Kotta	Grimsby Hospital
Mr	RD	Kumar	Coventry Hospital
Mr	TE	Lavy	Yorkhill Hospital
Mr	D	Laws	Singleton Hospital
Ms	RJ	Leitch	Sutton Hospital
Mr	CSC	Liu	Sussex Eye Hospital
Mr	C	Lloyd	Manchester Royal Eye Hospital
Mr	V	Long	St James' University Hospital
Dr	M	MacCrae	Princess Alexandra Eye Pavilion
Ms	C	MacEwen	Ninewells Hospital
Dr	J	Mackinnon	Yorkhill Hospital
Mr	G	Mackintosh	Yew Tree House
Mr	A	Mandal	Barnsley District Hospital
Mr	R	Markham	Bristol Eye Hospital
Ms	J	Marr	Royal Hallamshire Hospital
Ms	E	Mc Loone	Royal Victoria Hospital
Mr	J	McConnell	Ferrers
Mr	G	McGinntity	Eye & Ear Clinic
Mr	BK	McLeod	Sussex Eye Hospital
Mr	W	Moore	Great Ormond Street Hospital
Prof	AT	Moore	Moorfields Eye Hospital
Mr	B	Moriarty	Leighton Hospital
Mr	R	Morris	Southampton Eye Hospital
Dr	A	Mulvihill	Princess Alexandra Eye Pavilion
Mr	N	Neugebager	Leighton Hospital
Mr	WD	Newman	Alder Hey Children's Hospital
Mr	KK	Nischal	Great Ormond Street Hospital
Mr	G	O'Connor	Cork University Hospital
Miss	R	Ohri	Whipps Cross Hospital
Mr	M	O'Keefe	Children's Hopsital
Mr	M	Parulekar	Birmingham & Midland Eye
Mr	J	Pauw	Clayton Hospital
Mr	S	Perry	Kidderminster General Hospital
Mr	R	Phillips	Arrowe Park Hospital
Ms	R	Pilling	Bradford Royal Infirmary
Dr	BJ	Power	Dumfries and Galloway Infirmary
Mr	N	Price	Cheltenham General Hospital

Mr	R	Condon	St Peter's Hospital
Mr	PG	Corridan	Wolverhampton Eye Infirmary
Mr	M	Dang	Darlington Memorial Hospital
Mr	R	Darvell	Kent and Canterbury Hospital
Mr	BN	Das	Alexandra Hospital
Mr	S	Daya	Queen Victoria Hospital
Mr	R	De Cock	Kent and Canterbury Hospital
Ms	F	Dean	University Hospitals Coventry
Mr	C	Dees	James Cook University Hospital
Mr	C	Dodd	Manchester Royal Eye Hospital
Mr	RML	Doran	Victoria Eye Centre
Prof	G	Dutton	Yorkhill Hospital
Mr	C	Edelsten	Ipswich Hospital NHS Trust
Mr	R	Edwards	Kent and Canterbury Hospital
Mr	H	El-Kabasy	Southend Hospital
Mr	J	Elston	Oxford Eye Hospital
Mr	N	Evans	Royal Eye Infirmary
Mr	A	Evans	Queen Alexandra Hospital
Mr	GT	Fahy	Frederick Thorpe Eye Admin Unit
Mr	JD	Ferris	Cheltenham General Hospital
Prof	A	Fielder	Western Eye Hospital
Miss	DE	Flaye	Herts and Essex Hospital
Dr	B	Fleck	Princess Alexandra Eye Pavilion
Dr	A	Gaskell	Ayr Hospital
Mr	ND	George	Ninewells Hospital
Miss	M	Gibbens	Queen Mary's Hospital
Mr	CEA	Gibbons	North Devon District Hospital
Mr	L	Gnanaraj	Sunderland Eye Infirmary
Mr	P	Gregory	Conquest Hospital
Mr	R	Gregson	Nottingham University Hospital
Mr	J	Hakim	Queen Mary's Hospital
Mr	S	Hardman-Lea	Ipswich Hospital NHS Trust
Mr	MJ	Hassan	Barnsley District Hospital
Mr	M	Heravi	William Harvey Hospital
Ms	M	Hingorani	Bedford Hospital
Mr	PR	Hodgkins	Southampton General Hospital
Mr	R	Holden	Derbyshire Royal Infirmary
Mr	R	Humphrey	Odstock Hospital
Mr	C	Hutchinson	Royal Halifax Infirmary
Mr	A	Quinn	Royal Devon and Exeter
Mr	I	Qureshi	Birch Hill Hospital NHS Trust
Prof	J	Rahi	UCL Institute of Child Health
Mr	A	Rahman	Pilgrim Hospital
Mr	A	Reddy	Royal Aberdeen Hospital
Miss	C	Roberts	Western Eye Hospital
Mr	N	Rogers	Sheffield Children's Hospital
Mr	E	Rosen	10 St John Street
Ms	I	Russell-Eggitt	Great Ormond Street Hospital
Mr	SM	Scotcher	Hereford Hospital
Mr	CS	Scott	Royal Aberdeen Hospital
Mr	JA	Scott	Stirling Royal Infirmary
Mr	PW	Sellar	West Cumberland Hospital
Mr	A	Shafiq	Queen Victoria Road
Mr	J	Shankar	Wrexham Maelor Hospital
Mr	A	Shun Shin	Wolverhampton Eye Infirmary
Mr	PR	Simcock	Royal Devon and Exeter Hospital
Mr	IG	Simmons	St James' University Hospital
Mr	H	Soeldner	James Cook University Hospital
Mr	JD	Stokes	Ireland
Mr	M	Tappin	St Peter's Hospital Eye Unit
Mr	R	Taylor	York Hospital NHS Trust
Prof	D	Taylor	Institute of Ophthalmology
Mr	V	Thaller	Royal Eye Infirmary
Mr	MT	Thoung	Broomfield Hospital
Mr	W	Tormey	Waterford Regional Hospital
Mr	S	Tuft	Moorfields Eye Hospital
Mr	MK	Tutton	Countess of Chester
Mr	JM	Twomey	Musgrove Park Hospital
Mr	S	Verghese	West Cumberland Hospital
Ms	S	Vickers	Sussex Eye Hospital
Mr	A	Vijaykumar	The Royal Infirmary
Mr	A	Vivian	West Suffolk Hospital
Mr	PO	Watts	University Hospital of Wales
Ms	C	Williams	Bristol Eye Hospital
Mr	H	Wilshaw	Birmingham & Midland Eye
Mr	G	Woodruff	Leicester Royal Infirmary
Mr	G	Wright	Burnley General Hospital
Mr	B	Young	Regional Hospital

Appendix C: Cataract surgery and primary intraocular lens implantation in children ≤2 years old in the United Kingdom and Ireland: findings of a national survey

(Published work)

Cataract surgery and primary intraocular lens implantation in children ⩽2 years old in the UK and Ireland: finding of national surveys

A L Solebo,[1,2] I Russell-Eggitt,[2,3] K K Nischal,[2,3] A T Moore,[2,3,4,5] P Cumberland,[1,2] J S Rahi,[1,2,3,4,5] on behalf of the British Isles Congenital Cataract Interest Group

[1] MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, London, UK; [2] Ulverscroft Vision Research Group, UCL Institute of Child Health, London, UK; [3] Clinical and Academic Department of Ophthalmology, Great Ormond Street Hospital for Children, London, UK; [4] Moorfields Eye Hospital, London, UK; [5] UCL Institute of Ophthalmology, London, UK

Correspondence to: Dr J Rahi, MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK; j.rahi@ich.ucl.ac.uk

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ABSTRACT

Background: Current patterns of practice relating to primary intraocular lens (IOL) implantation in children ⩽2 years old in the UK and Ireland are investigated.

Methods: National postal questionnaire surveys of consultant ophthalmologists in the UK and Ireland.

Results: 76% of 928 surveyed ophthalmologists replied. 47 (7%) of the respondents operated on children aged ⩽2 with cataract. 41 (87%) of respondents performed primary IOL implantation, but 25% would not implant an IOL in a child under 1 year old. 88% of surgeons used limbal wounds, 80% manual capsulotomies, 98% posterior capsulotomies and 100% hydrophobic acrylic lenses. The SRK/T formula was most commonly used (70%). Exclusion criteria for primary IOL implantation varied considerably and included microphthalmos (64% of respondents), anterior and posterior segment anomalies (53%, 58%), and glaucoma (19%).

Discussion: Primary IOL implantation in children ⩽2 has been widely adopted in the UK and Ireland. There is concordance of practice with regards to surgical technique and choice of IOL model. However, there is some variation in eligibility criteria for primary IOLs: this may reflect a lack of consensus on which children are most likely to benefit. Thus, there is a need for systematic studies of the outcomes of primary IOL implantation in younger children.

Primary intraocular (IOL) implantation has become accepted practice for older children with cataract.[1 2] While primary IOL implantation is being increasingly undertaken in children in the first 2 years of life,[3 4] the long-term benefits and the factors associated with positive and negative outcomes are unclear.[1 2 5-9]

The British Isles Congenital Cataract Interest Group (BCCIG), a research network comprising British and Irish ophthalmic consultants, was established in 1995 in order to study the incidence, detection, causes, management and outcomes of congenital and infantile cataract.[10–14] A national epidemiological study to investigate outcomes following primary IOL implantation in children ⩽2 years old with congenital and infantile cataract is now being undertaken through the BCCIG. As a foundation for this research, we have investigated the surgical management of cataract in younger children in the UK and Ireland, with a focus on primary IOL implantation.

METHODS

In October 2008, 960 consultants comprising all members of the BCCIG, all consultant members of the Royal College of Ophthalmologists and Irish consultant ophthalmologists with a known interest in congenital cataract, were contacted using postal questionnaires accompanied by hand-addressed cover letters and postage-paid reply envelopes. Members of the BCCIG who did not respond to the mailing were sent reminders.

We sought to discover the number of children ⩽2 years old with congenital or infantile cataract managed over the previous year, the number undergoing surgery with and without primary IOL implantation and the details of surgical management. Respondents were asked to estimate the number of children managed over the preceding year. Exclusion criteria for primary implantation in children ⩽2 were requested, as were preferred IOL model and IOL power calculation formulae together with details of surgical technique including lens aspiration and vitrectomy approaches and capsulotomy practices. The postoperative measurement of axial length was also investigated.

Statistical analysis

Free text answers on exclusion criteria were coded. A descriptive analysis of the responses was undertaken.

RESULTS

Thirty-two of the 960 distributed questionnaires were returned as undeliverable. Of the remaining 928 contacted consultants, 709 (76%) replied to the survey. Replies were received between October 2008 and January 2009. Of the 709 respondents, 47 (7%) stated that they operated on children ⩽2 years old, estimating that over the preceding year they had operated on a total of 301 children. Six (13%) of the 47 surgeons did not perform primary IOL implantation in any child ⩽2. The 41 surgeons who did perform primary IOL implantation estimated that in the preceding year they had operated on 268 children (116 with unilateral, 152 with bilateral cataract), undertaking primary IOL implantation in 65% (table 1).

Exclusion criteria

Exclusion criteria for primary IOL implantation in children ⩽2 were provided by 36 of the 41 respondents. Six (17%) surgeons did not mention any ocular anomaly among their stated exclusion criteria. Twenty-three (64%) described specific anomalies which would prevent them from

Table 1 Surgical management of children ⩽2 years old with cataract: number of children undergoing surgery as estimated by respondents

	Unilateral cataract	Bilateral cataract	Total
How many children ⩽2 years old have you operated on over the last year? (47 surgeons)			
Median	2	2.5	5
Range (min to max)	0–10	0–15	0–25
Total	133	168	301
In how many children ⩽2 years old have you performed primary intraocular lens implantation over the last year? (41 surgeons)			
Median	2	1	2
Range	0–8	0–14	0–19
Total	87	86	173
As a proportion of children undergoing surgery	75% (87/116)	57% (86/152)	65% (173/268)

implanting an IOL. Of these, 16 cited short axial length or microphthalmos, with five specifying different lengths below which they would not implant (16, 18 and 20 mm). Anterior and posterior segment anomalies were exclusion criteria for 12 and 14 respondents respectively. Seven (19%) respondents considered the presence of any coexistent ocular anomaly to be sufficient cause for exclusion. Thus, microphthalmos is an exclusion criteria for 64% (23/36) of respondents, anterior segment anomaly 53% and posterior segment anomaly 58%. Nine (25%) cited microcornea, with surgeons again specifying differing corneal diameters, below 9 mm (three respondents) or 10 mm (three respondents). Seven (19%) cited persistent hyperplastic primary vitreous (PHPV, or persistent fetal vasculature), with five of the seven specifying "significant" PHPV. Other stated exclusion criteria included abnormal capsular support (10/36 or 28%, with four respondents specifying ectopia lentis), glaucoma (7/36, 19%) and uveitis (3/36, 8%).

The age of the child was cited by 6/36 (17%) of the 36 respondents. Different minimum age limits were used: 12 months, 6 months and 1 month old minimal ages by three, two and one respondent respectively. Thus, 25% (9/36) of respondents would not perform primary IOL implantation in any child under 1 year old. Seven (19%) consultant ophthalmologists commented on parental preference as an exclusion criterion for primary IOL implantation.

Details of routine surgical management

As shown in table 2, all respondents used a hydrophobic acrylic IOL, with 90% using an Acrysof model. Seventy per cent reported using the SRK/T formula for IOL power calculation, with 37% using it in combination with the Hoffer Q formula. Six respondents specified that they used either formula, dependent on the axial length of the child. With regards to routine surgical technique, 80% of surgeons used limbal wounds for surgery; manual capsulotomy techniques were used by 88%; posterior capsulotomies were created by all but one surgeon. Of those using posterior capsulotomies, 78% also performed anterior vitrectomy, with 16% stating that their surgical approach (anterior versus posterior) depended on the axial length or age of the child. The majority of respondents (71%) do not routinely postoperatively measure the axial lengths of pseudophakic children.

DISCUSSION

Cataract surgery in children ⩽2 years is undertaken by a small group of subspecialists in the UK and Ireland. While the technical demands of surgery are considerable, our finding that fewer than one in 20 responding consultants undertake cataract surgery in these children may be an indication of the level of postoperative ophthalmic, orthoptic, optometric and supportive nursing care necessary to achieve a good outcome. Primary intraocular lens implantation in children ⩽2 has been adopted by the majority of the responding surgeons who manage children with cataract. There exists concordance of surgical approach, with most surgeons choosing an AcrySof hydrophobic acrylic IOL, manual curvilinear anterior capsulorhexis, limbal wound access and posterior capsulotomy with anterior vitrectomy. However, our finding that variability exists with regards to exclusion criteria suggests that there is disparity of opinion on which children will benefit following primary IOL implantation, and which children are at least risk of complications and poor outcome. While this disparity may be due to differing personal preferences within a relatively new and evolving field, it may also be a reflection of absences within the evidence base on the practice of primary IOL implantation in children ⩽2 years.

The high (76%) response rate to this postal survey is, we believe, an indication of the current relevance of this issue to all ophthalmologists. This figure is high in comparison with other published work,[4 15 16] and strengthens the generalisability of our findings. We recognise that the use of free text responses may have precluded comprehensive responses in relation to exclusion criteria for primary IOL implantation. We also believe that the estimated total of 301 children undergoing cataract surgery over the preceding year, as reported in this survey, may be an overestimate: previous work undertaken through the BCCIG has shown that between 1995 and 1996, 168 children under 2 years were diagnosed as having congenital or infantile cataract in the UK, with surgery undertaken in 165.

Previously published literature exists on international practice styles and preferences in paediatric cataract surgery and IOL implantation,[4] and also preferences of surgical specifics such as the IOL model[15] and capsulotomy method.[16] In 2003, Wilson *et al*[4] surveyed members of the American cataract and paediatric subspecialty societies and reported that up to 89% of respondents would implant IOLs in a child ⩽2 years with unilateral cataract, and 78% in a child ⩽2 years with bilateral cataract. Hydrophobic acrylic IOLs were used by 71% of paediatric surgeons. There was disagreement on whether microphthalmos, anterior segment anomalies and persistent fetal vasculature were contraindications to IOL placement in children. While these findings are of interest, only 2% of the respondents to that survey were UK consultants. As such, the findings are not necessarily readily extrapolated to practices in the UK and Ireland.

Better understanding of visual development and amblyopia,[17 18] and the introduction of mechanical lensectomy,

Table 2 Details of surgical management

	No of respondents (n = 41)
IOL model	
Acrysof	37
MA60	14
MA30	13
SA60	8
SN60AF	4
SN60 IQ	3
AMO	4
Sensar	3
Tecnis	1
HoyaVA	1
IOL power calculation formulae	
SRK/T	28
Hoffer Q	21
SRK/T+Hoffer Q	14
Holladay I	6
SRK II	3
Haigis	1
IOL placement	
In the bag	40
Optic capture	1
Wound creation	
Limbal	33
Scleral	8
Limbal or scleral	2
Clear corneal	3
Anterior capsulotomy technique	
Manual	36
Diathermy	4
Vitrectorrhexis	3
Posterior capsulotomy and vitrectomy	
No posterior capsulotomy	1
No vitrectomy	9
Vitrectomy via anterior approach	25
Vitrectomy via posterior approach	17
Postoperative axial length routinely measured postoperatively	
Yes	12
No	29

IOL, intraocular lens.

mechanical vitrectomy, capsulotomy techniques, ophthalmic viscous devices and other novel technologies[1 2] have led to improvements in visual outcomes for children with cataract.[2 19] Primary IOL implantation has become the treatment of choice in older children, with medium- to longer-term outcome data becoming available,[2 3 20] and there is good biocompatibility evidence for IOL material implantation in young eyes.[21] Short-term visual rehabilitation following IOL implantation in early childhood is at least comparable with that with contact lens correction of surgical aphakia,[5 7 22 23] but there is uncertainty about both the long-term benefits and the risks of primary IOL implantation in children aged under 2 years, with regards to the predictability of refractive outcomes with different power equations, postoperative complication rates and the need for further surgery.[7 23-25] The Infant Aphakia Treatment Study, currently under way in North America, is investigating outcomes in a defined cohort of infants under 6 months old with unilateral cataract[6] following standardised cataract surgery with and without primary IOL implantation. Their findings will be welcomed by paediatric ophthalmic surgeons. Nevertheless, further research is necessary on outcomes within a more diverse group of patients, in particular older infants and those with bilateral cataract or other ocular disease, as well as outcomes in settings outside the USA where management practices and healthcare systems differ.

While our findings reflect the increasing adoption of IOLs for children ⩽2 years, 13% of consultants reported that they would not use primary IOLs in any child ⩽2 years old, a quarter would not use IOLs in a child under 1 year old, and there is notable variance in the cited exclusion criteria. A national epidemiological study into primary IOL implantation in children ⩽2 years, now under way through the BCCIG, should address important unanswered questions on the outcomes and predictors of outcomes of primary IOL implantation in a nationally representative cohort of children ⩽2 years old.

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Competing interests: None.

Members of the British Isles Congenital Cataract Interest Group: M Abdel-Khalek, Pilgrim Hospital, Lincolnshire, W Aclimandos, King's College Hospital, London, GW Adams, Moorfields Eye Hospital, London, S Aftab, Scunthorpe General Hospital, A Aguirre Vila-Coro, Huddersfield Royal Infirmary, L Allen, Addenbrokes Hospital, Cambridge, L Amanat, James Paget Hospital, Norfolk, L Amaya, St Thomas' Hospital, London, S Anwar, Leicester Royal Infirmary, S Armstrong, Countess of Chester Hospital, Cheshire, A Assaf, Milton Keynes Hospital, N Astbury, West Norwich Hospital, J Ashworth, Manchester Royal Eye Hospital, Bates, Pembury Hospital, Tonbridge Wells, A Beckingsale, Essex County Hospital, G Bedford, Dumfries & Galloway Royal Infirmary, L Benjamin, Stoke Mandeville Hospital, Buckinghamshire, B Billington, Royal Berkshire Hospital, S Biswas, Manchester Royal Eye Hospital, A Blaikie, Queen Margaret Hospital, Fife, T Blamires, Northampton General Hospital, P Bloom, Western Eye Hospital, London, D Boase, Queen Alexandra Hospital, Hampshire, M Boodhoo, St Peter's Hospital, Surrey, R Bowman, Yorkhill Hospital, Glasgow, J Bradbury, Bradford Royal Infirmary, J Brazier, Middlesex Hospital, London, A Bron, Oxford Eye Hospital, D Brosnahan, Our Lady's Children Hospital, Dublin, R Brown, North Staffordshire University Hospital, I Brown, Old Rectory, Shropshire, S Bryan, Whipps Cross Hospital, London, P Burgess, Princess Margaret Hospital, Swindon, J Burke, Royal Hallamshire Hospital, Sheffield, J Butcher, Countess of Chester Hospital, Cheshire, L Butler, Birmingham & Midland Eye Centre, D Calver, Guy's Hospital, London, A Casswell, Sussex Eye Hospital, A Chandna, Alder Hey Children's Hospital, Liverpool, AJ Churchill, Bristol Eye Hospital, J Clarke, James Cook University Hospital, Middlesborough, M Clarke, Royal Victoria Infirmary, Newcastle upon Tyne, Coffey, Ireland, M Cole, Torbay Hospital, Devon, R Condon, St Peter's Hospital, Surrey, P Corridan, Wolverhampton Eye Infirmary, M Dang, Darlington Memorial Hospital, Co Durham, R Darvell, Kent and Canterbury Hospital, B Das, Alexandra Hospital, Worcestershire, S Daya, Queen Victoria Hospital, West Sussex, R De Cock, Kent and Canterbury Hospital, F Dean, University Hospitals Coventry and Warwickshire, C Dees, James Cook University Hospital, Middlesborough, C Dodd, Manchester Royal Eye Hospital, R Doran, Victoria Eye Centre, Hereford, G Dutton, Yorkhill Hospital, Glasgow, C Edelsten, Ipswich Hospital, R Edwards, Kent and Canterbury Hospital, H El-Kabasy, Southend Hospital, J Elston, Oxford Eye Hospital, A Evans, Queen Alexandra Hospital, Portsmouth, N Evans, Royal Eye Infirmary, Plymouth, F Fahy, Leicester Royal Infirmary, J Ferris, Cheltenham General Hospital, A Fielder, Western Eye Hospital, London, D Flaye, Herts and Essex Hospital, B Fleck, Princess Alexandra Eye Pavilion, Edinburgh, A Gaskell, Ayr Hospital, ND George, Ninewells Hospital, Dundee, M Gibbens, Queen Mary's Hospital, Kent, C Gibbons, North Devon District Hospital, L Gnanaraj, Sunderland Eye Infirmary, P Gregory, Conquest Hospital, East Sussex, R Gregson, Nottingham University Hospital, J Hakim, Queen Mary's Hospital, Sidcup, S Hardman-Lea, Ipswich Hospital, M Hassan, Barnsley District Hospital, M Heravi, William Harvey Hospital, Kent, M Hingorani, Bedford Hospital, P Hodgkins, Southampton General Hospital, R Holden, Derbyshire Royal Infirmary, R Humphrey, Odstock Hospital, Salisbury, C Hutchinson, Royal Halifax Infirmary, J Innes, Hull Royal Infirmary, I Jalili, Roman Bank, Peterborough, C Jenkins, Kent County Ophthalmic and Aural Hospital, E Johnson, Gloucestershire Royal Hospital, D Jones, Royal Cornwall Hospital, A Joseph, North Staffordshire University Hospital, N Kaushik, Wrexham Maelor Hospital, Wales, N Kayali, Whipps Cross Hospital, London, S Keightley, North Hampshire Hospital, Basingstoke, P Khaw, Moorfields Eye Hospital, London, P Kinnear, Charing Cross Hospital, London, A Kostakis, Doncaster Royal Infirmary, S Kotta,

Grimsby District General Hospital, R Kumar, Coventry and Warwickshire Hospital, T Lavy, Yorkhill Hospital, Glasgow, D Laws, Singleton Hospital, Swansea, J Leitch, Sutton Hospital, Surrey, C Liu, Sussex Eye Hospital, C Lloyd, Manchester Royal Eye Hospital, C MacEwen, Ninewells Hospital, Dundee, G Mackintosh, Yew Tree House, Cheltenham, A Mandal, Barnsley District Hospital, R Markham, Bristol Eye Hospital, E Mc Loone, Royal Victoria Hospital, Belfast, J McConnell, Ferrers, Kent, G McGinnity, Royal Victoria Hospital, Belfast, B McLeod, Sussex Eye Hospital, W Moore, Great Ormond Street Children's Hospital, London, B Moriarty, Leighton Hospital, Cheshire, G Morrice, Stirling Royal Infirmary, R Morris, Southampton Eye Hospital, N Neugebager, Leighton Hospital, Cheshire, W Newman, Alder Hey Children's Hospital, Liverpool, J Nolan, University College Hospital, London, G O'Connor, Cork University Hospital, Ireland, R Ohri, Whipps Cross Hospital, London, M O'Keefe, Children's Hospital, Dublin, J Pauw, Clacton Hospital, Wakefield, S Perry, Kidderminster General Hospital, R Phillips, Arrowe Park Hospital, Wirral, B Power, Dumfries and Galloway Royal Infirmary, N Price, Cheltenham General Hospital, AG Quinn, Royal Devon and Exeter Hospital, I Qureshi, Birch Hill Hospital, Lancashire, A Rahman, Pilgrim Hospital, Lincolnshire, A Reddy, Royal Aberdeen Children's Hospital, E Rosen, St John Street, London, S Scotcher, Hereford Hospital, CS Scott, Royal Aberdeen Children's Hospital, J Scott, Stirling Royal Infirmary, P Sellar, West Cumberland Hospital, J Shankar, Wrexham Maelor Hospital, Wales, A Shun Shin, Wolverhampton Eye Infirmary, P Simcock, Royal Devon and Exeter Hospital, I Simmons, St James' University Hospital, Leeds, JD Stokes, Nottingham University Hospital, M Tappin, St Peter's Hospital, Surrey, DSI Taylor, Institute of Ophthalmology, London, R H Taylor, York Hospitals NHS Foundation Trust, V Thaller, Royal Eye Infirmary, Blackburn, M Thoung, Broomfield Hospital, Essex, W Tormey, Waterford Regional Hospital, Ireland, S Tuft, Moorfields Eye Hospital, London, M Tutton, Countess of Chester Hospital, Cheshire, J Twomey, Musgrove Park Hospital, Somerset, S Verghese, West Cumberland Hospital, Cumbria, S Vickers, Sussex Eye Hospital, Brighton, A Vijaykumar, The Royal Infirmary, Lancashire, A Vivian, West Suffolk Hospital, P Watts, Cardiff Eye Unit, C Williams, Bristol Eye Hospital, H Wilshaw, Birmingham & Midland Eye Centre, G Woodruff, Leicester Royal Infirmary, G Wright, Burnley General Hospital, Lancashire, and Young, Limerick Regional Hospital, Ireland.

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Appendix D: National study of primary IOL implantation in children ≤2 years old (IOLunder2 study) notification forms

IOLu2: National study of intraocular lens implantation in children ≤ 2 with congenital or infantile cataract
in association with the *British Isles Congenital Cataract Interest Group (BCCIG)*

Patient identification sheet

Eligibility:
Any child with bilateral or unilateral congenital or infantile cataract due to undergo cataract surgery on or before their 2nd birthday.

Hospital: **CONSULTANT:**

Patient details

SURNAME

HOSPITAL NUMBER:

GP NAME:

GP ADDRESS:

Thank you for completing this form; please store it safely in the red IOLu2 folder until it is returned to the research team

Appendix E: IOLunder2 study data collection instruments

IOLu2: National study of intraocular lens implantation in children ≤ 2 with congenital or infantile cataract in association with the *British Isles Congenital Cataract Interest Group (BCCIG)*

Any child with bilateral or unilateral, congenital or infantile cataract due to undergo cataract surgery on or before their 2nd birthday with or without IOL

Questionnaire 1: Pre operative clinical findings and operative planning

HOSPITAL NAME: **CONSULTANT NAME:**

CHILD'S DETAILS (please print or use patient sticker)

SURNAME:	
HOSPITAL NUMBER:	
NHS NUMBER:	
DATE OF BIRTH:	DD / MM / YY
FULL POSTCODE:	

SEX: ☐ **MALE** ☐ **FEMALE**

ETHNICITY:

White	Mixed Race	Asian or Asian British	Black or Black British	Other ethnic group
☐ British ☐ Irish ☐ Other	☐ White & Black Caribbean ☐ White & Black African ☐ White & Asian ☐ Other	☐ Indian ☐ Pakistani ☐ Bangladeshi ☐ Other	☐ Caribbean ☐ African ☐ Other	☐ Chinese ☐ Other ☐ Not stated / unknown

This page will be detached and held separately from the rest of the questionnaire

A. Age at detection of visual problem *(if known)*:	**Days** or	**Weeks** or **Months**
B1. Date cataract diagnosed by health professional: DD / MM / YY	**or**	**B2. Date of referral to you:** DD / MM / YY
C. Date of presentation to your team: DD / MM / YY		

II. AETIOLOGY OF CATARACT (if known at presentation: please tick relevant box and add further details)

☐Idiopathic ☐Persistent fetal vasculature ☐Metabolic ☐Hereditary ocular ☐Hereditary systemic ☐Trauma ☐ Intrauterine event ☐Other

Further details:

III. NON OPHTHALMIC DISORDERS / IMPAIRMENTS (if known at presentation)

A. Prematurity? ☐No ☐Yes, **/40 gestational age**

B. Non-ophthalmic disorder(s)? ☐No ☐Yes / under investigation, *please specify:*

C. Associated non-ophthalmic impairment(s)? ☐No ☐Hearing ☐Global developmental delay ☐Other, *please specify:*

IV. PRE-OPERATIVE OPHTHALMIC ASSESSMENT

A. Fixation and visual acuity ☐ NOT APPLICABLE / NOT DONE Date: DD / MM / YY

1. Vision assessment method: ☐Centrl/Steady/Maint'd ☐Fix/following ☐Other, specify:

Right eye	**Left eye**	**Both eyes open**

2. Nystagmus: ☐No ☐Latent ☐ Manifest

3. Strabismus: ☐No ☐Left ☐Right ☐Alternating ☐Constant ☐Intermittent ☐Exotropia ☐Esotropia

B. Electrodiagnostics

Electroretinogram: ☐ NOT APPLICABLE / NOT DONE

☐Normal ☐Abnormal *(please specify):*

Visual evoked potentials: ☐ NOT APPLICABLE / NOT DONE

☐Normal ☐Abnormal *(please specify):*

C. Clinical examination (findings in clinic / at Examination under Anaesthesia)

	Right eye	**Left eye**
1. Cataract	**☐No ☐Yes**	**☐No ☐Yes**
2. Morphology (please tick all that apply)	☐Dense ☐Partial ☐Total ☐Lamellar ☐Nuclear ☐Anterior ☐Posterior ☐Other,*specify:*	☐Dense ☐Partial ☐Total ☐Lamellar ☐Nuclear ☐Anterior ☐Posterior ☐Other,*specify:*
3. Clinical microphthalmos	☐No ☐Yes	☐No ☐Yes
4. Pupil dilation	☐Normal ☐Poor dilation ☐Synechiae	☐Normal ☐Poor dilation ☐Synechiae
5. Anterior segment abnormality	☐No ☐Yes, *specify:*	☐No ☐Yes, *specify:*
6. Corneal diameter	**HCD: __ . __ mm** Date measured: DD / MM / YY	**HCD: __ . __ mm** Date measured: DD / MM / YY
7. Persistent fetal vasculature	☐No ☐Yes Details:	☐No ☐Yes Details:
8. Other posterior segment abnormality	☐No ☐Yes, *specify:*	☐No ☐Yes, *specify:*

9. Pre-op IOP in mmHg	☐<21 ☐21-30 ☐>30 Corrected using CCT? ☐No ☐Yes	☐<21 ☐21-30 ☐>30 Corrected using CCT? ☐No ☐Yes
10. Pre-op Glaucoma?	☐No ☐Yes, diagnosed DD / MM / YY *Details:*	☐No ☐Yes, diagnosed DD / MM / YY *Details:*
11. Other cause of abnormal vision (eg neurological)	☐No ☐Yes, *specify:*	☐No ☐Yes, *specify:*

D. Cycloplegic Retinoscopy (following working distance correction) ☐NOT APPLICABLE / NOT DONE

Right eye	**Left eye**

V. OPERATIVE PLAN AND BIOMETRY

A. Is primary intraocular lens implantation planned? ☐**YES** ☐**NO**_____

If no, please specify reason(s)

Parents' Choice	
Axial length: ☐ <16mm ☐ <18mm ☐ <19mm ☐ <20mm	☐ **Anterior segment dysgenesis**
Age of child: ☐ <2 years ☐ <1 year ☐ <6month ☐ <1month	☐ **Other anterior segment abnormality**
Horizontal corneal diameter: ☐ <9mm ☐ <10mm	☐ **Persistent fetal vasculature**
☐ **Glaucoma** ☐**Zonule instability** ☐**Uveitis**	☐**Other posterior segment abnormality**
☐ **Surgeon's preference**	*Details:*
☐ Other *(please specify):*	

B. Biometry ☐ NOT APPLICABLE / NOT DONE Date: DD / MM / YY

	Right eye	**Left eye**
1. Axial lengths: ☐Applanation ☐Immersion ☐Through lids	_____**mm**	_____**mm**
2. Keratometry:	**K:** _____	**K:** _____
3. Anterior chamber depth (if measured) ☐Applanation ☐Immersion ☐Through lids	_____**mm**	_____**mm**
4. Capsular bag diameter (if measured)	_____**mm**	_____**mm**
5. Power formula(e) used: ☐SRK/T ☐Hoffer Q ☐Holladay I ☐SRK II ☐Haigis ☐Other: **A-constant or ACD used:**		
6. Power needed for emmetropia	_____**DIOPTRES**	_____**DIOPTRES**
7. Power selected for implantation	_____**DIOPTRES**	_____**DIOPTRES**
8. Planned post operative refraction	_____**D**	_____**D**

Name of person who completed this form (and designation, if not consultant)

Please use this box for any further comments, or continue on an extra sheet

Thank you for completing this form; please return it in the prepaid envelope to:

Lola Solebo, C/o Dr Jugnoo Rahi,
Centre for Paediatric Epidemiology,
Freepost RRZC-JXEY-URJL, Institute of Child Health, 30 Guilford St, London WC1N 1EH
Tel: 020 7813 8142, l.solebo@ich.ucl.ac.uk

IOLu2:
in association with the *British Isles Congenital Cataract Interest Group (BCCIG)*

Questionnaire 2: Per-operative details

STUDY ID NUMBER:	{researcher completed}
SURNAME:	
HOSPITAL NUMBER:	
DATE OF BIRTH:	DD / MM / YY

This page will be detached and held separately from the rest of the questionnaire.

	RIGHT EYE	LEFT EYE
A. Cataract surgery	☐No ☐Yes	☐No ☐Yes
B. Date of operation	DD / MM / YY	DD / MM / YY
C. Grade of surgeon	☐Consultant ☐Other	☐Consultant ☐Other
D. Surgical wound	☐Limbal ☐Scleral ☐Clear corneal	☐Limbal ☐Scleral ☐Clear corneal
E. Pupil dilation	☐Normal ☐Poor ☐Synechiae	☐Normal ☐Poor ☐Synechiae
F. Manual iris manipulation	☐None ☐Yes, stretch / hooks ☐Iridectomy ☐Yes, other, *specify:*	☐None ☐Yes, stretch / hooks ☐Iridectomy ☐Yes, other, *specify:*
G. OVD / Viscoelastic	☐OVD not used ☐Healon GV ☐Healon 5 ☐Healon ☐Other, *specify:*	☐OVD not used ☐Healon GV ☐Healon 5 ☐Healon ☐Other, *specify:*
H. Anterior capsulotomy *(including size)*	☐CCC ☐Push/pull ☐Diathermy ☐ Vitrect ☐Other, *specify:* **SIZE:** mm	☐CCC ☐Push/pull ☐Diathermy ☐ Vitrect ☐Other, *specify:* **SIZE:** mm
I. Lens aspiration	☐Manual ☐Automated	☐Manual ☐Automated
J. Posterior capsulotomy	☐None ☐Spontaneous rupture ☐Anterior approach ☐Posterior approach ☐CCC ☐Push/pull ☐Diathermy ☐ Vitrect ☐Other, *specify:*	☐None ☐Spontaneous rupture ☐Anterior approach ☐Posterior approach ☐CCC ☐Push/pull ☐Diathermy ☐ Vitrect ☐Other, *specify:*
K. Vitrectomy	☐None ☐Anterior approach ☐Pars plana approach ☐Pars plicata	☐None ☐Anterior approach ☐Pars plana approach ☐Pars plicata
L. Additive in AC infusion	☐None ☐Adrenaline ☐Heparin ☐Other, *specify:*	☐None ☐Adrenaline ☐Heparin ☐Other, *specify:*
M. Wound closure	Suture: ☐Vicryl ☐Other, *specify*: Paracentesis sutured?: ☐No ☐Yes	Suture: ☐Vicryl ☐Other, *specify*: Paracentesis sutured?: ☐No ☐Yes
N. Prophylactics or other medication used (given at closure)	☐None **Topical**: ☐Maxitrol ☐Chloramphenicol ☐Other, *specify*: **Intracameral**: ☐Miochol ☐Dexamethasone ☐Cefuroxime ☐Other, *specify*: **Subconj**: ☐Betnesol ☐Cefuroxime ☐Other, *specify*: ☐**Other** (eg intravitreal, systemic) *specify:*	☐None **Topical**: ☐Maxitrol ☐Chloramphenicol ☐Other, *specify*: **Intracameral**: ☐Miochol ☐Dexamethasone ☐Cefuroxime ☐Other, *specify*: **Subconj**: ☐Betnesol ☐Cefuroxime ☐Other, *specify*: ☐**Other** (eg intravitreal, systemic) *specify:*
O. IOL implanted	☐No ☐Yes, please continue below	☐No ☐Yes, continue below
P. IOL placement	☐Prior to PC / Vity ☐Following PC / Vity ☐In the Bag ☐Other, *specify:*	☐Prior to PC / Vity ☐Following PC / Vity ☐In the Bag ☐Other, *specify:*
Q. IOL model (use sticker if convenient)	☐MA30 ☐MA60 ☐SA60 ☐SN60AF ☐IQ (SN60WF) ☐AMO Sensar ☐Other, *specify*:	☐MA30 ☐MA60 ☐SA60 ☐SN60AF ☐IQ (SN60WF) ☐AMO Sensar ☐Other, *specify*:
R. IOL power (use sticker if convenient)	_____ **D**	_____ **D**

II. PER-OPERATIVE COMPLICATIONS

RIGHT EYE	LEFT EYE
☐No ☐Yes:	☐No ☐Yes:
☐ Iris prolapse	☐ Iris prolapse
☐ Anterior capsular tear – past equator? ☐Yes ☐No	☐ Anterior capsular tear – past equator? ☐Yes ☐No
☐ Dropped fragment	☐ Dropped fragment
☐ IOL explanted / exchange, *please specify reason:*	☐ IOL explanted / exchange, *please specify reason:*
☐ Hyphaema – widest diameter: mm	☐ Hyphaema – widest diameter: mm
☐ Other, *please specify:*	☐ Other, *please specify:*

III. POST OPERATIVE DROP / OINTMENT MEDICATION **RIGHT** EYE (for first post op week)

Is this your routine regimen? ☐No ☐Yes

		Name	Frequency
Steroid / NSAID	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly
	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly
Cycloplegia	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly
	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly

POST OPERATIVE DROP / OINTMENT MEDICATION **LEFT** EYE

		Name	Frequency
Steroid / NSAID	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly
	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly
Cycloplegia	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly
	☐G. ☐Oc.		☐ON ☐BD ☐TDS ☐QDS ☐2 hour ☐Hourly

Name of person who completed this form (and designation, if not consultant)

Please use this box for any further comments
(eg, other post operative medications)

Thank you for completing this form; please return it in the prepaid envelope to:

Lola Solebo, Clinical Research Fellow
C/o Dr Jugnoo Rahi, Centre for Paediatric Epidemiology and Biostatistics,
Freepost RRZC-JXEY-URJL, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Tel: 020 7813 8142 Email: l.solebo@ich.ucl.ac.uk

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Questionnaire 3 – Post operative findings
To be completed at 6 months post op

STUDY ID NUMBER:	{researcher completed}
SURNAME:	{researcher completed}
HOSPITAL NUMBER:	{researcher completed}
DATE OF BIRTH:	DD / MM / YY

	Date of surgery	6 month post op date
Right eye	DD / MM / YY	DD / MM / YY
Left eye	DD / MM / YY	DD / MM / YY

I. REFRACTIVE OUTCOMES

Earliest post operative refraction (following working distance correction)			
Right eye (RE)	*Date:* DD / MM / YY	*Left eye (LE):*	*Date:* DD / MM / YY
Refraction at 6 months post op (or nearest date)			
RE:	*Date:* DD / MM / YY	*LE :*	*Date:* DD / MM / YY

II. VISUAL REHABILITATION in operated eye(s):

A. Optical Correction: ☐No ☐Yes:

☐Glasses only ☐Contact lenses (CL) only ☐**Glasses** more than CL ☐**CL** more than glasses

Date optical correction started	DD / MM / YY **Right Eye** DD / MM / YY **Left Eye**
Glasses wear:	Overcorrected / myopic: ☐No ☐Yes by _____Dioptres ☐Poor compliance (<50% time) ☐Good compliance (≥50% time)
Contact lens wear (**CLW**):	☐Daily wear ☐Extended wear Overcorrected / myopic: ☐No ☐Yes by _____Dioptres ☐Poor compliance (<50% time) ☐Good compliance (≥50% time)
CLW complication or intolerance?	☐No ☐Yes, *please specify:*

B. Post operative occlusion: Formal monitoring of compliance (eg diary, logbook): ☐No ☐Yes

Compliance definitions: Poor (<50% prescribed time), Good (50% to 75%), Very good (>75%)

	Right eye	**Left eye**
Any occlusion up to 6 month review point?	☐No ☐Yes	☐No ☐Yes
Current prescribed regimen	Started: DD / MM / YY % waking day or hrs or ☐None	Started: DD / MM / YY % waking day or hrs or ☐None
Overall compliance	☐Poor ☐Good ☐Very good	☐Poor ☐Good ☐Very good

III. Any ADVERSE OUTCOMES or FURTHER SURGERY? ☐**No, please go to Q.IV** ☐**Yes, please continue**

	RIGHT EYE	**LEFT EYE**
A. Visual axis opacity (VAO) requiring intervention?	☐**Yes** PLEASE CONTINUE	☐**No** PLEASE GO TO Q.B
1. VAO type	☐Opacity anterior to IOL: ☐Pearls ☐Fibrosis ☐Other membrane ☐Opacity posterior to IOL: ☐Pearls ☐Fibrosis ☐Other membrane ☐Anterior capsular contraction to **mm** ☐Other, *specify:*	☐Opacity anterior to IOL: ☐Pearls ☐Fibrosis ☐Other membrane ☐Opacity posterior to IOL: ☐Pearls ☐Fibrosis ☐Other membrane ☐Anterior capsular contraction to **mm** ☐Other, *specify:*
2. Treatment	☐Nd:YAG laser ☐Surgery ☐Other, *specify:* Date 1st treatment DD / MM / YY Total number procedures for VAO:	☐Nd:YAG laser ☐Surgery ☐Other, *specify:* Date 1st treatment DD / MM / YY Total number procedures for VAO:
3. Complications of VAO treatment?	☐No ☐Yes, *specify:*	☐No ☐Yes, *specify:*
B. Any primary IOL implant complication?	☐**Yes** PLEASE CONTINUE	☐**No** PLEASE GO TO QUESTION C
1. Complication	☐Decentration (half optic edge visible, dilated pupil) ☐Dislocation (optic edge visible undilated pupil) ☐Pupil capture ☐Other, *specify:*	☐Decentration (half optic edge visible, dilated pupil) ☐Dislocation (optic edge visible undilated pupil) ☐Pupil capture ☐Other, *specify:*

2. Date of diagnosis	DD / MM / YY	DD / MM / YY
3. Surgical correction?	☐No ☐Yes, date: DD / MM / YY	☐No ☐Yes, date: DD / MM / YY
C. Significant post operative uveitis*? (*requiring more than usual post-op anti-inflammatory treatment) ☐**Yes** PLEASE CONTINUE ☐**No** PLEASE GO TO QUESTION D		
1. Treatment	☐Topical ☐Periocular ☐Systemic	☐Topical ☐Periocular ☐Systemic
2. Fibrinous?	☐No ☐Yes	☐No ☐Yes
3. Identifiable risk factors?	☐None ☐Non-concordance medication ☐Other, *specify:*	☐None ☐Non-concordance with medication ☐Other, *specify:*
D. Post operative endophthalmitis? ☐**Yes** PLEASE CONTINUE ☐**No** PLEASE GO TO QUESTION E		
1. Date of diagnosis	DD / MM / YY	DD / MM / YY
2. Pathogen isolated	☐No ☐Bacterial ☐Viral ☐Fungal ☐Other	☐No ☐Bacterial ☐Viral ☐Fungal ☐Other
E. Any other postoperative complications? ☐**Yes** PLEASE CONTINUE ☐**No** PLEASE COMPLETE FORM BELOW		
1. Complications (with dates of diagnosis and treatment)		

IV. AXIAL LENGTH AND KERATOMETRY DATA at 6 months post op (or nearest date) ☐Not applicable / Not done

	RIGHT EYE	LEFT EYE
Axial lengths	Method(s) used:	
	mm *Date:* DD / MM / YY	mm *Date:* DD / MM / YY
Keratometry	Instruments used:	
	Date: DD / MM / YY	*Date:* DD / MM / YY

Name of person who completed this form (and designation, if not consultant)

Please use this box for any further comments

Thank you for completing this form; please return it in the prepaid envelope to:

Lola Solebo, Clinical Research Fellow, C/o Dr Jugnoo Rahi, Centre for Paediatric Epidemiology and Biostatistics, Freepost RRZC-JXEY-URJL, Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Tel: 020 7813 8142 Email: l.solebo@ich.ucl.ac.uk

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in association with the BCCIG

Questionnaire 4 – Post operative findings
To be completed at 12 months post op

STUDY ID NUMBER:	{researcher completed}
SURNAME:	{researcher completed}
HOSPITAL NUMBER:	{researcher completed}
DATE OF BIRTH:	DD / MM / YY

	Date of surgery	12 month post op date
Right eye	DD / MM / YY	DD / MM / YY
Left eye	DD / MM / YY	DD / MM / YY

This page will be detached and held separately from the rest of the questionnaire.

I. VISUAL OUTCOME **Date:** DD / MM / YY

A. Method used: ☐Forced choice preferential ☐Other preferential looking, *specify:*
☐Cardiff Card ☐Single Kays ☐Crowded Kays ☐Lear symbols ☐Other, *specify:*

	Right:	Left:	Both eyes open:
(if measured) **Acuity wearing contact lenses**			
(if measured) **In glasses**			
(if measured) **Unaided**			

B. Stereopsis	☐Not applicable / not done ☐Gross only ☐Arc seconds:
C. Nystagmus	☐No ☐Latent ☐Manifest
D. Strabismus	☐No ☐Left ☐Right ☐Alternating ☐Constant ☐Intermittent ☐Exotropia ☐Esotropia

II. REFRACTIVE OUTCOMES AND VISUAL REHABILITATION

A. Refraction 1 year post operative, or nearest date

Right eye	*Date:* DD / MM / YY	*Left eye*	*Date:* DD / MM / YY

B. Visual rehabilitation in operated eye(s) at 1 year post op

☐Glasses only ☐Contact lenses (CL) only ☐**Glasses** more than CL ☐**CL** more than glasses

Glasses overcorrected	☐No ☐Yes by Dioptres
CL overcorrected	☐No ☐Yes by Dioptres
Compliance with correction:	☐Poor compliance (<50%) ☐Good compliance (≥50%)
CL complication or intolerance?	☐No ☐Yes, please specify:

C. Occlusion regimen from 6 months to 1 year post op: Formal monitoring of occlusion ☐No ☐Yes
(Poor compliance <50% prescribed time, Good 50 – 75%, Very good >75%)

	Right eye	Left eye
Change since 6 month review point?	☐No ☐Yes	☐No ☐Yes
New regimen	% waking day or hrs	% waking day or hrs
Compliance	☐Poor ☐Good ☐Very good	☐Poor ☐Good ☐Very good

III. Any ADVERSE OUTCOMES or FURTHER SURGERY? ☐**No, please go to Q.IV** ☐**Yes, please continue**

	RIGHT EYE	LEFT EYE
A. Visual axis opacity (VAO) requiring intervention (not noted on 6 month questionnaire)? ☐**Yes** PLEASE CONTINUE ☐**No** PLEASE GO TO Q.B		
1. VAO morphology	Anterior to IOL: ☐Pearls ☐Fibrosis Posterior to IOL: ☐Pearls ☐Fibrosis ☐Anterior capsular contraction to mm ☐Other, *specify:*	Anterior to IOL: ☐Pearls ☐Fibrosis Posterior to IOL: ☐Pearls ☐Fibrosis ☐Anterior capsular contraction to mm ☐Other, *specify:*
2. Treatment	☐Nd:YAG laser ☐Surgery ☐Other, *specify:* Date treatment DD / MM / YY Total number procedures for VAO:	☐Nd:YAG laser ☐Surgery ☐Other, *specify:* Date treatment DD / MM / YY Total number procedures for VAO:
B. Ocular hypertension / glaucoma* diagnosed post op? ☐**Yes** PLEASE CONTINUE ☐ **No** PLEASE GO TO Q.C *Glaucoma defined as combination of signs consistent with IOP<21: disc cupping / asymmetry, buphthalmos, myopic shift, HCD / corneal changes		
	☐OHT ☐GLAUCOMA*	☐OHT ☐GLAUCOMA*
1. Date of diagnosis	DD / MM / YY	DD / MM / YY
2. Glaucoma type	☐Open angle glaucoma ☐Pupil block element ☐Other, *specify:*	☐Open angle ☐Pupil block element ☐Other, *specify:*
3. Treatment (please tick all that apply)	☐Medical ☐Cyclodiode ☐Trabeculectomy ☐Drainage implant ☐Other, *specify:* Date 1st procedure: DD / MM / YY Total number procedures:	☐Medical ☐Cyclodiode ☐Trabeculectomy ☐Drainage implant ☐Other, *specify:* Date 1st procedure: DD / MM / YY Total number procedures:

C. Retinal detachment (RD)? ☐Yes PLEASE CONTINUE ☐No PLEASE GO TO Q.D		
1. Date of diagnosis	DD / MM / YY	DD / MM / YY
2. Secondary to cataract surgery?	☐Not known ☐Yes ☐No, *specify aetiology:*	☐Not known ☐Yes ☐No, *specify aetiology:*
3. Surgical intervention?	☐No ☐Yes Date 1st surgery: DD / MM / YY Total number surgical procedures for RD:	☐No ☐Yes Date 1st surgery: DD / MM / YY Total number surgical procedures for RD:

D. Any other postoperative complications, not covered in this or earlier 6 month questionnaire? ☐Yes PLEASE CONTINUE (please use another sheet if necessary) ☐No PLEASE GO TO Q.E		
1. Complications (and dates of diagnosis and treatment)		

E. Secondary intraocular lens implantation? ☐Yes PLEASE CONTINUE ☐No PLEASE GO TO Q.F		
1. Date of surgery	DD / MM / YY	DD / MM / YY
2. Further details (eg planned refractive outcome, complications)?		

F. Any other ophthalmic surgical procedure, not covered in this or earlier 6 month questionnaire (eg STRABISMUS)? ☐Yes PLEASE CONTINUE ☐No PLEASE GO TO THE NEXT SECTION		
1. Other surgical procedure (and dates of surgery)		

IV. AXIAL LENGTH AND KERATOMETRY DATA at 1 year post op (if measured) ☐*Not recorded*

RIGHT EYE	LEFT EYE
Axial lengths Method(s) used:	
mm *Date:* DD / MM / YY	mm *Date:* DD / MM / YY
Keratometry Instruments used:	
Date: DD / MM / YY	*Date:* DD / MM / YY

V. NEW DIAGNOSES

Any newly diagnosed / detected ophthalmic or systemic disorder? ☐Yes PLEASE CONTINUE ☐No THANK YOU		
1. Newly detected / diagnosed ophthalmic disorder	Date diagnosed DD / MM / YY	Date diagnosed DD / MM / YY
2. Newly diagnosed systemic disorder	Date diagnosed DD / MM / YY	
3. Newly diagnosed non-ophthalmic impairments	☐None ☐Hearing ☐Mobility ☐Global development delay ☐Speech/Language ☐Learning ☐Other (please specify):	

Name of person who completed this form (and designation, if not consultant)

Please use another sheet for any further comments, if necessary

Thank you for completing this form; please return it in the prepaid envelope to:

Lola Solebo, c/o Dr Jugnoo Rahi,
Centre for Paediatric Epidemiology, Freepost RRZC-JXEY-URJL, UCL Institute of Child Health, 30 Guilford St, London WC1N 1EH

Appendix F: IOLunder2 study parental / guardian information sheets and consent form

COVERING LETTER TO PARENTS

Dear Parent

Re: National study of surgery for congenital and infantile cataract.

We are contacting you as the parent of a young child with cataract who is being treated at X Hospital.

We would like to ask you and your child to take part in this national research study, which is being conducted through a group of consultant ophthalmologists in the UK who specialise in treating children. We would ask you to allow your consultant to let us have information that he or she will collect routinely during your child's treatment. This information will be combined with information about other children undergoing treatment at other hospitals in the UK and analysed to understand better which factors predict the best outcomes from treatment. Your child's treatment will not be affected or altered in any way by being involved in the study. The information sheet attached to this letter gives you more details about why and how the study is being done.

At this stage we are asking you to take part in a study that will look at what happens to children in the first two years after surgery. As it will be important to know what happens in the longer term, we would like to ask you, *separately*, whether you would be happy to be contacted in the future, through your child's ophthalmologist, to allow us to collect more information about outcomes.

If you are willing to take part, please sign the enclosed consent form and return it to us directly in the postage paid reply envelope or return it to your child's ophthalmologist.
If you decide not to take part, this will not affect your child's care in any way.

We would also like you to complete the enclosed short form that we have included which asks some questions about you, your child and family so that we can understand better the general background of your family. This helps us to make sure that we are including different types of families in our study, so that the findings can be applied generally. It would be very helpful if you could fill in the form and return it with the consent form, even if you decide *not* to take part in the study.

We plan to publish the findings of the study in scientific journals but we will pool information in our reports, so that it will not be possible to identify any individual who is included. All the information we are given will be held securely and kept strictly confidential.

We will be able to tell you about the final results of the study when it is finished.

Centre for Paediatric Epidemiology and Biostatistics
UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Head: Professor Carol Dezateux

If you need more information now, or you would like some help in filling in the forms, or if you would prefer to have the study explained in another language, please either contact the ophthalmology team or contact our research team.

With many thanks,

Yours sincerely,

Lola Solebo
(Researcher)
Ulverscroft Clinical Research Fellow

tel: 020 7905 2835
fax: 020 7905 2381
e-mail: l.solebo@ich.ucl.ac.uk

Jugnoo Rahi
(Study Lead)
Reader in Ophthalmic Epidemiology
Senior Clinical Lecturer/Honorary
Consultant Ophthalmologist
tel: 020 7905 2250
fax: 020 7905 2381
e-mail: j.rahi@ich.ucl.ac.uk

Information for parents

National study of surgery for congenital and infantile cataract.

We would like to ask you and your child to take part in this study.

1. The aim of the study.
We want to collect information about all children under two years of age having surgery for cataract in the UK in the next two years in order to understand better which factors predict the outcome of treatment. We are particularly interested in how having an artificial lens (inserted into the eye when the cataract is removed) affects outcomes in the long term.

2. Why is the study being done?
There have been great advances in the treatment of cataract in young children in the past ten to fifteen years. But there are still some unanswered questions about the more recent technological improvements. By analysing data on a large number of children, we hope to provide information that will help doctors and parents make decisions about the most effective treatment.

3. How is the study to be done?
This national research study is being conducted through a group of consultant ophthalmologists (eye surgeons) in the UK who specialise in treating children. We are seeking your permission to allow your child's ophthalmologist to let us have information that he/she will record routinely in your child's medical notes about treatment and progress. This information will be pooled together with information about other children undergoing treatment at other hospitals in the UK. It will then be analysed statistically to understand better which factors predict the best outcomes from treatment. Your child's treatment will not be affected or altered in any way by being involved in the study.

At this stage we are asking you to take part in a study that will look at what happens to children in the first two years after surgery. As it will be important to know what happens in the longer term, we would like to ask you, *separately*, whether you would be happy to be contacted in the future, through your child's ophthalmologist, to allow us to collect more information about outcomes.

4. Who will have access to the research records?
Throughout, all the information provided to us will be treated in strict confidence by the researcher team. All information will be held securely. Apart from your child's ophthalmologist, only the researchers will have access to the data collected during this study.

5. What are the potential benefits?
This study is unlikely to bring any immediate benefits to your child, whose treatment will have started by the time the study finishes. However it will help provide information about improving treatment which will be valuable to doctors

Centre for Paediatric Epidemiology and Biostatistics
UCL Institute of Child Health, 30 Guilford Street, London WC1N 1EH
Head: Professor Carol Dezateux

and parents of children undergoing treatment in the future. It will also help us to plan further research to understand new technological advances in cataract treatment as they happen.

6. Do I have to take part in this study?
If you decide, now or at a later stage, that you do **not** wish to take part in this research project, that is entirely your right. We would reassure you that this will not in any way affect any present or future treatment of your child.

7. Who do I speak to if problems arise?
If you have any questions or complaints about the way in which this research project has been, or is being conducted, please, in the first instance, discuss them with the researchers named below or with your child's ophthalmologist.

If the problems are not resolved, or you wish to comment in any other way, please contact the Head of Research and Development, by post via the Research and Development Office, Institute of Child Health, 30 Guilford Street, London WC1N 1EH, or if urgent, by telephone on 020-7242-9789.

8. Details of how to contact the Researchers:
You can contact any of the main researchers:

Lola Solebo (Researcher)

MRC Centre of Epidemiology for Child Health for Paediatric Epidemiology
Institute of Child Health,UCL
30 Guilford Street
London WC1N 1EH
telephone: 020 7905 2835
fax 020 7905 2381
email l.solebo@ich.ucl.ac.uk

Jugnoo Rahi
Reader in Ophthalmic Epidemiology/Honorary Consultant Ophthalmologist
MRC Centre for Paediatric Epidemiology
Institute of Child Health, UCL
30 Guilford Street
London WC1N 1EH
telephone : 020 7905 2250
fax 020 7905 2381
email j.rahi@ich.ucl.ac.uk

Centre Number: 1
Study Number:
Patient Identification Code:

CONSENT FORM - National study of surgery for congenital and infantile cataract

Child's name:……..

Please tick boxes to confirm agreement:

1. I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw my child from the study at any time without giving any reason, without my child's medical care or legal rights being affected. ☐

3. I confirm that I agree to information about my child's condition and treatment being shared with the research team at the Institute of Child Health and with regulatory authorities where it is relevant to my child taking part in this research. ☐

4. I agree to my child's GP being informed of my child's participation in the study ☐

5. I agree to allow my child to take part in the above study. ☐

6. I agree to the research team holding my child's details in order to be able to contact me in the future with regard to follow-up studies, and I agree to this contact being made. ☐

OR

I do not wish to take part in this study ☐

Name of parent / guardian of patient	Date	Signature
Jugnoo Rahi	01/01/2009	Jugnoo S Rahi
Researcher	Date	Signature

Please keep one copy, and send the other to the research team in the pre-paid envelope. The research team will ensure that a copy is filed in your child's clinical notes.

Appendix G: Hospital specific per operative data collection proforma

Delete/ circle as appropriate
C 86.6 EUA eyes
C 74.3 lensectomy
C 75.1 IOL implantation
C 71.3 lens aspiration

RIGHT EYE **LEFT EYE**

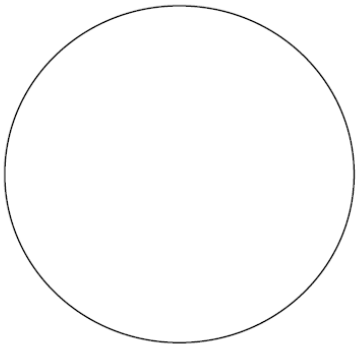
HCD (mm)

IOP

lens drawing
(note on any iris/AC anomaly/poor dilation)

K readings				K readings			
AL		AC depth		AL		AC depth	
Cap bag diam				Cap bag diam			
Biometry notes (incl ACD / pACD / A constant / planned post op refraction) ☐Hoffer Q ☐SRK/T							

OPERATION NOTE



Findings and extra details:
(note any lenticonus, PHPV, lens plaque etc)

OVD: Healon GV Other:
BSS+: Adrenaline Other:
Capsulotomy: ☐Push Pull ☐CCC ☐Diatherm ☐Vitrector
Size: mm
Lens aspirated: ☐Automated ☐Manual
Post caps'my: ☐Push Pull ☐CCC ☐Diatherm ☐Vitrector
Vitrectomy: ☐Anterior ☐P. plicata ☐P. plana
IOL: ☐Not used ☐Folded ☐Injected
IOL in bag: ☐Yes ☐No, details:
OVD out (prior to closure): ☐Not used ☐Yes ☐No
Wound closed: 10/0 vicryl Other:
Paracentesis: ☐Hydrated ☐Sutured

Intraoperative complications: ☐ No ☐ Yes:

☐ Iris prolapse ☐ Hyphaema ☐ Ant capsular tear ☐ PC tear out ☐ Frag drop

☐ IOL explant or exchange

☐ Other, specify / details:

Medication per op / on closure:

☐ Intracam Dexamethasone (*400µg*) ☐ Subconj Cefuroxime (*3mg*) ☐ Subconj Betnesol (*2mg*)

☐ Orbital floor Triamcinolone (*20mg in 0.5ml*)

☐ Intravenous Acetazolamide (*5mg/kg*)

☐ Other:

Post op instructions:

G. Maxitrol hourly for 24 hours then 2 hourly
Occ. Maxitrol ON,
G. Cyclopentolate 0.5% BD

Other:

F/up:

Name, signature, designation:

Lens sticker:

Appendix H: Four by four data tables

for calculation of positive and negative predictive values in the comparison of clinical and ultrasound determined microphthalmos

Bilateral cataract	**Right eye**	Microphthalmos on ultrasound	
		No	**Yes**
Clinical micro	**No**	31	1
	Yes	67	15

Bilateral cataract	**Left eye**	Microphthalmos on ultrasound	
		No	**Yes**
Clinical micro	**No**	26	0
	Yes	73	15

Bilateral cataract	**Right eye**	Axial length<16mm	
		No	**Yes**
Clinical micro	**No**	87	5
	Yes	11	11

Bilateral cataract	**Left eye**	Axial length<16mm	
		No	**Yes**
Clinical micro	**No**	86	4
	Yes	13	11

Bilateral cataract	**Right eye**	Microcornea	
		No	**Yes**
Clinical micro	**No**	61	4
	Yes	15	12

Bilateral cataract	**Left eye**	Microcornea	
		No	**Yes**
Clinical micro	**No**	62	2
	Yes	17	3

Unilateral (cataract eyes)	**Right eye**	Microphthalmos on ultrasound	
		No	**Yes**
Clinical micro	**No**	16	1
	Yes	18	5

Unilateral (cataract eyes)	**Left eye**	Microphthalmos on ultrasound	
		No	**Yes**
Clinical micro	**No**	9	1
	Yes	12	6

Unilateral (cataract eyes)	**Right eye**	Axial length<16mm	
		No	**Yes**
Clinical micro	**No**	33	4
	Yes	1	2

Unilateral (cataract eyes)	**Left eye**	Axial length<16mm	
		No	**Yes**
Clinical micro	**No**	21	5
	Yes	0	2

Unilateral (cataract eyes)	**Right eye**	Microcornea	
		No	**Yes**
Clinical micro	**No**	22	3
	Yes	4	3

Unilateral (cataract eyes)	**Left eye**	Microcornea	
		No	**Yes**
Clinical micro	**No**	15	3
	Yes	3	3

Appendix I: Pre operative visual function:

<1 week old at assessment		
IOL 17, Aphake 51		
No assessment	Qualitative assessment	Quantitative assessment
IOL - 11/17, 64.7% (41.2 - 82.3%)	IOL - 6	0 children
	Aphake - 9	
Aphake - 42/51, 82.4% (69.5 - 90.7%)		

1 week - 6 months		
IOL 21, Aphake 29		
No assessment	Qualitative assessment	Quantitative assessment
IOL -8/21, 38.1% (20.7 - 59.2%)	IOL - 9	IOL - 4
	Aphake - 17	Aphake - 2
Aphake - 10/29, 34.5% (19.9 - 52.67%)		

6m - 24m		
IOL 18, Aphake 4		
No assessment	Qualitative assessment	Quantitative assessment
IOL - 5/18, 27.8% (12.2 - 51.2%)	IOL - 6	IOL - 7
	Aphake - 1	Aphake - 1
Aphake - 2/4, 50% (15 - 85%)		

Pre-operative visual assessments undertaken in children with bilateral cataract by treatment group

<1 week old at assessment		
IOL 11, Aphake 20		
No assessment	Qualitative assessment	Quantitative assessment
IOL - 8/18, 44.4% (24.5 - 66.3%)	IOL - 3	0 children
	Aphake - 6	
Aphake - 14/20, 70% (47.9 - 85.9%)		

1 week - 6 months		
IOL 15, Aphake 19		
No assessment	Qualitative assessment	Quantitative assessment
IOL - 7/15, 46.7% (24.8 - 69.9%)	IOL - 5	IOL - 3
	Aphake - 10	Aphake - 1
Aphake - 8/19, 42.1% (23.1 - 63.8%)		

6m - 24m		
IOL 26, Aphake 4		
No assessment	Qualitative assessment	Quantitative assessment
IOL - 6/26, 23.1% (10.7 - 42.4%)	IOL - 10	IOL - 10
	Aphake - 2	Aphake - 0
Aphake - 2/4, 50% (15 - 85%)		

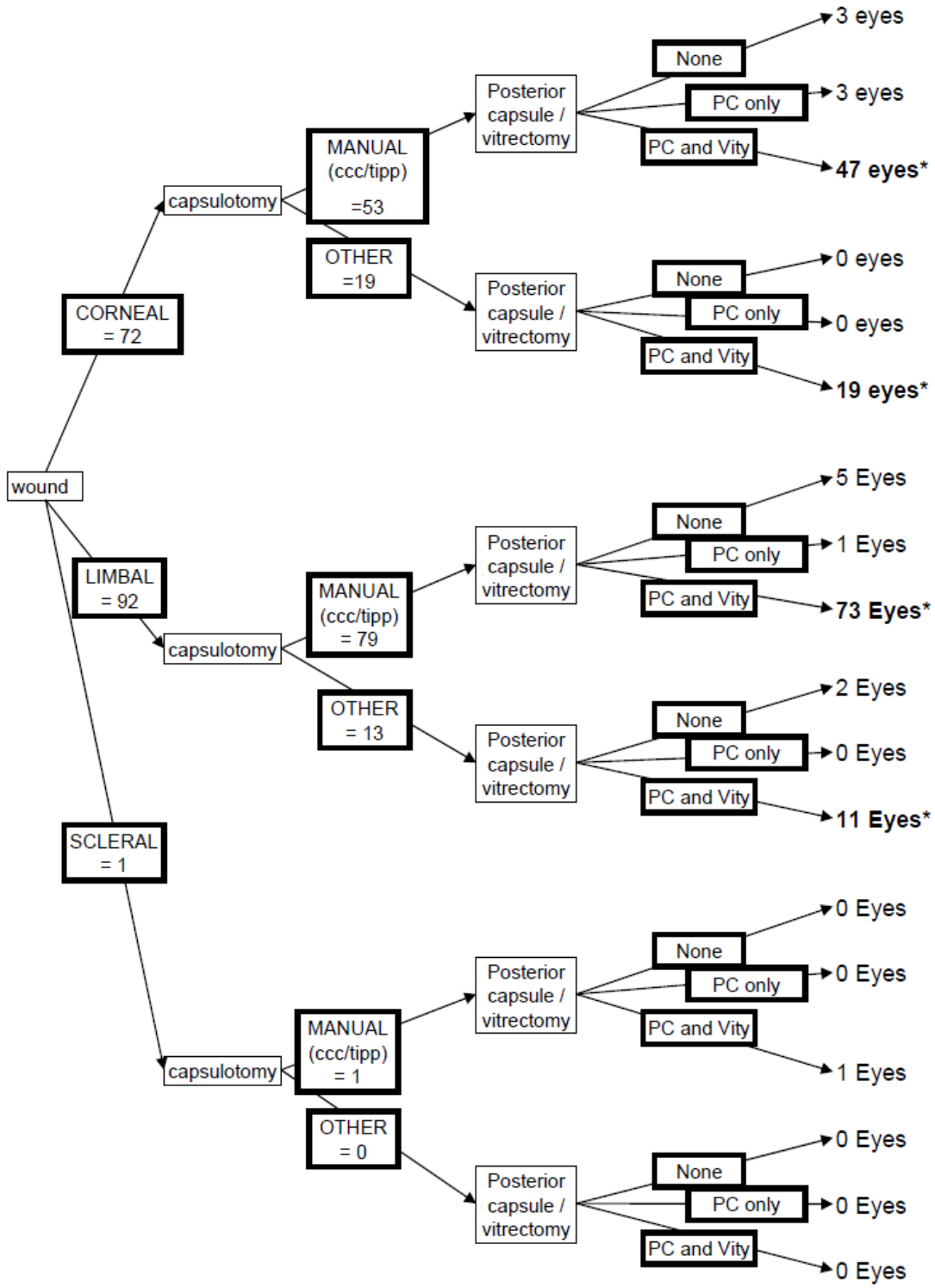
Pre-operative visual assessments undertaken in children with unilateral cataract by treatment group

Appendix J: Biometric data

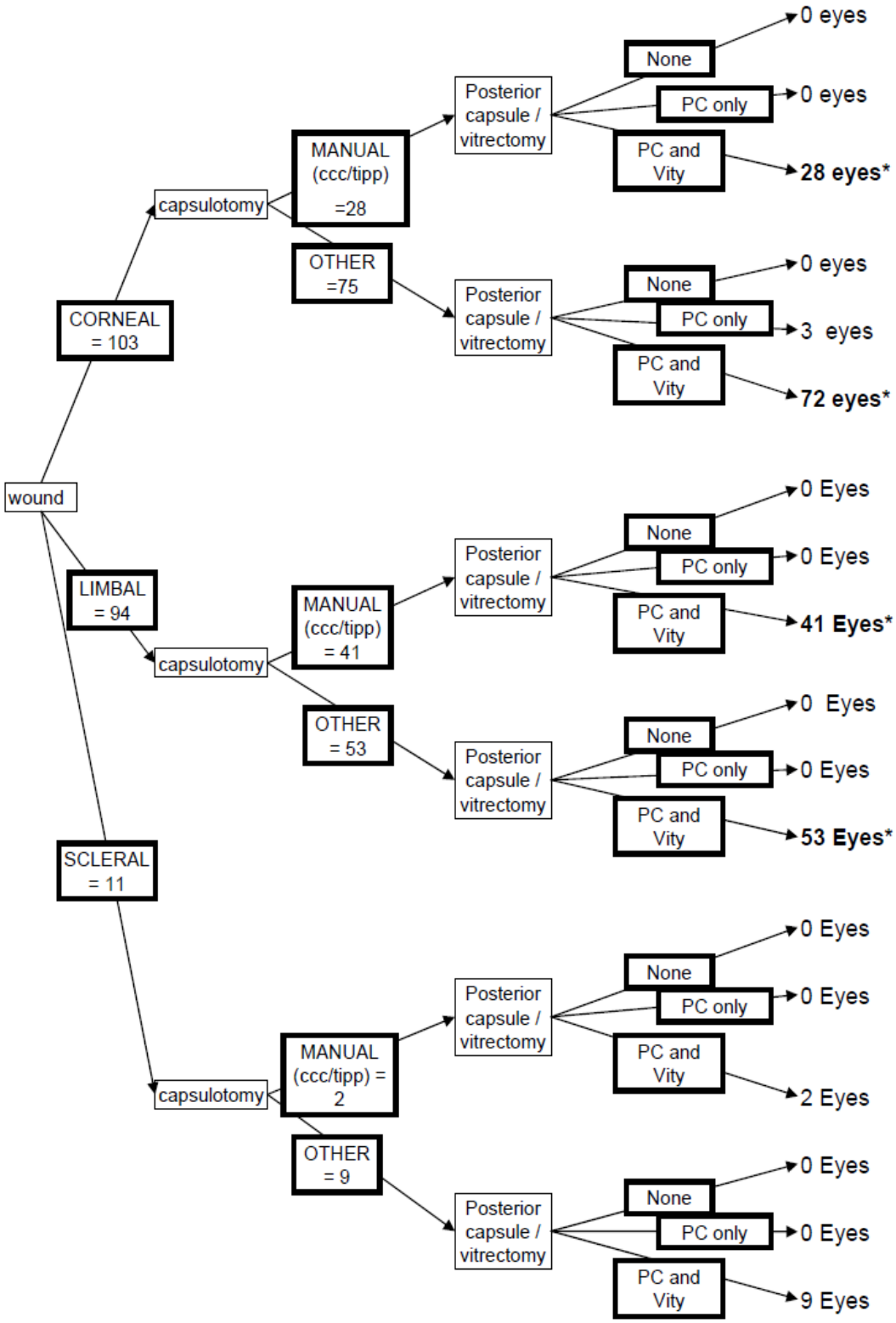
Anterior chamber biometrics of included children

	Bilateral cataract (n=57)	Unilateral cataract (n=52)
Corneal curvature(mm)		
Missing	4	5
Median	7.5	7.5
Range	6.4 - 8.3	6.4 - 8.4
Corneal astigmatism (mm)		
Missing	12	9
Median	0.3	0.3
Range	0 - 1.3	0 - 1.1
Anterior chamber depth (mm)		
Missing	30	29
Median	2.9	3.1
Range	1.5 - 4.5	1.6 - 4.5

Appendix K: Flowcharts of surgical procedures undertaken in operated eyes



Surgical procedures used in children in the IOL group with bilateral or unilateral cataract



Surgical procedures used in children in the APHAKE group with bilateral or unilateral cataract

Appendix L: Description of variables used in statistical analyses of outcome

IRIS PROLAPSE	
IOL	*IOL implantation – binary categorical variable*
Age at surgery	*Age at surgery uncorrected for gestational age, in days*
Gest age at surg	*Age at surgery corrected for gestational age, in days*
Significant ocular abnormality	*Presence of significant ocular anomaly – binary categorical variable*
Persistent fetal vasculature	*Presence of PFV– binary categorical variable*
Axial length	*Pre operative axial length in mm*
Horizontal corneal diameter	*Pre operative horizontal corneal diameter in mm*
AxL <16mm	*Axial length less than 16mm – binary categorical variable*
HCD <9.5mm	*HCD less than 9.5mm– binary categorical variable*
Microphthalmos	*Microphthalmic eye– binary categorical variable*
IO AL diff	*Interocular axial length difference in mm*
Microcornea	*Microcornea– binary categorical variable*
Exp. Surgeon	*Surgeon operating on >10 eyes– binary categorical variable*
Viscous OVD	*Viscosity of OVD used per operatively – ordinal categorical variable*
Right eye	*Laterality of eye = Right – binary categorical variable*
VISUAL OUTCOME	
IOL implant	*IOL implantation*
Age at diagn	*Age at diagnosis in days*
Time from diagnosis to surg	*Time from diagnosis of cataract / referral for cataract to primary surgery, in days*
Age at surgery	*Age at surgery uncorrected for gestational age, in days*
Gest age surg	*Age at surgery corrected for gestational age, in days*
Axial length	*Pre operative axial length in mm*
HCD	*Pre operative horizontal corneal diameter in mm*
Microphthalmos	*Microphthalmic eye*
IO AL diff	*Interocular axial length difference in mm*
Significant ocular abnorm	*Presence of significant ocular anomaly*
Medical disorder / impairment	*Presence of medical disorder or impairment – binary categorical variable*
Pre op strabismus	*Pre-operative constant strabismus – binary categorical variable*
Pre op nystagmus	*Pre-operative manifest nystagmus– binary categorical variable*
Standard surgery	*Standard surgery – binary categorical variable*
Peroperative complication	*Occurrence of per-operative complication – binary categorical variable*
Exp. Surgeon	*Surgeon operating on >10 eyes*
Good conc correctn	*Good concordance with contact lenses / glasses– binary categorical variable*

Post operative VAO	*Post operative visual axis opacity – binary categorical variable*
Post op Glaucoma	*Post operatie glaucoma– binary categorical variable*
Any post op complication	*Any post operative adverse event – binary categorical variable*
Secondary IO procedures	*Secondary (post operative) intraocular procedure– binary categorical variable*
Right eye	*Laterality of eye = Right– binary categorical variable*
Good concordance occl	*Good concordance with occlusion therapy (unilateral cataract) – binary categorical variable*
Cataract asymmetry	*Asymmetric cataract at initial presentation (bilateral cataract) – binary categorical variable*
Time between surg	*Time between first and second eye surgery, in days (bilat cat)*
Visual axis opacity (VAO)	
IOL implantation	*IOL implantation*
Gest age at surgery	*Age at surgery corrected for gestational age, in days*
Age at surgery	*Age at surgery uncorrected for gestational age, in days*
Persistent fetal vasculature	*Presence of PFV– binary categorical variable*
Axial length	*Pre operative axial length in mm*
Horizontal corneal diameter	*Pre operative horizontal corneal diameter in mm*
Exp. Surgeon	*Surgeon operating on >10 eyes– binary categorical variable*
Manual anterior capsulotomy	*Manual anterior capsulorhexis (continuous circular capsulorrhexis or two incision push pull) – binary categorical variable*
Viscous OVD	*Viscosity of OVD used per operatively*
Posterior capsulotomy	*Primary posterior capsulotomy undertaken*
Single piece IOL	*Single piece IOL implanted – binary categorical variable*
IOL in bag	*IOL implanted into capsular bag – binary categorical variable*
Per operative heparin	*Per operative intraocular heparin administration – binary categorical variable*
Per op iris trauma	*Per operative planned or unplanned iris trauma – binary categorical variable*
Per op IOL explant	*IOL explanted per operatively – binary categorical variable*
Post op intensive steroid	*Post operative prescription of intensive topical steroid regimen – binary categorical variable*
Post op systemic steroids	*Post operative prescription of systemic steroids– binary categorical variable*
Post op inflammation	*Post operative inflammatory event – binary categorical variable*
Right eye	*Laterality of eye = Right*
GLAUCOMA	
IOL implantation	*IOL implantation*
Age at surgery	*Age at surgery uncorrected for gestational age, in days*
Gest age at surg	*Age at surgery corrected for gestational age, in days*
Significant ocular abnormality	*Presence of significant ocular anomaly*
Persistent fetal vasculature	*Presence of PFV*

Axial length	*Pre operative axial length in mm*
Horizontal corneal diameter	*Pre operative horizontal corneal diameter in mm*
AxL <16mm	*Axial length less than 16mm*
HCD <9.5mm	*HCD less than 9.5mm*
Microphthalmos	*Microphthalmic eye*
IO AL diff	*Interocular axial length difference in mm*
Microcornea	*Microcornea*
Exp. Surgeon	*Surgeon operating on >10 eyes*
Viscous OVD	*Viscosity of OVD used per operatively*
Posterior capsulotomy	*Primary posterior capsulotomy undertaken*
Per op iris trauma	*Per operative planned or unplanned iris trauma*
Per op IOL explant	*IOL explanted per operatively*
Post op intensive steroid	*Post operative prescription of intensive topical steroid regimen*
Post op systemic steroids	*Post operative prescription of systemic steroids*
Post op inflammation	*Post operative inflammatory event*
Sec IO procedures	*Secondary (post operative) intraocular procedure*
Right eye	*Laterality of eye = Right*
PREDICTION ERROR (discrepancy between planned and actual refractive outcome)	
Gest age at surgery	*Age at surgery corrected for gestational age, in days*
Age at surgery	*Age at surgery uncorrected for gestational age, in days*
K	*Corneal curvature in mm*
K astigmatism	*Corneal astigmatism in mm*
Axial length	*Pre operative axial length in mm*
HCD	*Pre operative horizontal corneal diameter in mm*
AxL <16mm	*Axial length less than 16mm*
AxL <20mm	*Axial length less than 20mm*
HCD <9.5mm	*HCD less than 9.5mm*
IO AL diff	*Interocular axial length difference in mm*
ACDepth	*Anterior chamber depth in mm*
Formula	*IOL power calculation formula used – categorical variable*
IOL power	*Power of implanted IOL – numerical variable*
Ant segment abnormality	*Presence of anterior segmental abnormality*
Viscous OVD	*Viscosity of OVD used per operatively*
Posterior capsulotomy	*Primary posterior capsulotomy undertaken*
Ant vitrectomy	*Primary anterior vitrectomy undertaken*
Wound sutured	*Surgical wound closed with suture*
Exp. Surgeon	*Surgeon operating on >10 eyes*
Single piece IOL	*Single piece IOL implanted*
IOL in bag	*IOL implanted into capsular bag*
Right eye	*Laterality of eye = Right*

Appendix M: Correlations between factors of interest with regards to visual, refractive and adverse outcome

VISUAL OUTCOME _ Bilateral	Age at diagn	Time diagn	Age surg	Gest age surg	AL	HCD	Microphthal	IO AL diff	Signif ocular abnorm	Med disorder / impair	Pre op Strab	Pre op Nystag	Routine surgery	Per-op comp	Exp. Surg	Good Compl correctn	Post op VAO	Post op Glauc	Post-op comp	Sec IO procedures	Cataract asymmetry	Time between surg	Right eye	**IMD**
IOL implant	**-1 p=0.05**	-1.5 p=0.1	**1.01 p=0.01**	**1.01 p=0.01**	**2.1 p=0.001**	**13.9 p=0.02**	**0.08 p=0.001**	1.1 p=0.3	**0.1 p=0.003**	0.5 p=0.5	6.6 p=0.04	3.1 p=0.2	**5.5 =0.01**	**1.3 p=0.7**	1.9 p=0.2	1.6 p=0.1	**2.1 p=0.3**	0.9 p=0.9	1.0 p=0.9	**1.5 p=0.4**	2.9 p=0.1	-0.9 p=0.3	0.9 p=0.3	7.5 p=0.11
Age at diagn		**-0.4 p=0.002**	**0.5 p<0.001**	**0.5 p<0.001**	**0.5 p<0.0001**	**0.3 p=0.04**	**2.1 p=0.4**	0.6 p=0.007	**0.9 p=0.4**	0.2 p=0.8	**4.9 p=0.08**	**4.5 p=0.04**	0.3 p=0.8	-0.3 p=0.8	1.8 p=0.07	2.1 p=0.2	0.6 p=0.6	**1.5 p=0.2**	0.9 p=0.3	1.1 p=0.3	3.1 p=0.08	0.07 p=0.2	0.03 p=0.9	6.4 p=0.17
Time from diagnosis to surg			**0.25 p=0.05**	**0.27 p=0.04**	0.1 p=0.5	0.1 p=0.4	0.03 p=0.8	0.3 p=0.8	0.24 p=0.8	**-1.2 p=0.3**	**7.9 p=0.02**	0.3 p=0.5	1.1 p=0.3	**0.5 p=0.6**	0.9 p=0.3	1.9 p=0.08	1.3 p=0.2	-0.3 p=0.9	1.1 p=0.3	0.9 p=0.3	2.7 p=0.4	-0.9 p=0.3	0.2 p=0.9	11.1 p=0.2
Age at surgery				-	**0.7 p<0.001**	**0.5 p=0.001**	**2.5 p=0.0004**	0.2 p=0.4	**3.3 p=0.0009**	**-1.8 p=0.08**	**9.8 p=0.007**	**2.2 p=0.1**	-0.4 p=0.6	0.8 p=0.4	1.5 p=0.1	0.5 p=0.5	0.8 p=0.4	**1.8 p=0.06**	1.2 p=0.2	**0.8 p=0.4**	**5.2 p=0.02**	**0.2 p=0.08**	0.1 p=0.9	3.8 p=0.4
Gest age surg					**0.7 p<0.001**	**0.5 p<0.001**	**2.3 p=0.02**	0.2 p=0.2	**3.2 p=0.0001**	**-1.8 p=0.07**	**9.5 p=0.009**	**1.8 p=0.2**	-1.2 p=0.3	1.2 p=0.2	1.3 p=0.2	p=0.3	0.4 p=0.7	**1.5 p=0.1**	0.9 p=0.4	0.7 p=0.5	**4.5 p=0.04**	**0.2 p=0.1**	0.1 p=0.9	4.2 p=0.5
Axial length						**0.7 p<0.001**	5.4 p<0.0001	0.1 p=0.3	-	-0.9 p=0.4		**1.5 p=0.2**	**-0.3 p=0.5**	0.8 p=0.4	1.3 p=0.2	0.04 p=0.8	0.8 p=0.4	1.1 p=0.3	1.1 p=0.3	1.4 p=0.2	**8.3 p=0.004**	**0.3 p=0.04**	-0.1 p=0.9	8.9 p=0.07
HCD							3.5 p=0.004	0.1 p=0.7	-	0.2 p=0.8	0.3 p=0.6	1.6 p=0.2	**0.6 p=0.5**	0.01 p=0.9	0.1 p=0.8	0.4 p=0.6	0.8 p=0.4	0.9 p=0.3	1.8 p=0.8	-0.5 p=0.6	0.2 p=0.7	-0.6 p=0.7	-0.1 p=0.99	3.7 p=0.4
Microphthalmos								0.7 p=0.4	-	0.5 p=0.3	2 p=0.03	0.75 p=0.6	0.57 p=0.3	1.2 p=0.9	0.9 p=0.9	0.9 p=0.9	1.2 p=0.8	0.9 p=0.9	1.3 p=0.6	0.4 p=0.9	0.3 p=0.1	2.2 p=0.3	0.8 p=0.1	4.1 p=0.4
IO AL diff									0.6 p=0.6	0.8 p=0.2	2.3 p=0.3	0.5 p=0.4	**-2.7 p=0.006**	1.0 p=0.3	2.8 p=0.005	0.2 p=0.7	1.8 p=0.07	-0.5 p=0.6	1.0 p=0.3	1.7 p=0.09	0.1 p=0.7	0.06 p=0.7	-0.9 p=0.4	0.1 p=0.9
Significant ocular abnorm										**2.1 p=0.1**	0.8 p=0.9	0.9 p=0.8	1.1 p=0.9	1.3 p=0.6	0.9 p=0.9	0.2 p=0.5	0.9 p=0.9	3.7 p=0.06	1.5 p=0.3	0.9 p=0.8	0.4 p=0.3	1.0 p=0.3	1.0 p=0.8	2.7 p=0.6
Medical disorder / impairment											1.6 p=0.04	2.1 p=0.3	1.8 p=0.3	**0.5 p=0.3**	0.6 p=0.5	1.2 p=0.9	**0.3 p=0.1**	0.3 p=0.3	**0.9 p=0.8**	**0.3 p=0.09**	0.6 p=0.6	1.006 p=0.07	0.9 p=0.3	4.4 p=0.4
Pre op strabismus												**16.3 p<0.0001**	**6.6 p=0.2**	**2.4 p=0.3**	1.9 p=0.4	**4.5 p=0.1**	1.8 p=0.4	1.6 p=0.5	4.7 p=0.09	1.7 p=0.4	**17.1 p<0.0001**	0.1 p=0.9	-1.36 p=0.2	9.7 p=0.2
Pre op nystagmus													1.4 p=0.2	0.03 p=0.9	0.02 p=0.9	11.1 p=0.001	1.1 p=0.3	0.2 p=0.7	0.1 p=0.7	2.9 p=0.09	1.6 p=0.2	-0.95 p=0.3	0.02 p=0.9	4.3 p=0.4
Routine surgery														2.2 p=0.1	**5.8 p<0.0001**	4.5 p=0.2	1.0 p=0.9	1.1 p=0.9	1.3 p=0.6	1.1 p=0.8	1.1 p=0.9	1.2 p=0.2	1.0 p=0.9	5.7 p=0.2
Peroperative complication															1.1 p=0.9	1.1 p=0.9	2.1 p=0.2	0.8 p=0.7	1.4 p=0.5	2.0 p=0.2	0.7 p=0.7	1.3 p=0.2	0.8 p=0.7	5.1 p=0.3
Exp. Surgeon																1.6 p=0.6	1.4 p=0.4	1.2 p=0.8	1.5 p=0.3	0.9 p=0.8	0.4 p=0.2	**2.6 p=0.02**	0.9 p=0.9	**16 p=0.003**
Good Compl correctn																	2.6 p=0.1	1.2 p=0.3	0.02 p=0.9	2.7 p=0.1	0.05 p=0.8	-1.7 p=0.1	0.07 p=0.9	6.4 p=0.2
Post operative VAO																		0.8 p=0.7	-	-	0.7 p=0.6	-1.1 p=0.3	1.7 p=0.2	3.1 p=0.5
Post op Glaucoma																			-	-	0.4 p=0.4	-0.4 p=0.7	1.2 p=0.7	3.1 p=0.5
Any post op complication																				-	**0.4 p=0.1**	-1.1 p=0.3	0.8 p=0.8	5.1 p=0.3
Secondary IO procedures																					0.6 p=0.6	-0.04 p=0.09	1.8 p=0.1	8.9 p=0.3
Cataract asymmetry																						**1.7 p=0.1**	0.04 p=0.8	10.1 p=0.4
Time between surg																							0.0 p=0.9	8.2 p=0.08
Right eye																								0.04 p=1

VISUAL OUTCOME _ Unilateral	Age at diagn	Time diagn	Age surg	Gest age surg	AL	HCD	Microphthal	IO AL diff	Signif ocular abnorm	Med disorder / impair	Pre op Strab	Pre op Nystag	Routine surgery	Per-op comp	Exp. Surg	Good Compl occl	Good Compl correctn	Post op VAO	Post op Glaucoma	Post-op complication	Secondary IO procedures	Right eye	**IMD**
IOL implant	**2.2 p=0.03**	0.4 p=0.7	**-1 p=0.1**	**1.002 p=0.13**	**1.3 p=0.2**	**12.1 p=0.02**	0.8 p=0.8	**1.5 p=0.3**	**0.2 p=0.02**	0.3 p=0.6	0.8 p=0.7	2.6 p=0.1	**5.5 p=0.001**	2.2 p=0.3	2.2 p=0.2	1.3 p=0.2	1.1 p=0.3	2.6 p=0.06	0.6 p=0.5	1.0 p=0.9	1.6 p=0.5	1.2 p=0.8	0.8 p=0.94
Age at diagn		**0.2 p=0.2**	**0.9 p<0.0001**	**0.9 p<0.0001**	**0.7 p<0.0001**	**0.4 p=0.02**	**2.6 p=0.01**	**0.5 p=0.006**	0.9 p=0.4	0.3 p=0.7	**20.7 p=0.01**	2.0 p=0.4	-2.8 p=0.05	0.7 p=0.5	1.2 p=0.2	4.4 p=0.1	0.9 p=0.3	**2.8 p=0.006**	0.8 p=0.5	**0.4 p=0.7**	**2.6 p=0.08**	0.3 p=0.8	0.8 p=0.9
Time from diagnosis to surg			**0.5 p<0.001**	**0.6 p=0.001**	**0.4 p=0.01**	**0.3 p=0.09**	0.1 p=0.5	1.7 p=0.08	-0.6 p=0.6	0.04 p=0.97	**4.7 p=0.9**	1.9 p=0.4	**0.9 p=0.3**	-0.01 p=0.9	1.5 p=0.1	**6.8 p=0.03**	3.0 p=0.08	**2.3 p=0.03**	1.1 p=0.3	**2.7 p=0.008**	**2.6 p=0.008**	-0.3 p=0.8	4.2 p=0.4
Age at surgery				-	**0.6 p<0.0001**	**0.4 p=0.04**	**2.5 p=0.01**	0.4 p=0.05	0.5 p=0.3	0.2 p=0.8	**17.8 p=0.001**	2.1 p=0.3	**-2.7 p=0.007**	0.9 p=0.4	2.3 p=0.02	**7.5 p=0.02**	0.7 p=0.4	**3.2 p=0.002**	0.9 p=0.4	**1.1 p=0.2**	**3.2 p=0.001**	-0.05 p=0.9	2.7 p=0.6
Gest age surg					**0.6 p<0.0001**	**0.4 p=0.04**	**2.9 p=0.008**	0.4 p=0.08	0.7 p=0.4	-0.2 p=0.9	**17.5 p=0.002**	2.2 p=0.3	-2.6 p=0.008	-0.3 p=0.7	2.0 p=0.05	**9.3 p=0.01**	0.6 p=0.4	**3.1 p=0.002**	0.6 p=0.5	**1.1 p=0.3**	**3.1 p=0.002**	-0.1 p=0.9	2.1 p=0.7
Axial length						**0.6 p=0.001**	4.8 p<0.0001	**0.8 p<0.0001**	-	0.2 p=0.9	**12.1 p=0.002**	1.5 p=0.5	**-1.7 p=0.08**	1.1 p=0.3	2.5 p=0.01	0.9 p=0.6	1.6 p=0.2	**3.1 p=0.02**	2.8 p=0.005	1.7 p=0.09	**3.6 p=0.003**	-0.3 p=0.7	0.7 p=0.9
HCD							1 p=0.3	0.3 p=0.3	-	-0.4 p=0.7	**1.9 p=0.4**	1.3 p=0.9	**-2.2 p=0.03**	0.1 p=0.9	0.8 p=0.5	0.2 p=0.9	0.1 p=0.8	1.2 p=0.3	1.5 p=0.1	**0.7 p=0.5**	1.8 p=0.07	1.0 p=0.3	4.7 p=0.3
Microphthalmos								**3.5 0.04**	-	0.4 p=0.4	1.3 p=0.7	1.4 p=0.5	**0.3 p=0.1**	1.2 p=0.8	5.5 p=0.02	2.6 p=0.3	0.7 p=0.7	**4 p=0.06**	0.01 p=0.9	**2.6 p=0.2**	**4.9 p=0.03**	1.0 p=0.9	2.2 p=0.7
IO AL diff									-0.1 p=0.9	-0.6 p=0.5	1.9 p=0.4	2.1 p=0.1	-0.9 p=0.3	1.1 p=0.3	1.2 p=0.2	0.3 p=0.9	0.4 p=0.8	**1.7 p=0.07**	**2.2 p=0.8**	**0.2 p=0.8**	**2.4 p=0.02**	**-1.4 p=0.2**	1.7 p=0.8
Significant ocular abnorm										0.4 p=0.5	1.2 p=0.9	2.5 p=0.3	0.6 p=0.4	0.6 p=0.5	3.2 p=0.09	0.2 p=0.3	0.2 p=0.1	1.2 p=0.8	6.6 p=0.1	1.1 p=0.7	1.4 p=0.6	3.8 p=0.04	4.8 p=0.3
Medical disorder / impairment											2.7 p=0.3	**1.5 p=0.3**	2.9 p=0.09	0.9 p0.9	1.7 p=0.6	0.7 p=0.6	2.7 p=0.5	0.5 p=0.5	-1.2 p=0.1	1.2 p=0.9	0.4 p=0.5	0.8 p=0.8	2.9 p=0.6
Preop strabismus												6.6 p=0.2	6.2 p=0.05	10.1 p=0.007	0.4 p=0.8	9.0 p=0.06	5.5 p=0.06	9.8 p=0.08	1.2 p=0.6	0.9 p=0.6	8.3 p=0.02	0.6 p=0.7	5.8 p=0.7
Pre op nystagmus													0.8 p=0.7	2.0 p=0.4	3.4 p=0.2	5.6 p=0.2	6.8 p=0.03	4.3 p=0.1	0.7 p=0.7	1.3 p=0.5	4.4 p=0.4	1.9 p=0.4	6.6 p=0.6
Routine surgery														1.5 p=0.6	**2.9 p=0.1**	5.2 p=0.2	4.7 p=0.2	0.7 p=0.6	0.4 p=0.3	0.9 p=0.9	0.6 p=0.4	1.5 p=0.5	3.1 p=0.6
Peroperative complication															3.6 p=0.1	0.2 p=0.2	0.4 p=0.5	2.8 p=0.2	5.2 p=0.1	2.5 p=0.3	2.5 p=0.6	0.7 p=0.7	2.3 p=0.7
Exp. Surgeon																0.5 p=0.6	3.3 p=0.3	4.6 p=0.04	2.4 p=0.5	**4.8 p=0.03**	5.3 p=0.02	1.4 p=0.6	1.7 p=0.8
Good concordance occlusion																	6.0 p=0.05	0.04 p=0.9	3.4 p=0.2	4.2 p=0.1	0.1 p=0.9	1.4 p=0.5	1.0 p=0.9
Good concordance correctn																		1.3 p=0.2	1.2 p=0.3	0.01 p=0.9	1.6 p=0.2	0.005 p=0.9	7.4 p=0.5
Post operative VAO																			2.5 p=0.3	-	-	1.5 p=0.5	2.5 p=0.6
Post op Glaucoma																				-	-	1.1 p=0.8	5.2 p=0.3
Any post op complcn																					-	1.2 p=0.8	4.7 p=0.3
Secondary intraocular procedures																						1.2 p=0.8	27.3 p=0.04
Right eye																							2.3 p=0.7

IRIS PROLAPSE - Bilateral	**Age at surgery**	**Gest age at surg**	**Signif ocular abnorm**	**PFV**	**Axial length**	**HCD**	**AxL <16mm**	**HCD <9.5mm**	**Microphthal mos**	**IO AL diff**	**Microcornea**	**Exp. surgeon**	**Viscous OVD**	**Right eye**
IOL	**4.4 p<0.001**	**4.5 p<0.001**	**-4.18 p<0.001**	-0.42 p=0.3	**8.51 p<0.001**	**8.82 p<0.001**	**-3.58 p<0.001**	**8.38 p=0.004**	**-3.52 p<0.001**	1.0 p=0.3	**-2.38 p=0.02**	0.68 p=0.09	**2.46 p=0.01**	-0.26 p=0.80
Age at surgery		-	**-3.71 p<0.001**	1.8 p=0.07	**0.74 p<0.001**	**0.50 p<0.001**	**-4.97 p<0.001**	**-2.18 p=0.03**	**-4.18 p0.001**	0.03 p=0.7	**-3.77 p=0.001**	-0.11 p=0.9	4.55 p=0.17	0.05 p=0.96
Gest age at surg			**-3.46 p<0.005**	1.65 p=0.19	**0.70 p<0.001**	**0.46 p<0.001**	**-4.66 p<0.001**	**-2.16 p=0.03**	**-3.9 p<0.001**	0.03 p=0.8	**-3.23 p=0.04**	0.33 p=0.7	6.01 p=0.16	0.04 p=0.96
Significant ocular abnormality				-	-	-	-	-	-	-0.8 p=0.42	-	-0.13 p=0.9	0.51 p=0.66	-0.57 p=0.57
Persistent fetal vasculature					1.05 p=0.29	-0.8 p=0.36	0.00 p=0.99	1.38 p=0.17	0.78 p=0.43	-0.56 p=0.57	0.87 p=0.38	-1.09 p=0.27	**3.38 p=0.01**	-0.90 p=0.37
Axial length						**0.74 p<0.001**	-	-	-	0.13 p=0.16	-	-0.37 p=0.71	1.36 p=0.7	-0.29 p=0.76
Horizontal corneal diameter							-	-	-	0.07 p=0.07	-	0.55 p=0.59	4.70 p=0.19	-0.07 p=0.94
AxL <16mm								-	-	-1.74 p=0.08	-	0.56 p=0.58	-1.09 p=0.28	-0.83 p=0.41
HCD <9.5mm									-	**-2.32 p=0.02**	-	-0.55 p=0.59	1.27 p=0.20	-1.28 p=0.20
Microphthalmos										-1.11 p=0.27	-	0.04 p=0.9	**-20.32 p<0.001**	**-2.11 p=0.04**
IO AL diff											-0.28 p=0.78	-0.23 p=0.82	3.96 p=0.70	1.2 p=0.22
Microcornea												0.65 p=0.52	-0.66 p=0.51	-1.21 p=0.23
Exp. Surgeon													0.84 p=0.4	-0.13 p=0.89
Viscous OVD														0.0 p=0.99

IRIS PROLAPSE - Unilateral	**Age at surgery**	**Gest age at surg**	**Signif ocular abnorm**	**PFV**	**Axial length**	**HCD**	**AxL <16mm**	**HCD <9.5mm**	**Microphthalmos**	**IO AL diff**	**Microcornea**	**Exp. surgeon**	**Viscous OVD**	**Right eye**
IOL	**3.1 p<0.002**	**3.4 p<0.001**	**-3.97 p<0.001**	**-3.27 p=0.001**	**5.86 p<0.001**	**4.50 p<0.001**	-2.01 p=0.08	-	-1.64 p=0.1	**2.79 p=0.005**	-0.94 p=0.21	1.63 p=0.09	1.8 p=0.07	-0.07 p=0.94
Age at surgery		-	-1.51 p=0.54	-0.61 p=0.54	**0.67 p<0.001**	**0.58 p<0.001**	-0.75 p=0.46	-1.16 p=0.25	**-3.26 p=0.001**	0.44 p=0.99	-1.07 p=0.2	-0.95 p=0.34	7.90 p=0.06	0.13 p=0.47
Gest age at surg			-1.20 p=0.23	-0.50 p=0.6	**0.67 p<0.001**	**0.56 p<0.001**	-0.70 p=0.48	-1.16 p=0.25	**-3.21 p<0.001**	0.42 p=0.99	-0.85 p=0.39	-0.79 p=0.4	6.11 p=0.1	0.77 p=0.44
Significant ocular abnormality				-	-	-	-	-	-	1.27 p=0.2	-	0.84 p=0.40	0.97 p=0.33	1.09 p=0.28
Persistent fetal vasculature					-0.80 p=0.42	-0.97 p=0.33	-0.50 p=0.62	2.06 p=0.15	-0.37 p=0.71	-1.12 p=0.26	0.57 p=0.58	0.56 p=0.58	1.41 p=0.16	0.95 p=0.34
Axial length						**0.67 p<0.001**	-	-	-	**0.75 p<0.001**	-	-1.52 p=0.13	2.43 p=0.5	0.92 p=0.36
Horizontal corneal diameter							-	-	-	0.46 p=0.15	-	-0.56 p=0.57	**1.74 p=0.08**	-0.53 p=0.60
AxL <16mm								-	-	**-3.23 p=0.001**	-	0.93 p=0.35	-0.50 p=0.62	-0.03 p=0.97
HCD <9.5mm									-	-1.70 p=0.09	-	-0.92 p=0.36	1.55 p=0.12	2.06 p=0.15
Microphthalmos										**-4.97 p<0.001**	-	1.88 p=0.06	0.03 p=0.5	-0.13 p=0.89
IO AL diff											-1.43 p=0.15	1.11 p=0.27	1.48 p=0.69	**1.97 p=0.05**
Microcornea												-1.21 p=0.23	-1.61 p=0.1	-0.57 p=0.57
Exp. Surgeon													**2.17 p=0.03**	1.72 p=0.09
Viscous OVD														0.0 p=0.99

GLAUCOMA - Bilateral	Age at surgery	Gest age	Signif oc. abnorm	PFV	Axial length	HCD	AxL <16mm	HCD <9.5mm	Microphthalmos	IO AL diff	Microcornea	Exp. Surg	Viscous OVD	Post caps'my	Iris trauma	IOL explant	Intensiv steroid	System steroids	Post op inflamm	Sec IO procedures	Right eye
IOL implantation	**3.2 p=0.001**	**2.99 p=0.003**	**-3.7 p<0.0001**	-0.62 p=0.5	**-4.8 p<0.0001**	**-4.9 p<0.001**	**-3.2 p=0.001**	16.1 p<0.001	**-3.01 p=0.001**	-0.1 p=0.9	**-2.6 p<0.001**	1.09 p=0.3	**1.1 p=0.13**	2.4 p=0.1	**-1.05 p=0.3**	-	2.3 p=0.07	1.4 p=0.7	**3.1 p=0.02**	**2.9 p=0.01**	-0.99 p=0.3
Age at surgery		-	**-2.7 p=0.007**	-1.3 p=0.2	**0.8 p<0.001**	**0.5 p<0.001**	**4.3 p<0.001**	**1.5 p=0.1**	**3.3 p=0.001**	0.04 p=0.7	**2.7 p=0.005**	0.6 p=0.5	4.1 p=0.2	1.7 p=0.08	**-0.9 p=0.3**	-1.4 p=0.	-0.3 p=0.7	-1.1 p=0.3	**2 p=0.04**	0.6 p=0.8	0.1 p=0.9
Gest age at surg			**2.6 p=0.01**	-1.1 p=0.3	**0.8 p<0.001**	**0.4 p<0.001**	**4.2 p=0.0006**	**1.4 p=0.1**	**3.4 p=0.002**	0.05 p=0.6	**2.4 p=0.01**	0.5 p=0.6	4.2 p=0.2	1.7 p=0.1	**2.4 p=0.01**	-0.8 p=0.4	-0.6 p=0.5	-0.8 p=0.4	1.4 p=0.1	0.04 p=0.9	1.1 p=0.9
Significant ocular abnormality				-	-	-	-	-	-	0.4 p=0.6	-	0.9 p=0.90	0.06 p=0.9	0.9 p=0.3	**2.3 p=0.1**	5.1 p=0.3	0.7 p=0.4	0.4 p=0.3	0.6 p=0.3	0.5 p=0.4	0.03 p=0.9
Persistent fetal vasculature					-0.3 p=0.7	2.5 p=0.02	1.4 p=0.8	10.8 p=0.03	1.3 p=0.8	0.03 p=0.9	3.5 p=0.2	0.3 p=0.1	**3.9 p=0.3**	0.2 p=0.7	1.9 p=0.5	0.2 p=0.7	0.9 p=0.9	1.7 p=0.6	1.9 p=0.2	1.0 p=0.9	1.0 p=0.3
Axial length						**0.7 p<0.001**	-	-	-	0.07 p=0.5	-	0.7 p=0.4	1.7 p=0.6	1.3 p=0.2	**3 p=0.002**	-0.7 p=0.5	0.1 p=0.9	0.2 p=0.9	-0.2 p=0.8	0.2 p=0.8	-0.1 p=0.9
Horizontal corneal diameter							-	-	-	0.003 p=0.9	-	0.04 p=0.9	11.0 p=0.1	1.8 p=0.07	**2.3 p=0.02**	0.8 p=0.4	-1 p=0.3	-0.7 p=0.5	-1.7 p=0.09	-1.4 p=0.2	-0.02 p=0.9
AxL <16mm								-	-	0.9 p=0.5	-	2.2 p=0.2	0.3 p=0.3	3.4 p=0.3	**3.4 p=0.04**	5.3 p=0.02	**0.9 p=0.9**	0.6 p=0.6	1.0 p=0.9	0.7 p=0.6	0.9 p=0.6
HCD <9.5mm									-	**-2.2 p=0.02**	-	1.4 p=0.7	2.8 p=0.4	0.2 p=0.6	**3.7 p=0.09**	-	0.2 p=0.2	1.9 p=0.5	0.9 p=0.9	0.5 p=0.3	0.9 p=0.4
Microphthalmos										1.0 p=0.3	-	0.8 p=0.7	**5.9 p=0.1**	2.4 p=0.6	**5.8 p=0.03**	0.4 p=0.5	0.9 p=0.8	1.2 p=0.8	1.3 p=0.6	1.8 p=0.3	0.8 p=0.1
IO AL diff											-0.3 p=0.7	0.5 p=0.6	1.5 p=0.7	-0.9 p=0.3	-0.5 p=0.6	0.2 p=0.8	0.1 p=0.8	0.4 p=0.6	0.5 p=0.6	1.1 p=0.3	-1.5 p=0.1
Microcornea												1.5 p=0.4	0.7 p=0.8	1.1 p=0.3	**2.7 p=0.06**	0.06 p=0.8	0.7 p=0.6	0.8 p=0.7	0.6 p=0.4	0.4 p=01	0.9 p=0.7
Exp. Surgeon													1.6 p=0.6	1.9 p=0.2	3.5 p=0.02	0.3 p=0.5	**4.4 p=0.01**	0.3 p=0.1	1.2 p=0.7	0.7 p=0.5	1.0 p=0.9
Viscous OVD														**11.4 p=0.1**	2 p=0.6	0.8 p=0.8	2 p=0.6	**6.5 p=0.09**	0.6 p=0.7	1.2 p=0.7	0.2 p=0.9
Posterior capsulotomy															0.5 p=0.5	0.08 p=0.8	1.2 p=0.3	0.2 p=0.6	2.5 p=0.1	0.6 p=0.4	2.0 p=0.2
Per op iris trauma																2.5 p=0.5	1.1 p=0.8	1.3 p=0.7	1.7 p=0.4	1.1 p=0.9	1.2 p=0.9
Per op IOL explant																	0.5 p=0.5	0.4 p=0.5	0.4 p=0.4	1.6 p=0.2	0.4 p=0.5
Post op intensive steroid																		0.2 p=0.1	1.4 p=0.5	1.5 p=0.3	1.1 p=0.2
Post op systemic steroids																			1.3 p=0.8	3.3 p=0.04	1.1 p=0.3
Post op inflammation																				**5.4 p=0.001**	**2.1 p=0.09**
Sec IO procedures																					1.1 p=0.8

GLAUCOMA - Unilateral	Age at surgery	Gest age	Signif oc. abnorm	PFV	Axial length	HCD	AxL <16mm	HCD <9.5mm	Microphthalmos	IO AL diff	Microcornea	Exp. Surg	Viscous OVD	Iris trauma	IOL explant	Intensiv steroid	System steroids	Post op inflamm	Sec IO procedures	Right eye
IOL implantation	**1.9 p=0.06**	**1.9 p=0.06**	**-3.4 p=0.001**	**-2.9 p=0.004**	**-1.8 p=0.08**	**-3.6 p=0.0003**	-1.8 p=0.07	-	-0.6 p=0.5	**-0.6 p=0.6**	-2.7 p=0.007	0.8 p=0.4	1.9 p=0.1	**-2.2 p=0.03**	-	-0.1 p=0.9	0.2 p=0.8	1.2 p=0.7	0.9 p=0.4	-0.2 p=0.8
Age at surgery		-	1.1 p=0.3	0.008 p=0.9	**0.6 p<0.001**	**0.3 p=0.04**	0.2 p=0.8	-0.2 p=0.8	**2.6 p=0.01**	**0.3 p=0.06**	0.03 p=0.9	1.8 p=0.07	2.9 p=0.4	0.7 p=0.5	0.9 p=0.4	0.9 p=0.4	-1.4 p=0.2	1.4 p=0.8	**3.5 p=0.0004**	-0.2 p=0.8
Gest age at surg			0.8 p=0.4	-0.2 p=0.8	**0.6 p<0.001**	**0.3 p=0.06**	-0.02 p=0.9	-0.1 p=0.9	**2.3 p=0.02**	**0.3 p=0.1**	-0.2 p=0.9	1.6 p=0.1	1.9 p=0.6	0.5 p=0.6	1.0 p=0.3	0.7 p=0.5	-1.4 p=0.2	1.3 p=0.2	**3.5 p=0.0005**	-0.4 p=0.7
Significant ocular abnormality				-	-	-	-	-	-	0.2 p=0.8	-	2.3 p=0.2	1.1 p=0.3	**5.6 p=0.02**	1.9 p=0.2	1.5 p=0.5	0.6 p=0.6	1.5 p=0.5	1.5 p=0.5	1.9 p=0.9
Persistent fetal vasculature					0.5 p=0.6	1.6 p=0.1	1.5 p=0.7	1.0 p=0.3	1.03 p=0.9	0.6 p=0.5	2 p=0.3	1.7 p=0.4	3 p=0.4	2.2 p=0.2	2.7 p=0.1	1.5 p=0.5	2.9 p=0.2	1.04 p=0.9	0.7 p=0.6	0.7 p=0.5
Axial length						**0.6 p<0.001**	-	-	-	**0.7 p<0.001**	-	2.6 p=0.009	0.5 p=0.9	**1.8 p=0.07**	1.4 p=0.2	**1.8 p=0.08**	**-2.1 p=0.04**	0.8 p=0.4	**3.2 p=0.002**	0.02 p=0.9
Horizontal corneal diameter							-	-	-	0.3 p=0.2	-	0.09 p=0.9	**4.5 p=0.2**	**1.1 p=0.3**	-0.1 p=0.9	-0.2 p=0.8	-0.1 p=0.9	0.1 p=0.9	0.9 p=0.4	1.2 p=0.2
AxL <16mm								-	-	**2.8 p=0.005**	-	2.3 p=0.1	3 p=0.4	**18.5 p=0.02**	0.03 p=0.8	0.7 p=0.8	0.4 p=0.5	0.8 p=0.8	**4.2 p=0.04**	3.1 p=0.3
HCD <9.5mm									-	1.7 p=0.1	-	0.2 p=0.6	0.5 p=0.9	**3.1 p=0.08**	**-**	1.7 p=0.2	0.08 p=0.8	0.3 p=0.5	1.03 p=0.3	1.0 p=0.3
Microphthalmos										**4.1 p<0.001**	-	3.9 p=0.04	2 p=0.7	1.6 p=0.5	0.9 p=0.4	**4.5 p=0.04**	**5.9 p=0.02**	2.4 p=0.2	**3.2 p=0.06**	1.1 p=0.9
IO AL diff											0.3 p=0.8	0.9 p=0.3	0.2 p=0.9	**1.6 p=0.09**	1.1 p=0.3	0.6 p=0.5	-1.4 p=0.2	0.2 p=0.8	**2.8 p=0.02**	**-1.5 p=0.1**
Microcornea												0.5 p=0.4	6.3 p=0.1	**1.6 p=0.5**	0.2 p=0.7	1.7 p=0.4	1.0 p=0.9	0.4 p=0.2	0.5 p=0.3	0.8 p=0.7
Exp. Surgeon													**7.0 p=0.1**	4 p=0.1	0.5 p=0.5	**4.2 p=0.05**	**10.7 p=0.001**	3.7 p=0.06	3.2 p=0.04	2.3 p=0.1
Viscous OVD														2.4 p=0.5	0.4 p=0.9	**0.8 p=0.9**	0.3 p=0.4	0.2 p=0.3	3 p=0.4	6.3 p=0.1
Per op iris trauma															0.1 p=0.7	4.4 p=0.03	0.8 p=0.8	1.4 p=0.6	1.7 p=0.4	1.1 p=0.9
Per op IOL explant																2.3 p=0.1	0.1 p=0.7	2.1 p=0.2	0.9 p=0.4	1.1 p=0.3
Post op intensive steroid																	0.4 p=0.4	2.2 p=0.2	0.8 p=0.7	2.1 p=0.2
Post op systemic steroids																		0.5 p=0.5	0.5 p=0.4	0.5 p=0.4
Post op inflammation																			**4.9 p=0.02**	3.2 p=0.06
Sec IO procedures																				0.9 p=0.8

VAO - Bilateral	Manual ant cap	Single piece IOL	IOL in bag	Per op heparin
IOL implantation	**10.7 p<0.001**	-	-	2.3 p=0.2
Gest age at surgery	1.002 p=0.11	1.001 p=0.6	1.002 p=0.5	1 p=0.3
Age at surgery	**1.00 p=0.1**	1.0001 p=0.5	1.002 p=0.5	1 p=0.3
Persistent fetal vasculature	0.9 p=0.9	2.7 p=0.5	**0.04 p=0.05**	1.8 p=0.2
Axial length	**-2.3 p=0.03**	0.6 p=0.7	-0.7 p=0.9	0.06 p=0.9
Horizontal corneal diameter	**-1.4 p=0.02**	**-1.9 p=0.06**	**-2.5 p=0.05**	-1.5 p=0.5
Exp. Surgeon	**3.4 p=0.003**	0.4 p=0.2	**7.8 p=0.005**	2.2 p=0.2
Viscous OVD	**5.8 p=0.05**	**8.7 p=0.03**	1.4 p=0.7	**23.3 p<0.001**
Posterior capsulotomy	1.8 p=0.2	0.8 p=0.4	0.1 p=0.7	-
Single piece IOL	**24 p<0.0001**			
IOL in bag	1.3 p=0.3	**2.1 p=0.1**		
Per operative heparin	0.4 p=0.5	1.1 p=0.3	0.01 p=0.99	
Per op iris trauma	1.04 p=0.9	1.3 p=0.8	1.8 p=0.2	1.8 p=0.4
Per op IOL explant	0.7 p=0.4	**-**	**-**	0.7 p=0.4
Post op intensive steroid	**2.3 p=0.05**	1.6 p=0.5	4.5 p=0.04	2.9 p=0.09
Post op systemic steroids	0.8 p=0.7	**4.8 p=0.1**	0.8 p=0.4	2.1 p=0.4
Post op inflammation	1.8 p=0.3	1.9 p=0.4	1.4 p=0.2	2.2 p=0.11
Right eye	0.9 p=0.6	1.0 p=0.3	0.6 p=0.3	1.0 p=0.9

VAO - Unilateral	Manual ant cap	Single piece IOL	IOL in bag	Per op heparin
IOL implantation	**6.1 p=0.002**	-	-	0.6 p=0.6
Gest age at surgery	**1.005 p=0.02**	**0.99 p=0.05**	0.99 p=0.9	1.002 p=0.4
Age at surgery	**1.004 p=0.02**	**0.99 p=0.05**	0.99 p=0.9	1.002 p=0.3
Persistent fetal vasculature	0.6 p=0.4	0.4 p=0.3	**0.2 p=0.1**	0.4 p=0.5
Axial length	**-1.6 p=0.1**	**3.2 p=0.001**	0.3 p=0.8	-0.08 p=0.9
Horizontal corneal diameter	**-2 p=0.04**	**2.2 p=0.03**	-0.9 p=0.3	-0.9 p=0.3
Exp. Surgeon	**2.5 p=0.1**	1.7 p=0.7	1.3 p=0.8	0.6 p=0.6
Viscous OVD	**8.8 p=0.03**	0.25 p=0.4	1.2 p=0.1	2.5 p=0.5
Single piece IOL	0.8 p=0.4			
IOL in bag	1.1 p=0.3	0.2 p=0.7		
Per operative heparin	0.3 p=0.6	0.002 p=0.9	0.3 p=0.6	
Per op iris trauma	**0.3 p=0.1**	1.1 p=0.9	0.7 p=0.4	4.4 p=0.2
Per op IOL explant	0.3 p=0.6	**-**	**-**	0.7 p=0.4
Post op intensive steroid	0.7 p=0.5	1.1 p=0.9	**2.6 p=0.1**	**7.8 p=0.09**
Post op systemic steroids	0.6 p=0.5	1.1 p=0.9	**0.1 p=0.05**	3.3 p=0.3
Post op inflammation	1.5 p=0.5	1.4 p=0.6	0.3 p=0.2	0.9 p=0.9
Right eye	1.6 p=0.4	**2.9 p=0.1**	**0.2 p=0.1**	1.1 p=0.9

PREDICTION ERROR – Bilateral	Age at surg	K	K astig	Axial length	HCD	AxL <16 mm	AxL <20 mm	HCD <9.5 mm	IO AL diff	ACD	Forml	IOL power	Ant seg abnorm	Visc OVD	Posterior caps	Ant vitrect	Wnd sutured	Exp. Surg	Single piece IOL	IOL in bag	Right eye
Gest age at surgery	-	**0.48 p<0.001**	0.07 p=0.54	**0.70 p<0.001**	**0.46 p<0.001**	**-4.66 p<0.001**	**-4.92 p<0.001**	**-2.16 p=0.03**	0.03 p=0.8	0.25 p=0.09	1.78 p=0.8	**-0.39 p=0.01**	-0.42 p=0.67	6.01 p=0.16	1.36 p=0.17	-1.86 p=0.07	-0.009 p=0.8	0.33 p=0.7	-0.84 p=0.6	1.25 p=0.21	0.05 p=0.96
Age at surgery		**0.55 p<0.001**	0.1 p=0.37	**0.74 p<0.001**	**0.50 p<0.001**	**-4.97 p<0.001**	**-4.98 p<0.001**	**-2.18 p=0.03**	0.03 p=0.7	0.25 p=0.08	1.71 p=0.8	**-0.35 p=0.01**	-0.45 p=0.6	4.55 p=0.17	1.29 p=0.20	1.5 p=0.1	-0.05 p=0.8	-0.11 p=0.9	-0.59 p=0.6	1.49 p=0.3	0.04 p=0.96
K			0.02 p=0.6	**0.71 p<0.001**	**0.66 p<0.001**	**-3.57 p<0.001**	**-4.32 p<0.001**	**-2.73 p=0.03**	-0.10 p=0.34	0.28 p=0.19	7.25 p=0.22	-	-0.92 p=0.36	1.91 p=0.6	0.12 p=0.91	-0.50 p=0.61	-1.63 p=0.2	-0.55 p=0.58	0.53 p=0.46	-0.46 p=0.45	0.06 p=0.96
K astigmatism				0.02 p=0.9	-0.05 p=0.67	-1.74 p=0.08	-1.74 p=0.09	-0.40 p=0.69	0.11 p=0.3	-0.04 p=0.09	7.17 p=0.42	-0.07 p=0.1	1.96 p=0.24	2.12 p=0.54	-1.70 p=0.09	-1.29 p=0.19	-1.62 p=0.2	-0.35 p=0.71	0.36 p=0.72	0.96 p=0.34	-1.16 p=0.15
Axial length					**0.74 p<0.001**	-	-	-	0.13 p=0.16	0.32 p=0.12	5.40 p=0.3	-	-1.81 p=0.06	1.36 p=0.7	0.69 p=0.49	-1.36 p=0.17	-0.34 p=0.56	-0.37 p=0.71	-1.75 p=0.07	1.03 p=0.3	-0.29 p=0.76
HCD						-	-	-	0.07 p=0.07	0.24 p=0.3	0.89 p=0.96	-0.19 p=0.2	-	4.70 p=0.19	1.08 p=0.25	-0.40 p=0.69	-2.27 p=0.31	0.55 p=0.59	-0.09 p=0.97	1.42 p=0.15	-0.07 p=0.94
AxL <16mm							-	-	-1.74 p=0.08	-1.18 p=0.24	-0.21 p=0.84	-	**2.47 p=0.01**	-1.09 p=0.28	0.74 p=0.39	1.99 p=0.16	0.46 p=0.65	0.56 p=0.58	0.48 p=0.79	-0.93 p=0.35	-0.83 p=0.41
AxL <20mm								-	-0.74 p=0.46	-1.66 p=0.09	**3.4 p<0.001**	-	0.29 p=0.79	0.2 p=0.9	0.92 p=0.36	1.35 p=0.18	3.04 p=0.08	0.60 p=0.55	1.22 p=0.22	-0.28 p=0.78	-0.0 p=0.99
HCD <9.5mm									**-2.32 p=0.02**	-0.71 p=0.48	-	-	-	1.27 p=0.20	0.29 p=0.59	0.19 p=0.55	1.90 p=0.06	-0.55 p=0.59	-	-	-1.28 p=0.20
IO AL diff										-0.1 p=0.61	6.67 p=0.25	-0.13 p=0.33	-0.34 p=0.73	3.96 p=0.70	2.22 p=0.14	0.48 p=0.62	-0.93 p=0.35	-0.23 p=0.82	-0.8 p=0.42	-0.87 p=0.42	1.2 p=0.22
ACDepth											2.55 p=0.64	-	**-2.37 p=0.02**	2.81 p=0.42	1.18 p=0.24	-0.61 p=0.54	-0.46 p=0.5	0.51 p=0.6	-0.29 p=0.77	-0.37 p=0.7	0.18 p=0.86
Formula												4.86 p=0.43	1.37 p=0.17	0.04 p=0.97	-	**-2.51 HQ/ST p<0.01**	8.82 p=0.11	**2.11 p=0.03**	-1.52 p=0.1	-16.74 p=0.5	1.0 p=0.32
IOL power													-1.07 p=0.28	1.73 p=0.63	1.28 p=0.20	-0.55 p=0.58	-7.46 p=0.04	-0.77 p=0.44	**2.94 p=0.01**	-0.85 p=0.38	-0.38 p=0.71
Ant segment abnormality														2.79 p=0.43	0.46 p=0.49	-0.11 p=0.91	-0.63 p=0.53	-0.95 p=0.34	1.50 p=0.22	-1.32 p=0.19	0.18 p=0.86
Viscous OVD															**28.71 p<0.001**	0.95 p=0.35	-0.69 p=0.49	0.84 p=0.4	1.40 p=0.16	-1.88 p=0.06	0.0 p=0.99
Posterior capsulotomy																**3.11 p=0.002**	0.55 p=0.46	3.07 p=0.08	-0.07 p=0.94	1.35 p=0.18	3.08 p=0.08
Ant vitrectomy																	0.14 p=0.89	-1.64 p=0.1	0.81 p=0.4	0.40 p=0.67	1.34 p=0.18
Wound sutured																		0.35 p=0.73	0.38 p=0.54	0.15 p=0.70	-0.8 p=0.42
Exp. Surgeon																			-1.37 p=0.12	1.90 p=0.37	-0.13 p=0.89
Single piece IOL																				0.91 p=0.36	1.40 p=0.16
IOL in bag																					-1.79 p=0.07

PREDICTION ERROR – Unilateral	Age at surg	K	K astig	Axial length	HCD	AxL <16 mm	AxL <20 mm	HCD <9.5 mm	IO AL diff	ACD	Forml	IOL power	Ant seg abnorm	Visc OVD	Ant vitrectomy	Wnd sutured	Exp Surg	Single piece IOL	IOL in bag	Right eye
Gest age at surgery	-	**0.58 p<0.001**	0.02 p=0.29	**0.67 p<0.001**	**0.56 p<0.001**	-0.70 p=0.48	**-6.08 p<0.001**	-1.16 p=0.25	0.42 p=0.99	**0.37 p=0.03**	7.79 p=0.09	**-0.55 p<0.001**	**-2.68 p=0.007**	6.11 p=0.1	-0.04 p=0.98	**-6.66 p=0.01**	-0.79 p=0.4	-1.26 p=0.2	0.41 p=0.6	0.13 p=0.47
Age at surgery		**0.59 p<0.001**	0.03 p=0.33	**0.67 p<0.001**	**0.58 p<0.001**	-0.75 p=0.46	**-6.10 p<0.001**	-1.16 p=0.25	0.44 p=0.99	**0.39 p=0.02**	7.93 p=0.09	**-0.53 p<0.001**	**-2.91 p=0.003**	7.90 p=0.06	0.5 p=0.6	**-5.96 p=0.01**	-0.95 p=0.34	-1.27 p=0.2	-0.30 p=0.6	0.77 p=0.44
K			-0.08 p=0.5	**0.54 p<0.001**	**0.47 p<0.001**	-1.49 p=0.1	**-4.14 p<0.001**	-0.52 p=0.6	0.26 p=0.26	**0.51 p=0.01**	**11.79 p=0.02**	-	**-2.97 p=0.003**	2.83 p=0.42	1.10 p=0.26	-0.03 p=0.86	-1.78 p=0.07	-0.44 p=0.66	-0.36 p=0.72	0.18 p=0.86
K astigmatism				0.008 p=0.95	-0.002 p=0.96	0.55 p=0.57	-0.55 p=0.58	0.88 p=0.38	-0.16 p=0.26	0.25 p=0.32	1.15 p=0.89	-0.11 p=0.5	0.77 p=0.44	1.27 p =0.75	1.41 p=0.16	-0.33 p=0.3	-0.65 p=0.52	-0.0 p=0.99	-0.04 p=0.97	0.26 p=0.76
Axial length					**0.67 p<0.001**	-	-	-	**0.75 p<0.001**	**0.74 p<0.001**	9.40 p=0.06	-	-1.35 p=0.18	2.43 p=0.5	1.53 p=0.12	-1.60 p=0.21	-1.52 p=0.13	**-2.55 p=0.01**	-0.49 p=0.63	0.92 p=0.36
HCD						-	-	-	0.46 p=0.15	**0.79 p<0.001**	5.68 p=0.22	**-0.5 p=0.006**	-	1.74 p=0.08	1.15 p=0.25	1.7 p=0.19	0.56 p=0.57	-1.66 p=0.1	1.08 p=0.28	-0.53 p=0.60
AxL <16mm							-	-	**-3.23 p=0.001**	**-2.48 p=0.01**	0.72 p=0.95	-	0.72 p=0.47	-0.50 p=0.62	-1.50 p=0.13	0.10 p0.92	0.93 p=0.35	1.4 p=0.23	0.17 p=0.68	-0.03 p=0.97
AxL <20mm								-	**-4.84 p<0.001**	**-3.18 p=0.002**	0.68 p=0.49	-	1.15 p=0.25	0.55 p=0.58	1.28 p=0.26	1.01 p=0.3	1.77 p=0.33	**2.26 p=0.02**	0.29 p=0.78	-0.67 p=0.51
HCD <9.5mm									-1.70 p=0.09	-1.45 p=0.15	-	-	-	1.55 p=0.12	0.09 p=0.76	0.34 p=0.54	-0.92 p=0.36	-	-	2.06 p=0.15
IO AL diff										0.35 p=0.25	2.70 p=0.61	**-0.78 p<0.001**	-0.29 p=0.77	1.48 p=0.69	1.59 p=0.11	-0.23 p=0.63	1.11 p=0.27	-1.73 p=0.08	-1.09 p=0.27	**1.97 p=0.05**
ACDepth											3.53 p=0.47	-	1.11 p=0.26	2.39 p=0.49	-0.43 p=0.67	0.63 p=0.42	2.19 p=0.06	1.18 p=0.24	0.24 p=0.8	0.67 p=0.51
Formula												3.85 p=0.42	-0.03 p=0.4	-1.31 p=0.2	0.01	2.02 p=0.73	1.46 p=0.1	-0.18 p=0.86	-0.01 p=0.9	0.04 p=0.46
IOL power													-0.46 p=0.65	2.31 p=0.51	-1.08 p=0.28	-1.35 p=0.24	0.53 p=0.59	**3.80 p=0.003**	0.91 p=0.36	-0.11 p=0.91
Ant segment abnormality														**7.7 p=0.05**	-0.52 p=0.6	-1.08 p=0.28	0.96 p=0.34	0.37 p=0.71	-0.45 p=0.66	1.15 p=0.25
Viscous OVD															**17.77 p<0.001**	-0.13 p=0.28	**2.17 p=0.03**	-0.26 p=0.8	1.39 p=0.16	0.0 p=0.99
Ant vitrectomy																0.63 p=0.43	2.01 p=0.16	2.97 p=0.09	**14.23 p<0.001**	3.30 p=0.07
Wound sutured																	0.17 p=0.87	1.82 p=0.18	0.03 p=0.87	-0.4 p=0.68
Exp. Surgeon																		0.44 p=0.66	-0.18 p=0.86	1.72 p=0.09
Single piece IOL																			0.72 p=0.47	1.76 p=0.08
IOL in bag																				-1.90 p=0.06

Appendix N: Search terms for literature review reported within background chapter

Search methods for literature review of visual outcome following cataract surgery in first 2 years of life

Types of studies considered

Clinical studies of outcomes following surgery for congenital cataract undertaken within the first two years of life

Clinical studies of outcomes following surgery for infantile cataract undertaken within the first two years of life

Electronic search

The PubMED database was searched. The following search strategy / keyword terms were used:

#1 “CATARACT”

#2 “CATARACT EXTRACTION”

#3 (#1 OR #2)

#4 (#3 with a filter of ‘All Child 0-18yrs’)

Selection of studies

Study titles, then study abstracts, and then full text reports were assessed. At each stage, studies which were judged not to fit criteria A or B were excluded. Cases series involving fewer than 5 children, and cases involving cataract surgery in low income countries were also excluded.

Search methods for literature review of glaucoma following cataract surgery in first 2 years of life

Types of studies considered

Clinical studies of outcomes / complications following childhood surgery for childhood cataract

Clinical or basic science studies on anterior segment changes following childhood surgery for cataract

Electronic search

The PubMED database was searched. The following search strategy / keyword terms were used:

#1 “APHAKIC GLAUCOMA”

#2 “CATARACT” AND “GLAUCOMA”

#3 (#1 OR #2)

#4 (#3 with a filter of ‘All Child 0-18yrs’)

Selection of studies

Study titles, then study abstracts, and then full text reports were assessed. At each stage, studies which were judged not to fit criteria A or B were excluded. Cases series involving fewer than 5 children were also excluded.