Aus der Augenklinik und Poliklinik

der Universitätsmedizin der Johannes Gutenberg-Universität Mainz

Results of a pilot study at the Department of Ophthalmology at Mainz University Medical Center to establish a nationwide registry for childhood glaucoma in Germany

Ergebnisse einer Pilotstudie an der Augenklinik der Universitätsmedizin Mainz zur Etablierung eines deutschlandweiten Registers für kindliche Glaukome

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Table of Contents

List of Abbreviations

AFo12	Patient informed Assent Form over 12 years
AFu12	Patient informed Assent Form under 12 years
ANGPT	Angiopoietin
ANGPT1	Angiopoietin-1
ANZRAG	Australian and New Zealand Registry of Advanced Glaucoma
ARS	Axenfeld-Rieger syndrome
ASD	Anterior segment dysgenesis
B3GALTL	β1,3-galactosyltransferase–like
B3GLCT	Beta 3-Glucosyltransferase
CCT	Central corneal thickness
CDR	Cup/disc ratio
CFp	Parental informed Consent Form
CGRN	Childhood Glaucoma Research Network
CGSC	Chinese Glaucoma Study Consortium
cMQ	Control Medical History Questionnaire
COL1A1	Collagen type I alpha1 chain
COL4A1	Collagen type IV alpha1 chain
CVAQC	Cardiff Visual Ability Questionnaire for Children
CVFQ	Children's Visual Function Questionnaire
CYP1B1	Cytochrome P450 1B1
EDTA	Ethylenediaminetetraacetic acid
ER-QoL	Eye-related quality of life
EU	European Union
EUA	Examination(s) under anaesthesia
EUAF	Examination Under Anaesthesia Form

EU RD Platform	European Platform on Rare Disease Registration
FEVR	Familial Exsudative Vitreoretinopathy
FKS	Fragebogen zum Kindlichen Sehvermögen
FOXC1	Forkhead box protein C1
FOXD3	Forkhead box protein D3
FOXE3	Forkhead box protein E3
FVA	Functional visual ability
FVQ_CYP	Functional Vision Questionnaire for Children and Young people
GAT	Goldmann applanation tonometry
GDPR	General Data Protection Regulation
GenDG	Gendiagnostikgesetz (engl.: Gen Diagnostics Act)
GJA8	Gap junction alpha-8
GLC3A	Primary congenital glaucoma 3A
GLC3C	Primary congenital glaucoma 3C
GFQ	Gestational and Family History Questionnaire
HIS	Hospital information system
HR-QoL	Health-related quality of life
IF	Information form
IFo12	Patient Information Form over 12 years
IFp	Parental Information Form
IFu12	Patient Information Form under 12 years
IOP	Intraocular pressure
IVI_C	Impact of Vision Impairment for Children
JOAG	Juvenile open-angle glaucoma
LTBP2	Latent transforming growth factor beta binding protein 2
LVP-FVQ	L. V. Prasad-Functional Vision Questionnaire
MD	Medical doctor

MMC	Mitomycin C
mm Hg	Millimetres of mercury
MQ	Medical History Questionnaire
MYOC	Myocilin
OCT	Optical coherence tomography
OPD	Outpatient department
OR	Operating room
PA	Peters anomaly
PAT	Perkins applanation tonometry
PAX6	Paired box 6
PAI-CY	Participation and Activity Inventory for Children and Youth
PCG	Primary congenital glaucoma
PedEyeQ	Pediatric Eye Questionnaires
PedsQL™	Pediatric Quality of Life Inventory
PEF	Parent Examination Form
PITX2	Pituitary homeobox 2
PITX3	Pituitary homeobox 3
POAG	Primary open-angle glaucoma
PROM	Patient-reported outcome measure
QoL	Quality of life
ROP	Retinopathy of prematurity
SCG	Secondary childhood glaucoma
SWS	Sturge-Weber syndrome
TEK	Tunica interna endothelial cell kinase
TIGR	Trabecular meshwork inducible glucocorticoid response
TRIM44	Tripartite Motif-Containing Protein 44
UBM	Ultrasound biomicroscopy

UK	United Kingdom
UNICEF	United Nations International Children's Emergency Fund
VD	Verification Document
VQoL_CYP	Vision-related Quality of Life of Children & Young People
VR-QoL	Vision-related quality of life
WHO	World Health Organization
WMS	Weill-Marchesani syndrome

List of Figures

List of Tables

1 Abstract / Kurzzusammenfassung

The subject matter of this dissertation is part of a prospective monocentric clinical pilot study conducted at the Department of Ophthalmology at the University Medical Center Mainz, which serves as a precursor to a future national registry for childhood glaucoma in Germany. The idea behind establishing a nationwide childhood glaucoma registry is to collect, for the first time, clinical and epidemiological data about children with glaucoma throughout Germany and gain increased insights into diagnosis and treatment. This is coupled with the aim of improving the quality of life for affected individuals in the future. This dissertation aims to advance the pilot project with its acquired insights. In the literature review, various aspects of childhood glaucoma and registry formation are examined and compiled. The materials and methods section contains a description of the study materials and the procedures used for carrying out the pilot study. The presentation of the obtained results was conducted using descriptive statistics and qualitative methods, such as reporting observations. The partial analysis of the pilot study includes categorizing and evaluating the achieved results and formulating suggestions for improvement and future perspectives.

Die Thematik dieser Dissertation ist Teil einer prospektiven monozentrischen klinischen Pilotstudie an der Augenklinik der Universitätsmedizin Mainz, welche als Vorläufer für ein zukünftiges nationales Register für kindliche Glaukome in Deutschland dient. Der Gedanke hinter der Einführung eines bundesweiten Kinderglaukomregisters liegt darin, erstmalig klinische und epidemiologische Daten über Kinder mit Glaukom in ganz Deutschland zu sammeln sowie vermehrte Einblicke in Diagnostik und Behandlung zu gewinnen. Damit verbunden ist das Ziel, die Lebensqualität von Betroffenen zukünftig weiter verbessern zu können. Diese Dissertation zielt darauf ab, das Pilotprojekt mittels gewonnener Erkenntnisse voranzubringen. In der Literaturdiskussion werden verschiedene Bereiche des kindlichen Glaukoms sowie Aspekte der Registerbildung betrachtet und zusammengetragen. Der Abschnitt "Materialien und Methoden" enthält eine Beschreibung der verwendeten Studienmaterialien und Verfahren für die Durchführung der Pilotstudie. Die Darstellung der erlangten Ergebnisse erfolgte mittels deskriptiver Statistiken und qualitativer Methoden, wie etwa die Berichterstattung von Beobachtungen. Die anteilige Analyse der Pilotstudie umfasst die Einordnung und Bewertung der erzielten Ergebnisse sowie die Formulierung von Verbesserungsvorschlägen und Ausblicken.

2 Introduction

2.1 Initial situation

The subject matter of this dissertation is positioned within a research initiative, specifically, a pilot study that serves as a precursor to a future nationwide multicentre registry for childhood glaucoma in Germany. The pilot study was initiated in June 2016 by the founding study team members Prof. [redacted] and Prof. [redacted]. To gain clarity on certain aspects related to the decisions and actions taken before the author of this dissertation joined the pilot project, expert interviews with the founding team members were conducted. Transcripts of the interviews can be found under Addendum 7.1.1 and Addendum 7.1.2. Reference is made to these interviews at one point or another. Both persons are ophthalmologists at the Childhood Glaucoma Center at Mainz University Medical Center. Prof. [redacted] also is the statistical expert for the study. The fourth member being part of the study team was ophthalmologist MD [redacted].

According to Prof. [redacted], main emphasis of establishing a nationwide childhood glaucoma registry is to determine clinical and epidemiological information of children with glaucoma and learn about diagnostic and treatment-related insights across the nation. Furthermore, a nationwide registry shall facilitate extensive research of this rare illness. All of this would not yet be possible due to missing data. The setup of an initial, albeit localised, database on characteristics of childhood glaucoma and further demographic data within the scope of this pilot study should illustrate the need for a national glaucoma registry. This localised database was to be arranged in a single centre at the Childhood Glaucoma Center at Mainz University Medical Center. However, the recruitment and inclusion of probands, pseudonymization, data collection, data documentation, and set up of a database ought to be pilot tested first. The definition of the pilot study's design, conception of the study material, and the exchange with the Ethics Committee at the Rhineland-Palatinate State Medical Association ("Ethik-Kommission bei der Landesärztekammer Rheinland-Pfalz") and the local data safety commission were carried out by the founding team members. A prospective monocentric clinical study was planned. The study design included the involvement of two groups: one comprising children diagnosed with childhood glaucoma, and another group consisting of children of similar age with different eye conditions, excluding glaucoma. The latter served as a control group for the verification of data quality.

The author of this dissertation, having the status of a medical student, subsequently joined the pilot study team in May 2018. All work undertaken by the author of this dissertation for the execution of the pilot study was performed without compensation, during the available free time alongside medical school. There was no external funding involved.

2.2 Motivation and aim

This endeavor is fuelled by the aspiration to bring about transformative changes in the lives of young patients and their families. The commitment to advancing medical knowledge and improving the quality of care underscores the significance of this undertaking. Furthermore, the potential impact of this research on the lives of young glaucoma patients, their families and all other affected persons in the long term is an inspiring aspect. With each step taken, every error experienced and every obstacle overcome, progress is made toward a future where childhood glaucoma sees improvements in its understanding, management, and treatment.

This dissertation seeks to advance the pilot project, bringing it closer to a successful conclusion and thereby laying the groundwork for future projects to thrive, drawing upon its gained insights. The pilot study was conducted in Germany and all study material was designed in German. However, as a native English speaker, ensuring global accessibility and understanding of this work in English was considered important. It shall serve as an example and a foundation for comparable projects, both domestically and internationally.

2.3 Definition and classification of childhood glaucoma

Childhood glaucoma is the umbrella term for a heterogeneous group of disorders which may have a major impact on the life of the person affected (1). Since it is a rare (2), chronic, and vision-endangering disease, the potential threat of developing blindness requires lifelong medical care and follow-up (1, 3). Exact definition of childhood glaucoma and its classification into categories varies depending on whichever source one consults. Since November 2013 the 9th World Glaucoma Association Consensus Statement provides the first and so far, only international consensus classification system for childhood glaucoma (4, 5). The major contribution was made by the Childhood Glaucoma Research Network (CGRN), which is an international organization of ophthalmologists with a shared interest in childhood glaucoma (5, 6). In the following this thesis refers to the nomenclature published in the 9th World Glaucoma Association Consensus Statement, from now on called CGRN classification in this thesis, because it is the international standard agreed on.

At first it was agreed up to what age childhood glaucoma is still defined as such. In the United States a person younger than 18 years of age is considered a child. Europe and UNICEF (United Nations International Children's Emergency Fund) define childhood only up to the age of 16 (4).

Childhood glaucoma is broadly defined as damage to the eye which is related to intraocular pressure (IOP). The diagnosis is made when at least two of the signs listed in the middle column of Table 1 occur in the eye. In some cases, glaucoma is suspected but cannot be proven with certainty. Based on the diagnostic criteria for childhood glaucoma, features were introduced that determine a glaucoma suspect. The right column of Table 1 lists definition criteria of a glaucoma suspect. The abnormality of at least one feature is required (4).

Table 1: Definition criteria of glaucoma and glaucoma suspect created by the Childhood glaucoma research network (CGRN) (4)

Feature	Definition of glaucoma (two or more required)	Definition of glaucoma suspect (at least one required)
IOP	IOP > 21 mmHg (perhaps considering the effects of general anaesthesia on the IOP)	IOP > 21mmHg on two separate occasions
Optic disc	Optic disc cupping: progressive increase in cup-disc ratio, cup-disc asymmetry of ≥ 0.2, or focal rim narrowing	Suspicious optic disc appearance for glaucoma
Cornea	Corneal findings: Haab striae, corneal edema, or diameter ≥ 11 mm in newborns, > 12 mm in children < 1 year of age, or > 13 mm at any age	Increased corneal diameter or axial length in setting of normal IOP
Myopia / axial length	Progressive myopia or myopic shift coupled with abnormally increased ocular growth	
Visual field defect	Reproducible visual field defect that is consistent with glaucomatous optic neuropathy	Suspicious visual field for glaucoma

IOP = intraocular pressure; mm Hg = millimetres of mercury

Further explanations of the signs, epidemiology, known risk factors, and treatment that arise with the different subtypes of childhood glaucoma and glaucoma suspects are presented in chapter 2.4.

Childhood glaucoma is divided into two groups, primary childhood glaucoma and secondary childhood glaucoma, of which each is further classified. Primary childhood glaucoma comprises primary congenital glaucoma (PCG) and juvenile open-angle glaucoma (JOAG) (4). Childhood glaucoma is termed secondary if the outflow of aqueous humour is disturbed by congenital or acquired ocular anomalies or systemic diseases. However, an isolated trabeculodysgenesis falls into the category of PCG (7). In the 9th World Glaucoma Association Consensus Statement secondary childhood glaucoma is subdivided into four categories. The subdivision is based on the fundamental cause of the outflow disorder and hence development of glaucoma. All glaucoma forms meet the childhood glaucoma definition criteria agreed on in the 9th World Glaucoma Association Consensus Statement mentioned in Table 1 (4). Figure 1 gives an overview of the childhood glaucoma classification system.

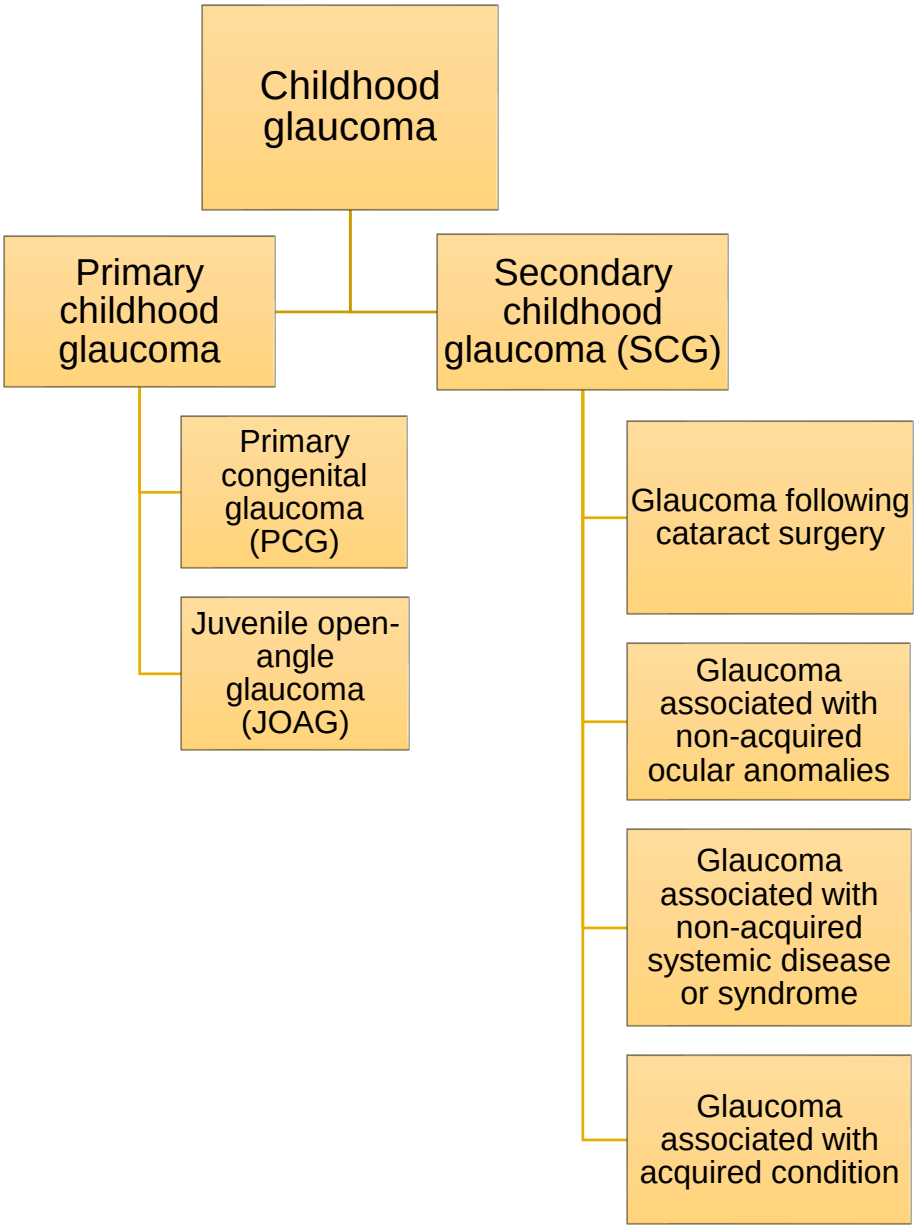


Figure 1: Classification of childhood glaucoma created by the Childhood glaucoma research network (CGRN) (4)

2.4 Presenting the different categories of childhood glaucoma

The different categories of childhood glaucoma can vary greatly in their appearance, epidemiology, risk factors and success of medical or surgical treatment. Some forms occur much more frequently than others. This chapter provides an overview of the different categories of childhood glaucoma. The category of glaucoma suspects is also reviewed in subchapter 2.4.3.

The frequency of primary childhood glaucoma compared to secondary childhood glaucoma (SCG) varies greatly depending on the source cited. In this regard, Table 2 and Table 3 together give an overview of 22 epidemiological studies on childhood glaucoma that were

published between 1986 and 2023. Table 2 is adapted from Hoguet *et al.* who analysed the distribution of the different forms of childhood glaucoma in their own study and six other studies according to the CGRN classification, glaucoma suspects excluded (8). The table was augmented by further 14 studies. Except for the studies from Alanazi *et al.* and Lopes *et al.* (2018), only studies were considered, which contributed data to all six glaucoma categories defined in the CGRN classification. The percentages were either directly provided in the publication of the studies, or a reclassification was performed by the author of this thesis based on the information given in the studies and the CGRN classification. In some cases, a recalculation was carried out in which the glaucoma suspects were subtracted.

Table 2: Distribution of childhood glaucoma cases according to CGRN classification in 21 studies on childhood glaucoma published from 1986 to 2023 and sorted chronologically (4, 9-22). In order to maintain comparability with Hoguet et al. (8), from which this table was adapted, only those studies were included that reported at least the number and/or percentage of cases and not only eyes.

Study	Number of glaucoma patients (excluding glaucoma suspects)	Study population; location	PCG (%)	JOAG (%)	Glaucoma following cataract surgery (%)	Glaucoma associated with nonacquired ocular disease (%)	Glaucoma associated with nonacquired systemic disease or syndrome (%)	Glaucoma associated with acquired condition (%)	Not enough information to catagorize / unclassified (%)
Barsoum-Homsy and Chevrette 1986 *	63	Paediatric glaucoma clinic; Montreal, Canada	14 (22)	0	7 (11)	24 (38)	9 (14)	9 (14)	-
Taylor *et al.* 1999 *	306	Children's hospital; Toronto, Canada	117 (38)	7 (2)	61 (20)	41 (13)	34 (11)	44 (14)	2 (1)
Papadopoulos *et al.* 2007 *	99	Consultant ophthalmologists; United Kingdom and Republic of Ireland	45 (45)	2 (2)	16 (16)	6 (6)	12 (12)	10 (10)	8 (8)
Qiao *et al.* 2009 *	1055	Hospitalized paediatric patients; Beijing, China	486 (46)	63 (6)	131 (12)	59 (6)	33 (3)	211 (20)	72 (7)
Aponte *et al.* 2010 *	30	Olmstead county residents; Minnesota, USA	1 (3)	4 (13)	6 (20)	2 (7)	4 (13)	13 (43)	-
Alanazi *et al.* 2013 (9)	180	Congenital glaucoma registry; Eye Specialist Hospital; Riyadh, Saudi Arabia	144 (80)	Not mentioned	2 (1)	25 (14)	4 (2)	1 (1)	4 (2)

Fung *et al.* 2013 *	164	Tertiary referral centre; Texas, USA	46 (28)	10 (6)	30 (18)	16 (10)	18 (11)	39 (24)	5 (3)
Hoguet *et al.* (8)	122	Tertiary childhood glaucoma clinic, Southern Florida, USA	39 (32)	9 (7)	22 (18)	10 (8)	14 (11)	28 (23)	-
Mokbel *et al.* 2018 (10)	207	Ophthalmic clinic; Mansoura, Egypt	114 (55.1)	2 (1.0)	15 (7.2)	11 (5.3)	4 (1.9)	61 (29.5)	-
Lopes *et al.* 2018 (11)	72	Childhood glaucoma registry database; Department of	(56.5)	Not mentio ned	(30.5)	(4)	(5)	(4)	-
Lopes *et al.* 2021 (12)	430	Ophthalmolo gy of the University Medical Centre; Sao Paolo, Brazil	218 (50.7)	2 (0.5)	63 (14.7)	59 (13.7)	38 (8.8)	50 (11.6)	-
Senthil *et al.* 2019 (13)	275	Tertiary eye care centre; Hyderabad, Telangana, India	107 (38.9)	38 (13.8)	22 (8.0)	47 (17.1)	13 (4.7)	48 (17.5)	-
Bouhe nni *et al.* 2019 (14)	58	Tertiary care children's hospital, Akron, Ohio, USA	3 (5.2)	17 (29.3)	1 (1.7)	3 (5.2)	12 (20.7)	22 (37.9)	-
Beck *et al.* 2020 (15)	85	Consultant members of the Scottish Glaucoma Club and Scottish Paediatric Ophthalmolo gy Club; Scotland, UK	6 (7,1)	5 (5,9)	25 (29,4)	12 (14,1)	8 (9,4)	29 (34,1)	-
Saave dra *et al.* 2020 (16)	89	Ophthalmolo gic national reference centre; Bogota, Colombia	42 (47.2)	18 (20.2)	5 (5.6)	12 (13.5)	1 (1.1)	11 (12.4)	-
Chan *et al.* 2021 (17)	33	Tertiary referral centre; Hong Kong	2 (6.1)	5 (15.2)	6 (18.2)	7 (21.2)	4 (12.1)	8 (24.2)	1 (3)
Knight *et al.* 2021 (18)	290	Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG)	167 (57.6)	56 (19.3)	5 (1.7)	49 (16.9)	6 (2.1)	3 (1.0)	4 (1.4)
Tam *et al.* 2022 (19)	246	Children's Hospital; Boston, USA	108 (29)	21 (5.6)	136 (36.5)	34 (9.1)	40 (10.7)	34 (9.1)	-

Dubey *et al.* 2023 (20)	405	Tertiary eye care hospital; Northern India	114 (28.1)	30 (7.4)	28 (6.9)	62 (15.3)	11 (2.7)	160 (39.5)	-
El Sayed *et al.* 2023 (21)	584	Pediatric ophthalmology unit at tertiary children's hospital; Egypt	445 (76.2)	2 (0.3)	55 (9.4)	31 (5.3)	38 (6.5)	13 (2.2)	-
Kaushik *et al.* 2023 (22)	1155	Newly diagnosed children aged <18 years in 13 centres across India	362 (34.4)	129 (12.2)	(6.7)	(14.7)	3.8	(28.2)	-

**** adapted from Hoguet et al. (8)***

Table 3 is listed separately because it contains the only international study. In contrast to Table 2 this study from Papadopoulos *et al.* only provided the number of eyes and not the number of patients (23).

Table 3: Distribution of childhood glaucoma cases according to CGRN classification in the international study of Papadopoulos et al. from 2020. Extensive data was only provided in number of eyes. The children included in these studies were aged younger than 18 years (23).

Study	Number of eyes with glaucoma (excluding glaucoma suspects)	Study population; location	PCG eyes (%)	JOAG eyes (%)	Eyes with glaucoma following cataract surgery (%)	Eyes with glaucoma associated with non-acquired ocular disease (%)	Eyes with glaucoma associated with nonacquired systemic disease or syndrome (%)	Eyes with glaucoma associated with acquired condition (%)	Not enough information to catagorize / unclassified (%)
Papadopoulos *et al.* 2020 (23)	691	17 international centres	314 (45.4)	53 (7.7)	60 (8.7)	92 (13.3)	54 (7.8)	109 (15.8)	9 (1.3)

Due to a variety of reasons, for example differences in the number of included patients, the methods and date of data collection and the existence of the CGRN classification at that point of time, the results in the studies mentioned above are not comparable with each other. A small number of patients also reduces statistical power and impairs interpretability. Not even the large-scale transnational study of Papadopoulos *et al.* should be interpreted as an international standard, since a bigger part of patients, about 60%, were recruited from only two centres in India (23). However, they provide the only reference to estimate the prevalences of the different categories of Childhood Glaucoma and are therefore presented here as an overall trend.

2.4.1 Primary childhood glaucoma

Both, PCG and JOAG meet the CGRN classification. The main differences are the age of onset, the severity of ocular anomalies, and the inheritance pattern as contrasted in Table 4 (4, 5, 24).

Table 4: Differences between PCG and JOAG (4, 5, 24)

	PCG	**JOAG**
Age of onset	Usually presents in neonates and infants 3 subcategories based on age of onset: - Neonatal onset (0–1 month) - Infantile onset (>1–24 months) - Late onset (>24 months)	Typically presents between 4 and 35 years of age
Ocular anomalies	Isolated angle (and perhaps mild congenital iris) anomalies	No congenital ocular anomalies or syndromes; open angle (normal appearance)
Ocular enlargement	Usually with ocular enlargement (buphthalmos)	No ocular enlargement (buphthalmos)
Typical inheritance pattern	Autosomal recessive (more common in consanguineous populations)	Autosomal dominant (variable penetrance and expressivity)

JOAG = Juvenile open-angle glaucoma; PCG= Primary congenital glaucoma

Regarding Table 2, the percentage of primary childhood glaucoma, as a proportion of all glaucoma categories, ranges from 16% to 80% or perhaps more. The former percentage refers to childhood glaucoma patients younger than 20 years of age living in Olmstead County, Minnesota, USA, from 1965 to 2004 (25). The latter percentage refers to childhood glaucoma patients in Saudi Arabia. The proportion of PCG here was 80%. Since Alanazi *et al.* did not state whether JOAG was included in the statistics of PCG or whether there were no patients with JOAG to report, the percentage of primary childhood glaucoma may have been even higher (9). Results from a recent international study propose an average proportion of 45.4% of eyes diagnosed with childhood glaucoma (23). No information on the occurrence of primary childhood glaucoma in Germany could be found in the course of literature research for this thesis.

2.4.1.1 Primary congenital glaucoma

In general, PCG is the most common category of childhood glaucoma that is not associated with any syndrome (26).

The occurrence of PCG fluctuates depending on the country and ethnicity. Incidence reaches from 1:30,000 births in Australia, 1:10,000-30,200 live births in western Europe to 1:1,250 live births in Slovakian gypsies (7, 26-28). In Arab countries the incidences range from 1:8,210 births in Palestinian Arabs in West Bank and Gaza Strip to 1:3,030-1:2,500 live births in Saudi Arabia (9, 29, 30). The more frequent occurrence of PCG in the above-mentioned gypsy community and in Arab countries derives from an increased percentage of parental consanguinity of 45.6% or higher (9, 28, 29). There seems to be a significantly higher occurrence of PCG in non-white patients (23).

The exact proportion of PCG in childhood glaucoma is comparable to previously mentioned primary childhood glaucoma and differs greatly depending on the study location and population. Following what different researchers have found in their studies, Table 2 indicates, that the diagnosis of PCG accounts for 3%-80% of all childhood glaucoma patients. For North America the share ranges from 3-38% (8, 14, 25, 31-33). The occurrence of PCG seems to be more frequent in Ireland/Great Britain; and Australia/New Zealand with a share of 45% and 57.6%, respectively (7, 18). In Scotland, however, the percentage seems rather low with 7,1% (15). Regarding the Chinese speaking region, Qiao *et al.* and Chan *et al.* came to differing results. A proportion of 46% was identified in the Beijing area in China, but only 6.1% in Hong Kong, although 30 of the 33 children with glaucoma were of Chinese origin (17, 34). One study from India presented a proportion of 38.9% (13). Studies from South America point out a share of 47.2% (42 out of 89 glaucoma patients) in Columbia and 50.7-56.5% in Brazil (11, 12, 16). And in the Arab countries Egypt (55.1%) and Saudi Arabia (80%), the percentage of PCG compared to the other childhood glaucoma categories seems to be one of the highest (9, 10).

There is a slight predominance of PCG in males, but familial cases tend to have an equal sex distribution. 70% of the cases are bilateral (26). PCG is characterized by a developmental disorder of the trabecular meshwork in the angle of the anterior chamber, the exact cause of which is still uncertain (24). Incomplete maturation of tissue from the neural crest during the third trimester of pregnancy is the current conception of pathogenesis. First noticeable symptoms for parents or paediatricians are usually photophobia, tearing, eye rubbing, blepharospasm, irritability, corneal clouding, and ocular enlargement/buphthalmos. They typically occur in newborns and infants younger than 6 months. Further ophthalmological examination may reveal high IOP, enlarged axial length, deepened optic disc excavation, corneal edema, increased corneal diameter, and fissures in the Descemet membrane of the cornea called Haab striae (26). Haab striae develop when the Descemet membrane stretches

and breaks due to elevated IOP (35). Gonioscopy may expose abnormal angle anatomy with high iris insertion and hyperaemic vessels in the peripheral iris (26).

PCG may occur sporadically. But in 10-40% of cases, PCG can already be found in the family history. Most hereditary forms of PCG follow an autosomal recessive mode of inheritance with variable penetrance of up to 100% (36). This matches the more frequent occurrence of PCG in populations with consanguinity (24). The chance of discovering a genetic cause for PCG through genetic testing is currently only 40%. In 60% of patients no genetic cause can be found (37). Mutations in the *CYP1B1* (Cytochrome P450 1B1) gene, which is contained in the GLC3A (primary congenital glaucoma 3A) locus, are the most common cause of PCG and account for 87% of familial and 27% of sporadic cases (36, 37). However, variants in the *LTBP2* (latent transforming growth factor beta binding protein 2) gene, which is positioned in the GLC3C locus, have also been reported in patients with PCG (38, 39). Additionally, the ANGPT/TEK (Angiopoietin/ tunica interna endothelial cell kinase) signalling pathway is known for its essential role in the development of the Schlemm´s canal (40). Mutation variants of either the *ANGPT1* (Angiopoietin-1) gene or the *TEK* gene have been identified in patients with PCG (40, 41). Furthermore, variants associated with the pathogenesis of PCG were found in the *MYOC* (Myocilin), the *FOXC1* (Forkhead box protein C1), and the COL1A1 (Collagen type I alpha1 chain) gene (38).

The therapy of PCG is primarily surgical. Angle surgery in the form of goniotomy and trabeculotomy, either conventional or circumferential, is the preferred first line treatment performed in these cases and possesses success rates of 70-90% (24, 26, 42). In case of angle surgery failure, filtering procedures such as trabeculectomy, glaucoma drainage device surgery, or cyclodestructive procedures represent further IOP-reducing therapy options (26, 43). Concerning conservative therapy, topical and systemic IOP lowering medication may be necessary prior to surgery and as an adjunct in case of insufficient pressure reduction after surgery (24). Preferred substances in use are beta-adrenergic antagonists (beta-blockers), carbonic anhydrase inhibitors, and prostaglandin analogues (26).

There are some differential diagnoses for PCG in infancy that share common signs or symptoms in clinical examination which make it difficult to distinguish. One such differential diagnosis is X-linked megalocornea (4). As the name already reveals, this disease is typically passed on in an X-linked fashion. Characteristic signs are increased but stable bilateral corneal diameters at birth and normal IOP (44).

2.4.1.2 Juvenile open-angle glaucoma

The occurrence of JOAG is estimated at 1 in 50,000 individuals in the United States (45). Table 2 indicates, that JOAG may account for up to 29.3% of all childhood glaucoma patients. The lowest incidence was mentioned in a study by Mokbel *et al*. who however only analysed the

medical files of glaucoma patients <16 years of age. In this retrospective survey only two of 207 patients presented to Mansoura Ophthalmic Centre of the University of Mansoura in Egypt had JOAG (10). In contrast, Bouhenni *et al.* came to a significantly higher proportion of JOAG. They revealed 58 patients aged 18 years or younger who were diagnosed with childhood glaucoma at a Children's hospital in Ohio, USA. 17of them had JOAG accounting for 29.3% of all childhood glaucoma cases (14). Results from the international study of Papadopoulos *et al.* propose an average proportion of 7.7% of eyes diagnosed with childhood glaucoma (23). To see the amount of JOAG in other studies view Table 2.

JOAG is often revealed incidentally during routine eye examinations or screenings in consequence of family history, because it is frequently asymptomatic (24). Nevertheless, Kwun *et al*. found that 58% of JOAG patients do complain about either blurred vision, pain or decreased visual acuity at the initial hospital visit (46). The first examination often reveals an optic disc excavation and advanced glaucomatous damage to the visual field. In its appearance, JOAG can hardly be distinguished from adult primary open-angle glaucoma (POAG) (24) which is defined as a chronic progressive optic neuropathy that can result in death of retinal ganglion cells and characteristic visual field loss (47). Some sources even classify JOAG as a subgroup of POAG (46, 48, 49). Perhaps this is a reason why JOAG is not mentioned in some epidemiological studies on childhood glaucoma (9, 11, 31). In both, POAG and JOAG, the angle appears normal, and no syndromes or congenital ocular anomalies are associated (24, 47). In both forms there can be increased IOP, with JOAG often presenting extremely high pressures, sometimes even above 40-50 mmHg (24).

Contrary to earlier assumptions that the inheritance of JOAG would show an autosomal dominant pattern with incomplete penetrance, it is more a matter of genetic heterogeneity (50). Up to 36% of all JOAG cases may be associated with a mutation in the myocilin gene (*MYOC*), formerly called *TIGR* (trabecular meshwork inducible glucocorticoid response) gene (45). Mutations in the *MYOC* gene lead to accumulation of misfolded proteins in the trabecular meshwork cells (51), which results in cell death (52) and loss of IOP regulation (52). 4.92% of patients with JOAG in Taiwan are suggested to have mutations in the *CYP1B1* gene (53).

Regarding therapy, there is a lack of evident literature to evaluate the effectiveness of medical therapy. JOAG responds better to topical antiglaucomatous medication than PCG does, but often a surgical approach is needed (24). Pathania *et al.* proposed good success rates when performing primary trabeculectomy without the use of Mitomycin C (MMC) (54). Other surgical therapies include goniotomy, trabeculotomy, and glaucoma drainage devices (24).

2.4.2 Secondary childhood glaucoma

Table 5 shows some prevalent examples of the four subgroups of SCG defined in the CGRN classification. The following sub-chapters go into more detail on a few exemplary disorders.

Table 5: Classification of Secondary childhood glaucoma and prevalent examples listed by the Childhood glaucoma research network (CGRN) (4)

Glaucoma **following cataract surgery**	Glaucoma associated with **non-acquired ocular anomalies**	Glaucoma associated with **non-acquired systemic disease or syndrome**	Glaucoma associated with **acquired condition**
Congenital idiopathic cataract	Axenfeld-Rieger anomaly	Connective tissue disorders: Weill-Marchesani syndrome, Marfan syndrome, Stickler syndrome	Uveitis
Acquired cataract	Peters anomaly	Metabolic disorders: Lowe syndrome, Mucopolysaccharidoses, Homocystinuria	Trauma
Congenital cataract associated with ocular anomalies/ systemic diseases	Aniridia	Phacomatoses: Neurofibromatosis type 1, Sturge-Weber syndrome, Klippel-Trenaunay-Weber syndrome	Retinopathy of prematurity
	Persistent fetal vasculature	Chromosomal disorders such as Down syndrome	Steroid induced
	Sclerocornea	Congenital rubella	Tumors
	Congenital ectropion uveae		Post-surgery other than cataract surgery
	Congenital iris hypoplasia		
	Microcornea		
	Microphthalmos		
	Ectopia lentis		

SCG represents a summary of conditions that can promote the development of glaucoma in a wide variety of pathogenic mechanisms (47). The exact proportion of SCG, in accordance with the CGRN classification, also varies depending on the study location and population. By far

the smallest proportion of SCG, as can be seen in Table 2, was found in the study by Alanazi *et al*. in which the percentage of primary childhood glaucoma or rather PCG was also the highest. The authors assigned 20% of the newly diagnosed patients with congenital glaucoma seen between 2001 and 2003 at King Khaled Eye Specialist Hospital in Riyadh, Saudi-Arabia, to the group of SCG (9). The highest percentages of SCG, as shown in Table 2, can be found in investigations by Aponte *et al.* (83%) who reviewed medical records for a specified 40-year period (8, 25) and Beck *et al.* (87%) who consulted club members in Scotland (15). An orienting international average of 45.6% is provided by the study of Papadopoulos *et al.* who included 17 international centres (23). According to Table 2, the occurrences of the subgroups of SCG do not result in a recurring pattern across the globe. However, Papadopoulos and colleagues identified two correlations, namely that glaucoma after cataract surgery occurred more often in white patients, and glaucoma associated with acquired conditions was more frequent in patients from South Asia (23). Since the country of origin of the children and parents is not mentioned in many epidemiological studies, the findings of these scientists can hardly be confirmed in other previous investigations. One of the few counterexamples, however, is Chan *et al*., who explicitly mentioned that 90.9% of the children in their retrospective analysis were of Chinese origin (17).

No information on the occurrence of SCG in Germany could be found during literature research for this thesis.

2.4.2.1 Glaucoma following cataract surgery

The development of glaucoma following paediatric cataract surgery is a well-known (55) and lifelong risk (56). When including ocular hypertension, up to 60% of cases are troubled with glaucoma after cataract surgery (55). About 10 to 25% of aphakic and pseudophakic eyes develop glaucoma by the 10th postoperative year (57).

Cataract surgery is one of the most widespread reasons for secondary glaucoma (56). In accordance with the CGRN classification and as can be seen in Table 2, the proportion of glaucoma following cataract surgery ranges from 1% to 36.5% of all childhood glaucoma types in different studies. The lowest rate results from data collected by Alanazi *et al.* in Saudi-Arabia (9). The highest rate was mentioned by Tam *et al.* who retrospectively evaluated medical data from childhood glaucoma patients who presented to Boston Children's Hospital (19). View Table 2 to see the amount of glaucoma following cataract surgery in other studies. Results from an international study propose an average proportion of 8,7% of eyes diagnosed with childhood glaucoma (23).

It has been known for a long time that glaucoma after cataract surgery appears to be a problem of patients at a younger age (56). So the timing must be carefully considered to prevent the development of glaucoma on the one hand and amblyopia on the other (55). Trivedi *et al.* were

able to differentiate the age with their study: In their assessments, glaucoma occurred exclusively in children who received their cataract surgery by the latest at 4.5 months of age. In this age group, the incidence of glaucoma was 24.4% in pseudophakic eyes and 19.0% in aphakic eyes (58). Other studies found increased incidences for glaucoma when cataract surgery was performed either in the first 20 weeks of life (59) or before the 9th or 12th months of age (56).

Noack and Lagrèze carried out a survey in 113 operative eye centres in Germany. A total of 433 lensectomies was reported for 2005. However, due to the response rate of only 53%, this number is most likely not the actual total. The authors estimated the annual incidence of congenital cataracts in Germany to be 380-820 eyes. Neither this nor another study found in the course of literature research for this thesis provides any information on the incidence of glaucoma following cataract surgery in Germany (60).

Medication represents the initial therapy for children with glaucoma or ocular hypertension after cataract surgery. When this fails to adequately control the glaucoma, surgery and cyclodestructive laser are needed (56). The implantation of glaucoma drainage devices is a promising surgical therapy option, especially for aphakic glaucoma, which is often refractory to therapy (61).

2.4.2.2 Glaucoma associated with non-acquired ocular anomalies

The diseases in this subgroup feature ocular anomalies which are usually already present at birth. In several cases, when systemic abnormalities are part of the clinical picture, the condition is referred to as syndrome instead of anomaly. Frequent members of this subgroup are Axenfeld-Rieger anomaly, Peters anomaly (PA), aniridia, and sclerocornea (62). These examples have in common that they are all assigned to the group of anterior segment dysgenesis (ASD) (63), a condition that features defects in the development of the anterior eye (64). Being affected by one of the non-acquired ocular anomalies associated with glaucoma does not inevitably mean that glaucoma must develop. About 50% of patients with PA (62) and also 50% of patients with Axenfeld-Rieger anomaly or Axenfeld-Rieger syndrome (ARS) develop glaucoma (65). Glaucoma also occurs in 50 to 75 % of aniridia patients. Regular lifelong monitoring is required since glaucoma can develop over time if not yet present at birth (62).

As shown in Table 2, the frequency of glaucoma associated with non-acquired ocular anomalies ranges from 4 to 38% of all childhood glaucoma categories as defined by the CGRN classification. 4% were found in a publication by Lopes *et al.* (2018) (11) and 38% by Hoguet *et al*. in study data obtained by Barsoum-Homsy and Chevrette in Montreal, Canada in 1986 (8). Further study results hereto can be seen in Table 2. Results from an international study propose an average proportion of 13.3% of eyes diagnosed with childhood glaucoma (23).

Patients with Axenfeld-Rieger anomaly and ARS feature iris attachments to the posterior embryotoxon, a particularly prominent Schwalbe line (62), which is the outer limit of the Descemet membrane of a cornea (66). Other findings may be iris abnormalities including generalized stromal thinning or atrophy, iris hole formations or ectropion uveae. Gonioscopy frequently reveals peripheral iris adhesions (62). Systemic abnormalities that patients with ARS have in addition to the ocular findings are most frequently of the face, heart, and male genitourinary system. Axenfeld-Rieger anomaly and ARS are usually inherited as an autosomal dominant trait (67). Mutations in the *PITX2* (Pituitary homeobox 2) or *FOXC1* gene are the most common genetic causes (65). In 40% of patients with ARS a mutation in one of these genes can be found (67).

PA is characterized by the presence of a congenital central corneal opacity. Correspondingly, the cornea is defect in the posterior stroma, Descemet membrane, and endothelium. Iris and lenticular abnormalities can be involved as well. PA with systemic features, such as facial dysmorphism, abnormalities of the central nervous system, and short stature is called Peters plus syndrome. These patients have a higher risk of glaucoma than patients only with PA (62). Mutations in the following genes have been associated with PA: *PAX6* (Paired box 6), *PITX2*, *PITX3* (Pituitary homeobox 3), *FOXC1*, *FOXE3* (Forkhead box protein E3), *CYP1B1*, and *COL4A1* (Collagen type IV alpha1 chain) (68). The genetic origin of Peters plus syndrome is due to mutations in the *B3GLCT* (Beta 3-Glucosyltransferase), formerly called *B3GALTL* (β1,3-galactosyltransferase–like gene) gene (68, 69).

Aniridia is a congenital and bilateral ocular disorder (62) and features total or partial absence of the iris (70). Other ocular manifestations are keratopathy, optic nerve and macular hypoplasia, cataract, and iris deficiency (71). Mutations in the *PAX6* gene *(62)*, but also in the *FOXC1*, *PITX2*, *CYP1B1*, *FOXD3* (Forkhead box protein D3) and *TRIM44* (Tripartite Motif-Containing Protein 44) genes have been reported with the occurrence of aniridia (70). Around two thirds of aniridia cases are inherited (72).

With sclerocornea the cornea is transformed by thick collagen bundles and vascularization in a non-progressive manner. Sometimes the complete cornea is covered. Other ocular abnormalities such as aniridia or Axenfeld-Rieger anomaly and systemic features can be associated (62). Mutations in the following genes have been found in few cases with sclerocornea: *PAX6*, *FOXE3*, and *GJA8* (Gap junction alpha-8) (73-75). Familial and sporadic cases of sclerocornea are roughly balanced (62).

In contrast to glaucoma after cataract surgery, the therapy for glaucoma associated with non-acquired ocular anomalies mainly depends on the underlying disease and its severity. In general, medication usually is the first-line approach, but surgery, such as angle surgery,

trabeculectomy, glaucoma drainage devices, and transscleral cyclophotocoagulation, is often required at an early stage (62).

2.4.2.3 Glaucoma associated with non-acquired systemic disease or syndrome

This subgroup of SCG consists of congenital systemic diseases and syndromes, which can involve ocular problems including glaucoma. Sturge-Weber syndrome (SWS) and Weill-Marchesani syndrome (WMS) are examples of this group. Development of glaucoma is not absolute, but lifelong monitoring is recommended (76).

With reference to Table 2, glaucoma associated with non-acquired systemic disease or syndrome may account for up to 20.7% of all childhood glaucoma patients. This number was worked out from the data provided by Bouhenni *et al*. (14). The perhaps lowest occurrence can be found in the data published by Saavedra *et al*. Out of a total of 89 patients diagnosed at an ophthalmologic national reference centre in Bogota, Colombia, they had only one case (16). See Table 2 for more studies. Results from an international study by Papadopoulos *et al.* propose an average proportion of 7,8% of eyes diagnosed with childhood glaucoma (23).

SWS appears in approximately one of 20,000-50,000 live births (77). It is a sporadically occurring neurocutaneous disorder which derives from a somatic activating mutation in the *GNAQ* (Guanine nucleotide-binding proteins, Q polypeptide) gene (78). The main characteristic of this syndrome is a capillary vessel malformation (nevus flammeus or port-wine stain) of the facial skin (79). Glaucoma is the most frequent ocular complication of SWS (80) and its treatment often is quite challenging. Primary treatment either consists of IOP-lowering medication or a surgical approach such as trabeculotomy, goniotomy or combined trabeculotomy-trabeculectomy (81).

WMS is a connective tissue disorder. In addition to systemic abnormalities such as short stature and cardiovascular defects, this syndrome is characterized by ocular malformations usually effecting the lens (82). In WMS, lens subluxation, spherophakia, and high myopia can cause a shallow anterior chamber and the development of glaucoma (83) which occurs in 80% of all WMS-cases (84). WMS can be inherited in an autosomal dominant and recessive manner (82). In case of shallowing anterior chamber or posterior synechiae developing from repeated lens-iris touch, early lensectomy should be promoted (76). Miotics and mydriatics should be avoided because they can result in pupillary block (82).

2.4.2.4 Glaucoma associated with acquired condition

This subgroup summarizes acquired conditions that can be associated with ocular hypertension or glaucoma. Uveitis, trauma, and Retinopathy of prematurity (ROP) are three examples (85). In accordance with the CGRN classification and Table 2, the proportion of glaucoma associated with acquired condition ranges from 1% to 43% of all childhood glaucoma types. 1% results from the data in a previously mentioned study by Alanazi *et al*. in

Saudi-Arabia (9) and from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) (18). 43% were found by Hoguet *et al*. in study data from Minnesota, USA, published by Aponte *et al*. (8). View Table 2 to see the amount of glaucoma associated with acquired condition in other studies. Results from an international study published in 2020 propose an average proportion of 15,8% of eyes diagnosed with childhood glaucoma (23).

Uveitis is one of the major reasons for glaucoma with acquired condition (2). In 41-67% of cases, juvenile idiopathic arthritis (JIA) is the underlying illness. Idiopathic uveitis is the second most frequent uveitis aetiology with 29%. Medication represents the first-line therapy when IOP is elevated even without the presence of glaucoma (85). Often surgery is needed but should preferably be performed in an eye without active inflammation to reduce intraocular damage. Angle surgery, trabeculectomy, and glaucoma drainage devices represent invasive options. Ciliary body destruction should rather be avoided because the ciliary body is already impaired by the ongoing inflammation (85).

Trauma to the eye, either blunt or penetrating, can promote an increase in intraocular pressure and glaucoma development. Reasons for this are, for example, the occurrence of uveitis, hyphaema or a dislocated lens. Topical IOP-lowering medication in the form of beta-blockers is the first-line therapy option. Adrenergic agonists and systemic acetazolamide are further alternatives to reduce increased IOP. Surgery should be considered if certain risk factors are present including hyphaema, corneal injury, and presence of optic atrophy (85).

ROP affects infants born prematurely with a birth weight below 1500 g or born before the 32nd week of pregnancy. If born after the 32nd week of pregnancy, the disease can only occur in children who were ventilated with high partial pressures or required blood transfusions (86). Secondary glaucoma occurs in 2-30% of children with the underlying disease ROP, especially if it was left untreated (87). Medical treatment and peripheral iridectomy are the main pillars of glaucoma therapy (85).

2.4.3 Glaucoma suspects

Suspects have characteristics similar to those of childhood glaucoma patients, but they do not fulfil the defining criteria of glaucoma cases (4). View chapter 2.3 to find distinguishing criteria for suspects established by the CGRN.

There are few studies that included not only children with glaucoma but also childhood glaucoma suspects. Despite the small number of studies that reported glaucoma suspects, a look at some suggests that this could be a significant proportion of patients. Hoguet *et al.* for example mentioned that 79 out of 205 patients examined in their study were not classified as glaucoma cases but as glaucoma suspects according to the CGRN definition (8). Kooner and colleagues mentioned, that in their retrospective review of 75 paediatric glaucoma suspects at the Children's Medical Center in Dallas, Texas, USA, suspicious optic disc appearance and

elevated IOP were the most commonly observed criteria. However, the definition of glaucoma suspects was not based on the CGRN classification, but on the authors' own criteria. In many cases a family history of some type of glaucoma could be found. 14.7% of these 75 patients required IOP lowering medication due to constantly high IOP (88). For the first time in literature, Greenberg *et al.* investigated the incidence and risk factors of glaucoma conversion in childhood glaucoma suspects defined by the CGRN classification. In a retrospective case series, the authors analysed 214 cases of glaucoma suspects and ocular hypertension in a tertiary referral centre. Mean follow up time was 39 months and 10.2% converted to glaucoma patients. The authors suggest periodic monitoring of childhood glaucoma suspects. Normal IOP on presentation is no guarantee, given that 50% of glaucoma suspects who converted to glaucoma patients did not present elevated IOP. No considerable differences in gender, family history, and central corneal thickness were found between children who developed glaucoma and those who did not (89).

During literature research for this thesis, no information on the occurrence of childhood glaucoma suspects in Germany could be found.

2.5 Diagnostics of childhood glaucoma

A quick diagnosis of glaucoma and the early start of therapy can reduce the extent of visual impairment for the child's whole life. If childhood glaucoma is suspected, this should be clarified as soon as possible. The diagnostic criteria for childhood glaucoma have previously been pointed out in Table 1. However, reliably examining the eyes of young children is a particular challenge. A thorough examination of children up to the age of four to five years often requires them to be under anaesthesia due to a lack of cooperation at the slit lamp. In addition to examining the patient's eyes, anamnestic information also plays an important role in determining the diagnosis. The gestational and family history as well as the child's ocular, general paediatric and syndromic history should be enquired. Problems during pregnancy, the diagnosis of childhood glaucoma in other family members, the presence of other diseases, malformations, or previous ocular illnesses or surgery could support the diagnosis (35).

2.5.1 Components of the eye exam

The following chapters describe the components of the examination of children suspected to have glaucoma as suggested in the 9th World Glaucoma Association Consensus Statement. In addition to the ocular examination, a general examination by a paediatrician is advisable if systemic associations are known to exist in connection with the type of glaucoma on hand (35).

2.5.1.1 General appearance, visual behaviour, and acuity assessment

By simply observing the infant or child, first signs such as photophobia, blepharospasm, enlarged eye size, and corneal oedema can be determined. A visual acuity test adapted to the

age should be added. If the child has certain signs suggestive of possibly inherited glaucoma, it is advisable to examine the parents as well (35).

2.5.1.2 Intraocular pressure measurement

Healthy infants have an IOP approximately 3 mmHg lower than that of adults. The reference range here is 8-18 mmHg (90). Of all the parameters that define the diagnosis of glaucoma, the IOP is the least accurate and often unreliable when assessing an infant or young child. The measurement is influenced by several factors, such as crying and eye movements of the child, anaesthetics and sedation agents during the examination under anaesthesia (EUA), possible use of specula to keep the eye open, and the central corneal thickness (CCT) (35).

Goldmann applanation tonometry (GAT) and its hand-held version, the Perkins applanation tonometry (PAT) for use during EUA, are the reference standard for the IOP measurement (35). GAT is performed on the patient while sitting at the table-mounted slit lamp (90). It is unsuitable for use in the operating room (91), so PAT was developed for patients who are unable or unlikely to cooperate at the slit lamp examination, such as children and anesthetized patients. PAT is adequately comparable with Goldmann tonometry (92). The iCare™ is a device that makes use of corneal contact while no topical anaesthetic drops are required (93). It can also be used while the child is lying down (90). Mendez-Hernandez *et al*. recommend the iCare™ PRO as an alternative to the reference standard (94). Yet, GAT should be considered as soon as the child appears to be able to cooperate at the slit lamp (35). A further tonometry method, the widely abandoned Schiötz tonometry, measures the IOP with a pen, which sinks into the anesthetized cornea due to its weight. This measurement method is used for scarred corneas or in developing countries where applanation tonometry is not possible (90).

2.5.1.3 Anterior segment examination

The anterior segment of the eye is best evaluated in neonates and infants with the use of a hand-held slit lamp or during EUA with an operating microscope. When the child is old enough to cooperate, inspection at the table-mounted slit lamp is preferred. The cornea should be scanned for the presence of enlargement, Haab striae, corneal edema, opacities, and posterior embryotoxon. Abnormalities of iris, pupil, and lens should be evaluated to determine the type of glaucoma (35). Gonioscopy is the examination of the angle of the anterior chamber using a contact glass (66). During gonioscopy the maturation and openness of the angle and iris insertion should be examined. Perhaps the angle appearance can be documented photographically (35).

2.5.1.4 Corneal diameter measurement

Children are born with a horizontal corneal diameter of around 10 mm, which increases to 11 mm during the first year of life. The corneal diameters can be stated horizontally and vertically. Some clinicians only measure the horizonal diameter. The diameters are measured during

EUA with a calliper from limbus to limbus or with a ruler on a close-up digital photo of the awake child (35).

2.5.1.5 Measurement of central corneal thickness

The measurement of the corneal thickness is called pachymetry. It is carried out with special ultrasound or optics-based devices (95) while in practice, ultrasonic pachymetry is mostly used (96). Mean CCT of healthy children is 553.69 µm (97). A thin central cornea leads to erroneously low IOP reading and vice versa (93).

2.5.1.6 Posterior segment examination

The pupil is ideally dilated during fundoscopy. The examiner should focus on the appearance of the optic disc as it is the most crucial and sensitive criterion for the identification of glaucoma as well as its progression. Examination should focus on the size of the optic disc, the cup/disc ratio, focal areas of rim loss and defects of nerve fibre layers. Progressive increase in CDR is considered a definition criterion for childhood glaucoma (4).

Fundoscopy also serves to rule out other congenital non-glaucomatous diseases that can damage the optic nerve. If the child presents an opaque cornea which hinders examination of the fundus with fundoscopy, ocular ultrasound may detect deep excavations of the optic nerve head. In order to keep track of optic disc change, photographs should be obtained (35).

2.5.1.7 Measurement of refraction

Refraction describes the ametropia of an eye and which correction with glasses is necessary (98). Measurement of refraction can play an important role for diagnosis and therapy control. Also, progressive myopia or a myopic shift, perhaps additional to an increase of ocular axial length may imply inadequate control of IOP (35).

To measure objective refraction, automatic measuring devices, so-called autorefractors, are standard today. They are often combined with an additional keratometer which measures the surface curvature of the cornea (99). With hand-held autorefractors there are alternative portable devices, such as the Retinomax (100). The Retinomax family also includes a combination device with keratometer and can be used intraoperatively as well (101).

2.5.1.8 Other investigations

Ultrasound (B scan) can be applied to measure the ocular axial length or detect retinal or optic disc pathologies especially when ocular media is opaque (35). Initial measurement of the axial length helps to diagnose glaucoma. Regular monitoring serves as parameter for progression and/or treatment response (35). Mean value of axial length of children aged 2-72 months without ophthalmological symptoms is 20.97 mm ± 1.48 mm (102). Normal growth of the globe ends around the age of 6 to 7 years (35).

Both, anterior segment optical coherence tomography (OCT) or ultrasound biomicroscopy (UBM) can be used to assess detailed structures of the anterior segment, such as corneal scars or the iridocorneal angle, when cornea or lens are opaque (35). OCT scans without the need of touching the eye (103) and generates cross-sectional images of structures in biological tissue (104). UBM is a special form of ultrasound imaging in which higher frequencies are used and thus only the structures in the anterior segment can be displayed in detail (99). In smaller children, UBM is only suitable during EUA because cooperation of the patient is needed (35).

To measure the visual field, perimetry can be tried in cooperative children to identify and track visual field defects due to glaucoma. With children from the age of seven to eight years, static automated perimetry should be possible (35).

Optic disc imaging devices, which depict the optic nerve head and retinal nerve fibre layer, can be useful. In children, they can primarily be used to monitor a possible structural change over time. Because cooperation is needed, optic disc imaging can be utilized as soon as a child is assessable at the slit lamp (35).

2.5.2 Examination under anaesthesia

Given the risks to which children are exposed during general anaesthesia, such as neurotoxicity for the central nervous system, the decision to perform EUA is not taken lightly. On the other hand, a child who may have glaucoma should be examined as soon as possible in order to initiate therapy and thus avert glaucoma damage. Ideally the ophthalmologist is able to carry out the definite operation right after the EUA. This can avoid unnecessary anaesthesia and a delay in therapy (35).

Most narcotics have an IOP-lowering effect which correlates with the depth of anaesthesia (105). Propofol is one such example, so Strzalkowska *et al.* recommend measuring at the beginning: The IOP during awareness is most closely represented when measured immediately after the application of a propofol bolus of 2-4 mg per kg bodyweight. In this moment the child is still breathing on its own but slightly sedated (106). Another example is sevoflurane. However, even at the earliest possible point of time after the start of sedation, inaccuracies in the measurement under the influence of sevoflurane can be expected. Blumberg *et al.* found out that the use of the anaesthetic agent ketamine is most likely to maintain the awake IOP of the child (107). The time of induction of anaesthesia and IOP measurement should be documented (35).
An international survey among ophthalmologists of the CGRN worked out the fact that sevoflurane inhaled agent is mostly utilized for EUA due to convenience and safety reasons. Ketamine was second most widely used precisely because of this favourable quality of not distorting the IOP too much (35).

Table 6 displays parameters and instruments for a thorough examination of a child under general anaesthesia.

Table 6: Data to collect in examinations under general anaesthesia on the basis of the 9th World Glaucoma Association Consensus Statement (35) and Hoffmann (108)

	Data	Instruments
Essential	Date	
	Anaesthetic agent	
	IOP including used tonometer	e.g., PAT, iCare®
	Corneal diameters	Caliper, ruler
	Axial length	Ultrasound
	Refraction	Retinoscope and lenses, autorefractor
	Pachymetry	Ultrasound pachymeter
	Anterior segment findings including gonioscopy	Surgical microscope, Koeppe or 4-mirror goniolens
	Posterior segment findings	Indirect ophthalmoscopy (28D or 20D lens), direct ophthalmoscope, surgical microscope
Optional	Optic disc digital photos	e.g., Retcam II®
		OCT
		UBM

IOP = intraocular pressure; OCT = optical coherence tomography; PAT = Perkins applanation tonometry; UBM = ultrasound biomicroscopy

2.5.3 Regulation of genetic analysis in Germany

When it comes to the field of human genetic testing in Germany, one inevitably must deal with the Gene Diagnostics Act, in German called “Gesetz über genetische Untersuchungen bei Menschen” (Gendiagnostikgesetz – GenDG). According to §27 (1) of the Gene Diagnostics Act (GenDG) of 31st July 2009 the law came into force in Germany on 1st February 2010. It regulates, inter alia, genetic examinations and genetic analyses carried out within the framework of genetic examinations on born humans and the handling of genetic samples and genetic data (§2 (1) of the Gene Diagnostics Act (GenDG)). As regulated by §7 (1) of the Gene Diagnostics Act (GenDG), diagnostic genetic examinations are exclusively reserved for physicians. The responsible physician is obliged to inform the patient about the nature, significance, and scope of the genetic examination (§9 (1) Gene Diagnostics Act (GenDG)). The law also stipulates that genetic testing or analysis, or the collection of samples, may only be carried out with the written consent of the person concerned. The person concerned also

decides how the results are to be handled regarding their notification or destruction ((§8 (1) Gene Diagnostics Act (GenDG). For diagnostic genetic testing, the physician in charge is supposed to offer genetic counselling to the patient once the test results are ready. If the patient is found to have a genetic condition that cannot be treated according to current scientific and technological standards, the physician must offer counselling. Furthermore, the law distinguishes between genetic counselling from simply providing test results. Only qualified physicians can perform genetic counselling ((§10 (1) Gene Diagnostics Act (GenDG). But both, the physician who performs the genetic consultation as well as the physician responsible for ordering the genetic examination can provide test results to the person concerned ((§11 (1) Gene Diagnostics Act (GenDG). If the person being examined is unable to give consent, the requirements for providing information, genetic counselling, and obtaining consent must be followed with regard to the representative, as stated in § 14 (1) sentence 4 of the Gene Diagnostics Act (GenDG)

Exceptions to the Gene Diagnostics Act are, however, e.g., research purposes as stated in §2 subsection 2 sentence 1 (GenDG). There is a lack of clear regulation in this area, as there is currently no specific law governing the use of genome analysis for research purposes. Only the EU General Data Protection Regulation and Federal Data Protection Act apply (109).

2.6 Impact of glaucoma on the quality of life and functional vision of affected children

Those affected by childhood glaucoma are forced to deal with their chronic vision-threatening diagnosis (3). Associated burdens such as repetitive diagnostics, surgery, long-term therapies with antiglaucoma medications (1), and appointments in hospitals interfere with the child's daily life (3). A possible visual impairment may handicap a normal development and education and hinder social integration and independence (3). Thus, the children and their parents/caregivers (from now on, for the sake of simplicity, only called "parents") are exposed to a lot of emotional and possibly financial stress. All these hardships should ultimately encourage to improve or maintain the quality of life (QoL) of the children concerned (1).

2.6.1 Determining quality of life in children

In general, the World Health Organization (WHO) defines QoL as an individual's perception of his or her position in life in the context of the culture and value systems which they live in and in relation to their aims, expectations, values and concerns (110). The perception of QoL differs between the age groups of children. This should be considered during assessment (111).

Since QoL is a subjective condition (111) that only the patients themselves can assess, it is essential to consider the patients' opinions (112). It makes sense to use patient-reported outcome measures (PROMs), which are questionnaire instruments directly fielded by patients themselves. PROMs measure a patient's outcome concerning their health and related topics

(113). Children can reliably and validly self-report on their health-related quality of life (HR-QoL) from the age of 5 years, if they are offered age-appropriate means to do so (114). In the case of small or particularly sick children or children with cognitive impairments, the subjective part of the assessment is more difficult. Here, asking the parents to reflect their child's presumed opinion of his or her QoL is perhaps the only way of obtaining information. This is then called a proxy report. Especially when stating subjective aspects, proxy reports may diverge from the child's own opinion. Nevertheless, it is a valuable information (111). PROMs can be used to assess the patient's quality of life (115), but also for example functional status and participation (113).

2.6.2 Assessing the quality of life and functional vision in children affected by glaucoma

It must be mentioned first that no childhood glaucoma-specific PROM exists to date (116, 117). To still be able to investigate the influence of glaucoma on children's QoL, studies were conducted using various health- or eyesight-related PROMs. Unfortunately, it cannot be denied that childhood glaucoma has a significant negative impact on the QoL of affected children. To support these children in dealing with the effects of their illness, professional psychological assistance should be offered (118).

In a few studies, the impact of glaucoma on children was assessed in one or more of these four different concepts: functional vision or functional visual ability (FVA), vision-related quality of life (VR-QoL), eye-related quality of life (ER-QoL) and HR-QoL. FVA is the ability to use vision in performing activities in children's daily life (3). In order to find out whether a treatment has a positive influence on a child's functioning, it is first necessary to evaluate the individual's perception of his or her own visual ability (119). In 2017 Elsman *et al.* published a study worth mentioning in which the authors tested a new instrument, the Participation and Activity Inventory for Children and Youth (PAI-CY). The topic of this questionnaire could be designated as a fifth concept and an addition to the four mentioned above. Various age-versions were developed and implemented in the Netherlands in Dutch (120). It can investigate participation of visually impaired children and various age versions of the PAI-CY have already been translated to English and Nepali (121). However, until now no research has been published in which the PAI-CY has been applied on children with glaucoma.

Table 7 lists six child-specific PROMs which have been applied on children with Childhood glaucoma. Most assessments took place in English-speaking populations since the original language of the questionnaires is almost exclusively English.

Table 7: Six child-specific PROMs already used to assess Quality of Life and functional visual ability in children with glaucoma.

PROM, year of publication	Concept evaluated	Age range (years)	Self- / proxy-reported	Original langua-ge(s)	Example study which published use in Childhood glaucoma, year of publication
Cardiff Visual Ability Questionnaire for Children (CVAQC), 2010 (119)	FVA	5-18	Self	English	Dahlmann-Noor *et al.*, 2017 (3), AlDarrab *et al.*, 2019 (122), Huang *et al.*, 2017 (123)
L. V. Prasad-Functional Vision Questionnaire Second Version (LVP-FVQ II), 2012 (124)	FVA	8-16	Self	Indian English, Hindi, Telugu	Gothwal *et al*., 2020 (1)
Children's Visual Function Questionnaire (CVFQ), 2004 (125)	VR-QoL	0-7	Proxy	English	Silva *et al.*, 2022 (126)
Impact of Vision Impairment for Children (IVI_C), 2011 (127)	VR-QoL	8-18	Self	English	Gothwal *et al.*, 2020 (1), Dahlmann-Noor *et al.*, 2017 (3), AlDarrab *et al.*, 2019 (122), Freedman *et al*., 2014 (128)
Pediatric Eye Questionnaires (PedEyeQ), 2019 (129)	ER-QoL	0-17	Self and proxy	English	Leske *et al*., 2021 (130)
Pediatric Quality of Life Inventory (PedsQL™) 4.0, 2001 (131)	HR-QoL	2-18	Self and proxy	English, Spanish	Dahlmann-Noor *et al.*, 2017 (3), Knight *et al.*, 2022 (116)

ER-QoL = eye-related quality of life; FVA = functional visual ability; HR-QoL = health-related quality of life; PROM = patient-reported outcome measure; VR-QoL = vision-related quality of life

Dahlmann-Noor *et al.*, for example, enrolled 119 2- to 16-year-old children with glaucoma in their study who visited Moorfield's Eye Hospital in London, UK. Mean age was 9.4 years. Ultimately, it turned out that in all three assessed concepts, FVA, VR-QoL and HR-QoL, children with glaucoma were below average compared to children with normal vision. Concerning HR-QoL, psychosocial aspects were more deeply affected than the physical. Older children felt less impaired than younger children, and the better the visual acuity, the higher the QoL. Bilateral glaucoma worsened FVA but not the VR-QoL or HR-QoL, compared to unilateral glaucoma. Interestingly, the analysis revealed that parents considered a greater influence of glaucoma on their child's HR-QoL than the children did themselves, suggesting that visually impaired children have their own standard of normality (3). Regarding VR-QoL, Freedman *et al.* came to an equivalent result concerning US-American children with glaucoma: higher visual acuity in the better seeing eye correlated with better VR-QoL (128). However, after conducting a study in Australia, Knight and colleagues came to a different conclusion compared to Dahlmann-*Noor et al.* regarding one point: In terms of HR-QoL, they observed that children aged 13-17 years expressed more troubles compared to younger children (8-12 years). These mainly concerned autonomy, social well-being and worries about ocular health. Knight *et al.* described their awareness of the divergent result and suggested that adolescents are more concerned about the impact their condition could have on their future adult life. The outcome may have also arisen from methodical differences and further research is needed to find out what impact ageing has on HR-QoL (116). In a large-scale study taken place in Minnesota and Texas, USA, Leske *et al*. enrolled 1,037 children with eye conditions aged 0-17 years to evaluate ER-QoL and FVA. Among these were 24 cases of glaucoma. A control group with normal sighted children also completed the questionnaires. The results of the questionnaires were not presented individually for each included eye condition, but the researchers generally found reduced ER-QoL and functional vision in children with eye diseases compared to those with normal vision. Leske and colleagues used the Pediatric Eye Questionnaires (PedEyeQ) (130) which were developed in the USA (129).

As most PROMs are only available in a few languages, mostly English, some research groups carried out translations into their own language and applied these on children with glaucoma. This was the case with AlDarrab *et al.* who translated the CVAQC and the IVI_C from English to Arabic and slightly adapted the content to the Saudi culture. They assessed children at an Eye Specialist Hospital in Riyadh, Saudi Arabia. The authors highlighted that lower visual acuity, at least 3 performed glaucoma surgeries, and bilateral glaucoma worsened the results in both questionnaires significantly. Additionally, children with an increased number of daily eye drops applied to both eyes, achieved lower scores in the CVAQC (122).

During literature research for this thesis, no data could be found regarding the assessment of FVA, VR-QoL, HR-QoL or ER-QoL in childhood glaucoma patients living in Germany.

2.6.3 Review of patient-reported outcome measures (PROMs) for German-speaking childhood glaucoma patients

This section explores the suitability of existing PROMs for assessing FVA and QoL in German-speaking children with glaucoma and their parents. The consideration is carried out in synopsis of the already existing child-appropriate PROMs for children and young people with visual impairment summarized by Tadić and colleagues in 2017 (113).

In the category functional vision /visual ability Tadić *et al.* presented four PROMs (113) of which two, the L. V. Prasad-Functional Vision Questionnaire (LVP-FVQ) and LVP-FVQ II, are not suitable for Germany, because they were designed for children living in developing countries (132). The other two PROMs Tadić *et al.* pointed out are the Functional Vision Questionnaire for Children and Young people (FVQ_CYP) and the CVAQC mentioned in Table 7 (113). Terheyden and Finger published a study in 2019 in which they stated that the CVAQC was not yet available in German (133). To date, these two PROMs are still not yet available in German meaning there is no PROM on hand to assess FVA in German-speaking children with Childhood glaucoma.

Tadić et *al.* also pointed out three child-suitable PROMs which evaluate VR-QoL of which two are listed in Table 7: The CVFQ, the IVI_C and the Vision-related Quality of Life of Children & Young People (VQoL_CYP) (113). Pieh *et al.* translated the CVFQ into German in cooperation with the original authors, introduced it 2009 and named it “Fragebogen zum Kindlichen Sehvermögen (FKS)” (134). Farin and colleagues tested the FKS in a German hospital on children aged 3-7 years with and without ophthalmological issues. The authors acknowledged the applicability to assess children’s VR-QoL (135). The VQoL_CYP was developed in the UK and designed for children from 10 to 15 years (136) until age-appropriate extensions were introduced in 2020 now including children aged 8-17 years (137). According to Terheyden and Finger, no German version of the IVI_C or VQoL_CYP could be found in 2019 (133). To date, these two PROMS and the extensions of the VQoL_CYP are still not yet available in German.

Concerning the only collection of questionnaires assessing ER-QoL in children, which are the PedEyeQ mentioned in Table 7, there are currently only English and Spanish versions available (138).

Lastly, in order to measure HR-QoL in chronically ill children, one can for example use the previously mentioned PedsQL™ (139), the KINDL® (140) or the KIDSCREEN instruments (141). The PedsQL™ and the KINDL® hold some additional disease-specific modules, however, both do not yet offer an additional module for children with glaucoma (139, 142). The original version of the PedsQL™ is US American and its generic core instrument, the PedsQL™ 4.0 Generic Core Scales, was translated into German by Felder-Puig *et al.* A publication in 2004 demonstrates the equivalence to the original version (143).

The KINDL was developed in 1994 and revised in 1998 to its currently available version called KINDL^R (140). It is an original German-language measure suitable for children and adolescents from 3 to 17 years (144). It has been translated into many other languages (140) and can be used for healthy as well as ill patients (145). The self-reported generic core instrument is available in three age groups: 4-6 years (named Kiddy-KINDL^R), 7-13 years (Kid-KINDL^R), and 14-17 years (Kiddo-KINDL^R). Ravens-Sieberer and Bullinger also created proxy-reported questionnaires in the age-groups 3-6-years (named Kiddy-KINDL^R for parents) and 7-17 years (Kid-/Kiddo-KINDL^R for parents). In addition to each generic age-adapted core instrument there is an additional sub-scale named "Disease" or “Erkrankung” in German which is intended for ill children. The freely available manual explains use and evaluation of the KINDL^R. As per the instructions, it is not necessary to accompany the child or parents while the questionnaires are being filled out. But support is to be provided to children who’s reading skills are insufficient to understand the questions. However, it is crucial that both, child and parents, complete their respective questionnaires separately. As indicated by the manual, answering in an interview or even telephone interview format is an alternative to filling out the PROM in person. However, it isn't explicitly specified whether this also applies to the parental versions. Additionally, according to the manual, it is essential that the questionnaires are completed in their entirety to ensure proper evaluation. No time limit should be set for the patient and parents to fill in the PROM (144). Lastly, the development of another PROM evaluating HR-QoL, the KIDSCREEN instruments from 2001 to 2004 was funded by the European Union and took place simultaneously in 13 European countries, one of them being Germany (146). They come in three versions, a long-version KIDSCREEN-52 and two shorter versions KIDSCREEN-27 and KIDSCREEN-10 Index, of which each is available as self-report measure for children and adolescents aged 8-18 years and as third-party version for caregivers (141). Each of the six versions is accessible for free download in German (147).

2.7 Registries

This chapter covers the subject of registries, providing an overview of their general definition and purpose. It also highlights the unique characteristics of registries tailored for rare diseases like childhood glaucoma. Furthermore, the chapter delves into the planning of a registry and essential considerations when pilot testing. Moreover, already existing (inter)national childhood glaucoma registries are introduced, and two single centre Childhood Glaucoma registries are compared.

2.7.1 Definition and purpose of a registry

The National Institutes of Health of the U.S. Department of Health and Human Services, for example, define the term “registry” as “a collection of information about individuals, usually focused around a specific diagnosis or condition” (148). This refers to both the process of collecting and storing information as well as the programs and records that hold the data. To

emphasize that it is medical information, which is being collected, registries may also be known as patient registries, clinical registries, clinical data registries, disease registries, or outcomes registries. A certain condition serves as the inclusion criterion (149). Patients transmit their data to the registry on a voluntary basis and thereby provide first-hand information to health care professionals and researchers. This contributes to an increase in understanding the condition over time and/or track incidences or prevalences of certain illnesses and treatments (148). Larsson *et al.* conducted an international study which included 13 registries in 5 countries. The researchers point out that disease registries can improve health outcomes, reduce healthcare costs and increase the benefit of healthcare because they greatly facilitate the comparison and dissemination of medical procedures (150).

Regarding ophthalmology, registries serve to track, collect, and evaluate data of rare ophthalmic diseases or challenging conditions in terms of epidemiology, visual outcomes of procedures, or adverse events. The strength of registries is systematic, detailed and specific clinical data collection (151).

A registry must not be mistaken for a clinical trial. In a clinical trial, active interventions are carried out, while in a registry, a passive observational approach is chosen in which no specific treatment intended to change the patient's outcome is tested. However, a certain treatment may be an inclusion criterion (149).

2.7.2 Characteristics of rare disease registries

In general, the European Union defines that “a rare disease is one that affects no more than 1 person in 2000” (152).

Due to the small number of patients with a rare disease, often literature merely contains case reports or small case series. This can lead to an incompletely characterized clinical picture with insufficient knowledge of disease characteristics and long-term treatment outcomes. In addition, clinicians often lack the opportunity and experience to manage affected patients. For these reasons an international and long-term managed disease registry may be the only feasible way to comprehensively increase knowledge and treatment options for patients. For patient groups, too, rare disease registries are often welcome projects. Not only does establishing a rare disease registry increase knowledge about a certain disease, but also connect affected patients, families, and clinicians. Rare disease registries also initiate research on a molecular, physiological, and genetic basis and the evaluation of medicine and medical devices. Apart from the participants and clinicians or investigators who supply the information, rare disease registries may also provide advantages to other stakeholders such as the biopharmaceutical industry or the government. Typically, the inclusion criteria for rare disease registries are less strict compared to other general disease registries. Here, the mere diagnosis of a physician is often sufficient to enable inclusion in the registry. A major aim is to be able to

include as many affected patients as possible. Here, a good balance must be struck to collect as much important data as possible without overloading the dataset. Unambiguously formulated data elements with little room for misinterpretation and standardised procedures for uniform data collection and management are helpful as well (149).

Gliklich *et al.* recommend the use of PROMs in rare disease registries to measure the effect of a treatment on the quality of life. However, even these authors admit that it can be difficult to select the right PROMs for a rare disease because there might be no disease-specific measures available and generic measures for more common diseases do not fit well due to lack of details. It is complicated to generate more appropriate PROMs because development and evaluation are expensive due to the small number of patients and the large number of language translations required (149).

Another focus of a rare disease registry is long-term data collection. The question here is how to generate regular data collection from patients over a long period of time. This can be done during regular appointments with the specialist or/and the clinician. However, there is a risk that the patient or the doctor could lose interest in participating in the study. Gliklich *et al.* suggest that, depending on the objectives of the registry, patients could have access to the registry and thus be able to put in information themselves and view the data sets. While data entered by patients themselves is not as detailed or conveyed in medical language as information from a doctor, it is still reliable information. To further reassure patients that the registry is meeting its goals and is a worthwhile endeavour, transparency in processes, analyses and publications can be helpful (149).

The European Platform on Rare Disease Registration (EU RD Platform) serves as a platform specifically dedicated to rare disease registries in the EU. It aids in locating registries, data collection, and the establishment of new registries following EU standards. All rare disease registries can be included in this platform.

2.7.3 Planning a registry

Gliklich *et al.* outline a structured approach for planning a registry, which involves several key steps. To begin, it is essential to clearly determine the registry's purpose. Subsequently, an evaluation should be conducted to conclude if a registry is the most appropriate method to achieve the intended goals. Identifying the key stakeholders who will be involved in the registry's development and utilization is the next crucial step. Additionally, assessing the feasibility and long-term sustainability of the registry is vital to ensure its viability. Once the decision to proceed with the registry is made, the planning process advances to the next phase. This entails assembling a dedicated registry team to effectively organise and realise its operations. Creating a robust governance and oversight plan helps ensure clarity to stakeholders. To further refine the registry's design, it is essential to define the extent and

precision required for its specific objectives. This includes specifying the dataset to be collected, determining the relevant patient outcomes, and identifying the target population. Piloting data collection tools is deemed crucial to assess the time and cost implications of data collection, as well as to identify any issues related to missing data and validity. A critical aspect of the planning process of a registry involves developing a comprehensive study plan or protocol that outlines the registry's methodology and procedures. Finally, creating a detailed project plan is necessary to effectively manage and coordinate all aspects of the registry's implementation (153).

2.7.3.1 Pilot testing

Pilot studies are analogous to feasibility studies designed to provide direction for the preparation and increase the chance of success of a comprehensive investigation. As per Thabane and colleagues, in a pilot study, the data collected should not achieve statistical significance unless the study is sufficiently powered to detect minimal clinically important differences, which is atypical for this type of study. There are several valid justifications for conducting a pilot study, which include assessing the feasibility of critical processes that are vital for the success of the main study. These processes encompass evaluating the required time and resources, identifying potential concerns linked to human and data management, and, e.g., ensuring the safety of the treatment. Further motivations for conducting a pilot study may encompass determining the recruitment rate, clarity of identifying individuals who meet or do not meet the inclusion and exclusion criteria, evaluating the quality of data collection tools in terms of comprehensibility for participants when responding to study questions, and ascertaining if there is enough space on the data collection form to accommodate all received data (154). Conducting a pilot study can also reveal issues in registry logistics, for example, being able to systematically identify subjects for inclusion (153).

The sample size for a pilot study is determined by practical considerations related to recruitment and the requirements for assessing feasibility. It is customary for the sample size to be determined by practical factors such as patient flow and financial limitations (155).

A carefully planned pilot study establishes distinct feasibility objectives, analytical strategies, and criteria to gauge the feasibility. Feasibility objectives serve as the fundamental framework for interpreting the outcomes of the pilot study and should encompass crucial aspects such as the rates of recruitment, consent, completion, and variance estimates, thus, being able to make a definitive determination on whether it is indeed viable to advance to the main study. In this regard, there are four possible outcomes: the infeasibility of the main study, feasibility with necessary modifications, feasibility without modifications, and, concerning the latter, the authors distinguish whether closer monitoring is required or not (154). Study elements that are found to be unfeasible should be adapted in the following trial or eliminated entirely (155).

Analysing a pilot study, which is used to plan a randomized controlled trial, should primarily involve descriptive analysis or emphasize the estimation of confidence intervals (156). However, no explicit recommendations were found regarding the approach to analysing a pilot study in preparation for a patient registry or database.

2.7.3.2 Processing of personal data

According to the General Data Protection Regulation (GDPR) in the European Union from 2016, “personal data” is information that can be related to an identifiable or identified natural person, also named “data subject”, and “processing” data means performing any kind of operation on personal data, for example collecting, organizing, storing, using, or destroying (157). "Pseudonymization" is a method to detach processed personal data from the data subject’s identity (158). It needs additional information that should be stored separately to restore the connection. The individual or public entity responsible for deciding why and how personal data is processed, named “controller” by the GDPR, must put in place suitable technical and organizational safeguards, like pseudonymization. These safeguards are meant to shield protected personal data. Only data that is necessary for a specific purpose shall be processed and made accessible. A “processor” may be a person who processes personal data in the interest of a controller (157). An organisation or company may process “sensitive data” (159), such as genetic or health-related data (160), if it is for scientific research purposes (159).

Pseudonymisation can either be “first-level”, which according to Lablans *et al.* is direct pseudonymisation of data before usage for research purposes. It is to be distinguished from transforming an existing pseudonym into another (161). The easiest method for first-level pseudonymization involves replacing an identifier (for example a probands name) with a number that increases sequentially, beginning from number 0, for instance. No number should be repeated. This technique is called the “counter”. Due to its simplicity, it makes a suitable choice for small datasets. While it does reveal the order of data collection, it remains a suitable method for separating personal data from the data subject. However, it may not be suitable for larger, more complex datasets. Another, albeit stronger, pseudonymisation method involving numbers is to use a “random number generator”, which assigns a random number to an identifier. However, there is the risk of collisions, which means two identifiers may receive the same pseudonym (162). In 2015, Lablans *et al.* introduced the "Mainzelliste," a first-level pseudonymization tool which generates pseudonyms, through which alone re-identification is not possible. Re-identification is possible via web-browser. The Mainzelliste replaced the "PID-Generator." The PID-Generator had been a standard tool for German networks until that point but became unsuitable for modern research infrastructure implementations (161). The Mainzelliste is currently being used by various medical joint research projects, including several registries (163).

2.7.4 Existing Childhood Glaucoma registries

Since the year 2000, the European Commission subsidises Orphanet, a network of meanwhile 41 countries in the European Union and beyond. Orphanet is a European project and describes itself as the reference source for rare diseases by providing information and contributing to knowledge (164).

The condition “Childhood glaucoma” as defined by the CGRN classification is not (yet) recorded in their database of rare diseases. However, Congenital glaucoma (ORPHAcode 98976), glaucoma secondary to spherophakia/ectopia lentis and megalocornea (ORPHAcode 238763) and some other diagnoses that are associated with the development of SCG can be found in the Orphanet database, for example Axenfeld-Rieger syndrome (ORPHAcode 782), Peters anomaly and Peters plus syndrome (ORPHAcodes 708 and 709), Isolated Aniridia (ORPHAcode 250923), Sturge-Weber syndrome (ORPHAcode 3205), and Weill-Marchesani syndrome (ORPHAcode 3449) (165).

Orphanet’s report of rare disease registries in Europe from December 2021 summarizes all registries of specific rare diseases or disease groups in the European Union and other participating countries, which were listed in their database at that time. There is no registry listed in this report that deals exclusively with childhood glaucoma, including all its different categories specified by the CGRN. Only more broadly based registries can be found, which generally include congenital/ rare eye diseases or some of the diagnoses associated with SCG stated in the last paragraph (166).

Additionally, there is the European Platform on Rare Disease Registration (EU RD Platform), which serves as a dedicated platform for rare disease registries in the EU. It aids in locating registries, data collection, and the establishment of new registries according to EU standards. All rare disease registries can be included in this platform (167).

During international literature research, however, one comes across publications that draw their data from established childhood glaucoma registries. The investigations revealed an international childhood glaucoma registry (Thau: Robison D. Harley, MD CGRN International Pediatric Glaucoma Registry (5)) and two childhood glaucoma registries involving only one central care centre so far (Lopes (11), Alanazi (9)/Zaman (168)). Also amongst the results were three registries, that include both, adults-onset glaucoma, and childhood glaucoma: the ANZRAG, a binational glaucoma registry of Australia and New Zealand (Souzeau (169)/Knight (18)), one Chinese national glaucoma registry, the CGSC (Chinese Glaucoma Study Consortium) (Zhang (170)), and one regional glaucoma registry situated in Dallas, Texas, USA (Kooner (171)/Fung (33)). Also worth mentioning is a national paediatric cataract registry which includes cases of postoperative glaucoma (Nystrom (55)).

Considering, this thesis deals with the initiation of a national German childhood glaucoma registry by conducting a pilot study in one central care centre, the subsequent assessment focuses on similar projects. Here, the comparison of the only two existing single centre childhood glaucoma registries, realized, however, as retrospective pilot or cohort studies, is particularly interesting, as shown in Table 8. However, the two papers that mention that the study is being conducted as a pilot study do not provide details of its analytical strategies or feasibility objectives.

Table 8: Comparison of two single centre Childhood Glaucoma registries (9, 11, 168)

Category	Registry at King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia (9, 168)		Registry database at the Department of Ophthalmology and Visual Sciences of the Federal University of São Paulo, Brazil (11)
	Alanazi *et al.* 2013	Zaman *et al.* 2014	
Study type	Registry-based cohort study	Pilot study	Pilot study
Study design	Prospective	Transfer of retrospective data from a paper-based registry	Retrospective
Registry design	Paper/Computer-based (Microsoft Access database)	Web-based registry (Lime Survey software + MySQL software)	Web-based (Google Forms + cloud)
Period of data collection	2001-2003 (29 months)	2000-2003	Two datasets (of one period of data collection not stated, the other includes patients treated from March 2017 onward)
Childhood Glaucoma classification criteria	Own criteria: IOP >21 mmHg + associated signs e.g., globe enlargement, enlarged corneal diameter, corneal haze, Haab striae, and increased axial length. SCG: with associated ocular or systemic anomalies.		CGRN classification
Inclusion criteria	All patients newly diagnosed with childhood glaucoma at King Khaled		Patients born between 2006 and 2016 and diagnosed with childhood glaucoma who were

	Eye Specialist Hospital during the above-mentioned time period		registered in the patient electronic health records
Exclusion criteria	Children with aphakic glaucoma, traumatic glaucoma, uveitic glaucoma, and other acquired glaucomas in children		*Not stated*
Number of patients/ eyes included	180/325	80/ *not stated*	72/*not stated*
Drop-outs	*Not stated*	*Not stated*	*Not stated*
Financial aspects mentioned	*Not stated*	*Yes*	*Not stated*
Data protection method	*Not stated*	*Not stated*	Patients are identified by a random code only accessible to the investigators
Registry committee	A clinical coordinator, a physician, rest not stated	Two ophthalmologists, a biostatistician, two IT specialists, a registry manager	*Not stated*

CGRN = childhood glaucoma research network; IOP = intraocular pressure; mm Hg = millimetres of mercury; SCG = secondary childhood glaucoma

3 Material and Methods

The author of this dissertation conducted first-level pseudonymisation of data, proband recruitment, testing of study logistics and data collection, testing and primary adaptation of original study material as well as in- and exclusion criteria, and proportional study outcome analysis using descriptive analysis and qualitative methods, such as insights derived from observations. The testing of study material as well as the in- and exclusion criteria was to be performed on 20 children per group for which a time range of 6 months per group was considered realistic. The number of 20 per group was assumed to bring enough variance in the data for evaluation, according to Prof. [redacted]. All data were supposed to be newly collected and existing patient data to be excluded. A statistical evaluation of the raw data collected with the tools was not planned in this phase due to the nature of conducting a pilot study with a restricted number of cases.

3.1 Introduction of in- / exclusion criteria

The following inclusion criteria for the pilot phase was set by Prof. [redacted] and Prof. [redacted]: Age under 18 years at the date of inclusion, glaucoma diagnosis of at least one eye (experimental group) or no glaucoma diagnosis but at least one eye with other diagnosed eye disease (control group), and written consent from all legal guardians. Exclusion from the pilot study applied if any of the inclusion criteria were not met.

3.2 Proband enrolment methods

The feasibility of recruiting participants depended on the interest and willingness of the participants themselves, or more precisely, their parents, as well as maintaining a low dropout rate and meeting the predetermined goal of enrolling 20 participants in the experimental group within six months. Here, too, the emphasis was on observing how the enrolment of participants in the experimental group could be incorporated into the daily clinical activities of the Department of Ophthalmology at Mainz University Medical Center within a future database or registry.

MD [redacted] conducted and demonstrated the recruitment of the first three probands and oral briefings with their legal guardians in the experimental group. The subsequent proband recruitments and oral briefings were solely executed by the author of this thesis. The only exceptions were the consultation about nature, significance, and implications of the genetic examination, providing the genetic results to the person concerned, and the act of blood collection from the child. The writer of this thesis was limited to working part-time on the pilot study, which meant only being available during certain hours on selected weekdays but tailored to the usual presence or arrival of a (potential) participant at either the outpatient

department, on the ward, and in the operating room. Continuous presence and availability in the eye clinic were therefore not guaranteed.

3.3 Introduction of original study material

This subchapter introduces all study material provided to the author of this dissertation by the founding study members. Most study materials were newly designed. All material were to be tested in the pilot phase, however, focus was on the experimental group, as it constituted the target population for the future database and registry. All documents were kept in German exclusively. Standard study material for the experimental group consisted of three information forms, one informed consent and two informed assent forms, furthermore, two questionnaires, one form to record the EUA and a PROM in age-appropriate parent and child version, if applicable. Additionally, the initial plan involved the collection of blood and saliva samples in the experimental group as a preparation step for pseudonymized whole exome sequencing, with the potential inclusion of the results in the database. Sample storage and conduction of pseudonymized whole exome sequencing were to be handled in cooperation with the Human Genetics Department of the University Medical Center Mainz.

However, prior to recruiting the first proband for the pilot study, but after initial approval of the Ethics Committee, the concept of sample collection for pseudonymized whole exome sequencing was removed from the pilot study and replaced with an alternative approach due to a lack of research funding. More to this in chapter 3.3.4. Minor adjustments to the designed study materials, also during study execution, were permitted with prior mutual agreement.

Figure 2 and Figure 3 provide an overview of the documents and samples comprising the standard data set for an individual patient within the experimental and the control group, respectively, as approved by the Ethics Committee. The experimental group's materials can be categorized into four, while the control group's materials fall into three categories, each differentiated by colour. Inclusion of materials marked with an asterisk (*) was necessary to deem a patient's dataset to be complete. Elaborate descriptions of the documents are provided in the subsequent chapters. Chapter 4.3 presents these two figures once again, but with modified content after a few adjustments had been made during the study’s realization.

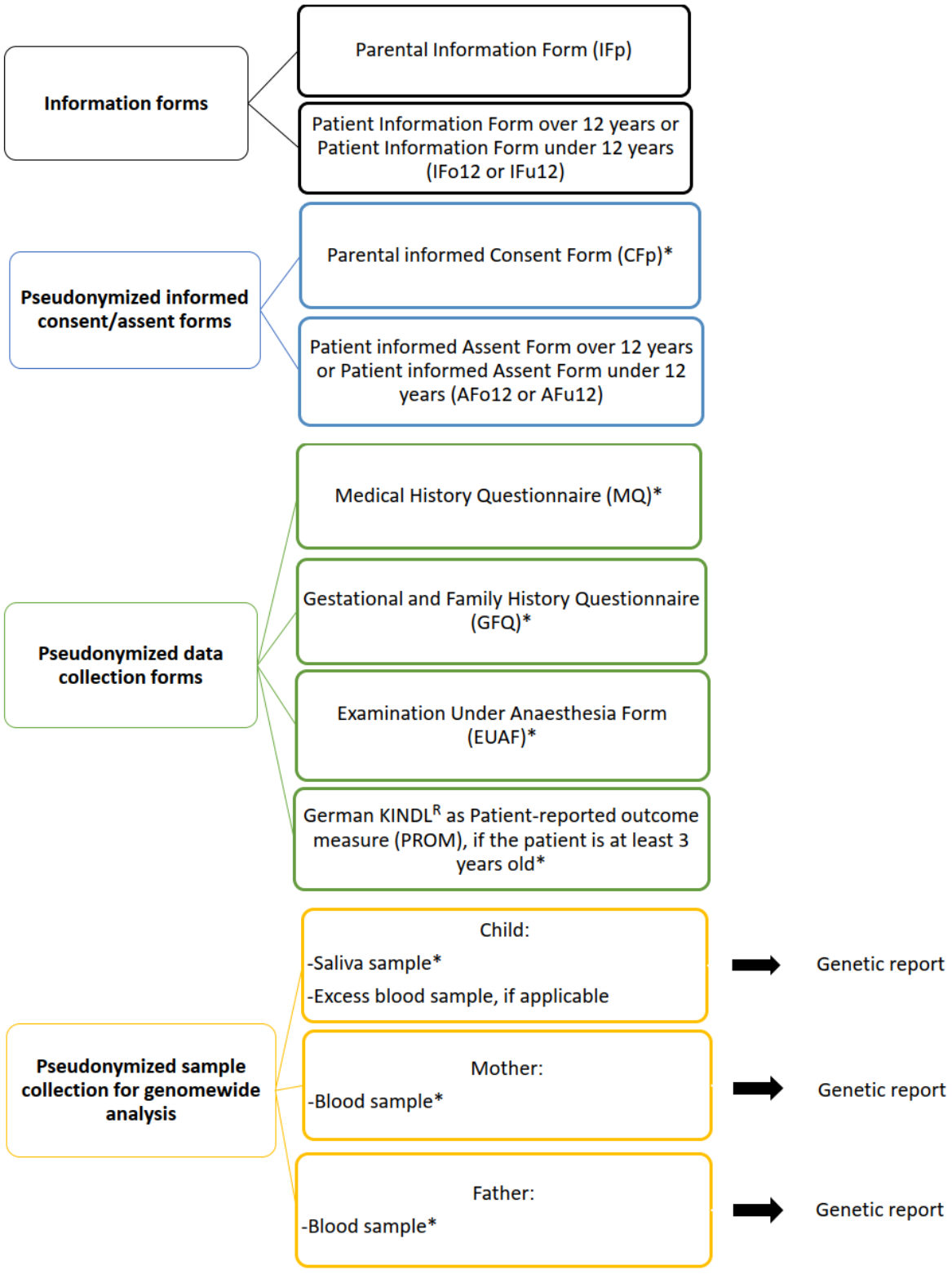


Figure 2: Display of original standard study material and samples that comprised the data set for an individual patient within the experimental cohort.

Concerning the control group, standard study material was identical to the experimental group, but excluding the form documenting the EUA, any samples or genetic analysis. No separate forms were designed. The control group served as a comparison group for data quality

verification in a specific subset of the data. However, the standard dataset still included all information, consent and assent forms, questionnaires, and the PROM to ensure that conditions in both groups were comparable.

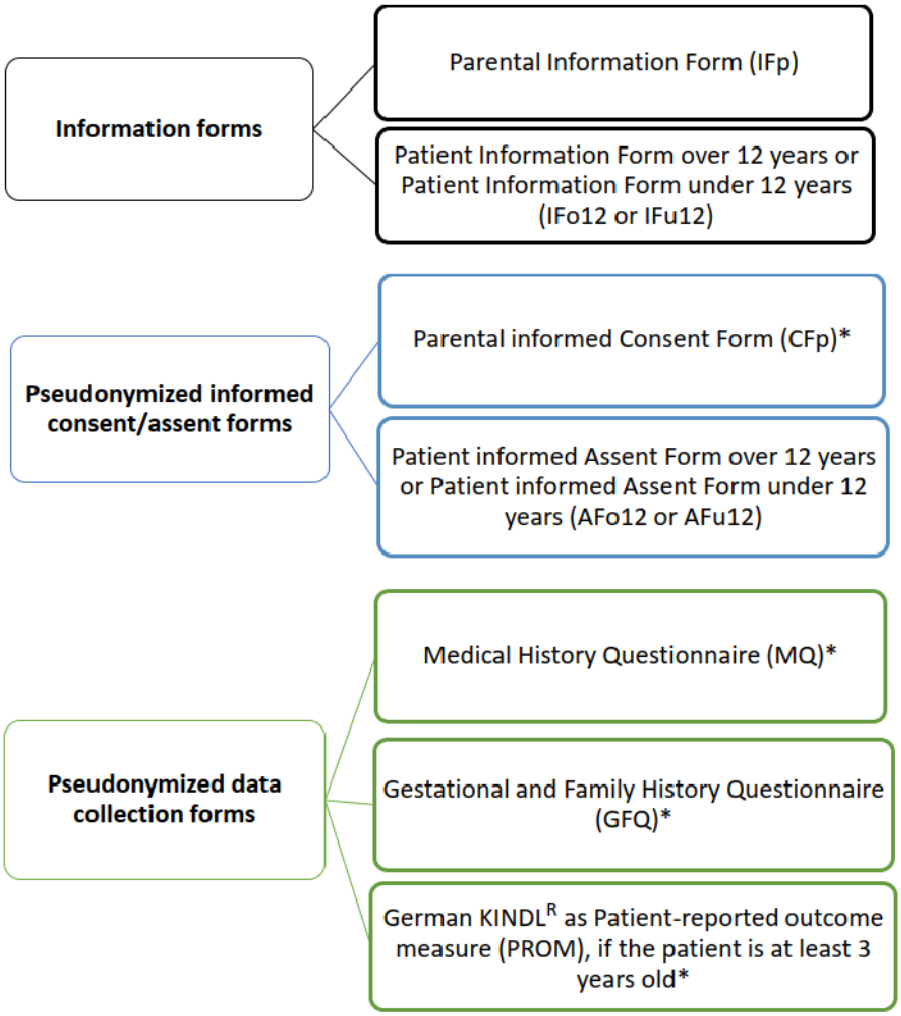


Figure 3: Display of original standard study material and samples that comprised the data set for an individual patient within the control cohort.

3.3.1 Information forms (IF)

Prof. [redacted] and Prof. [redacted] designed three information forms to let the reader get a first idea of the pilot study. One was intended for parents, called Parental Information Form (IFp), in German named “Elterninformation” and two others for the literate children written in child-friendly language. A distinction was made between children under and over 12 years of age. View Addendum 7.2.1 for the original Parental Information Form. For a start, this document was to be given to parents whose child or children potentially met the inclusion criteria. Additionally, an age-appropriate patient information form was to be handed out to the potentially participating child. However, the text was designed in a manner that primarily addresses a child with glaucoma. View Addendum 7.2.2 for the original Patient Information Form under 12 years (IFu12) for children younger than 12 years of age (in German:

“Patienteninformation für Kinder” and view Addendum 7.2.3 for the Patient Information Form over 12 years (IFo12) designed for children above the age of 12 (in German: **“**Patienteninformation für Jugendliche ab 12 Jahre”). These three forms were to remain with the legal guardians and the patient and did not need to be returned to a study member.

In each of the three versions, the reader is presented with the study's context and purpose. Furthermore, the IFp includes information about its safety and advantages. The forms were dated with the date of its creation, which was April 24th, 2017. To ensure non-disclosure, data of patients and parents were to be pseudonymised and the code only accessible to the study team. The collected data was to be pseudonymized on paper as well as in an electronic way and stored on a secure server at Mainz University Medical Center. Participation was voluntary, and participants/parents were aware that they could withdraw at any time without having to give any reasons or risking disadvantage for the child. Data and samples obtained before a participant’s withdrawal were to be destroyed immediately. If the participant did not withdraw, samples and data would be destroyed at the end of the pilot study or no later than 10 years. The collection of pregnancy data, data of familial diseases, and examination results in the context of ophthalmic treatment at Mainz University Medical Center were mentioned explicitly in the information form - in greater detail in the parental version than in the patient versions. Direct information retrieval from the parents would require about 15 minutes. The resident ophthalmologist treating the participant shall be involved at a later point in time and complete a standardized follow-up questionnaire. Regarding the genetic analysis, a blood sample of 18 ml from the parents and a saliva sample from the participant would be necessary. If blood is obtained anyway during the usual diagnostics before the eye operation/EUA of the child, it may also be used so no additional blood sampling of the child would be necessary. Since the pilot study was only intended to find out the sufficiency of the sample quantity for anonymous whole exome sequencing, no results would be available to the participant. Data and samples would be stored for no longer than 10 years.

3.3.2 Informed consent and assent forms

Written consent of all legal guardians was an inclusion criterion for the study. Based on the three different information forms, Prof. [redacted] and Prof. [redacted] designed one Parental informed Consent Form (CFp) and two informed assent forms. Inclusion in the study was only permitted when all legal guardians, usually both parents, had hand-signed the hard-copy CFp, in German “Einwilligungserklärung”. By signing, the person declared to have read the information form and agrees to the points mentioned therein. The person also confirmed an oral briefing on the nature, significance, risks, and scope of the registry, that all questions were answered satisfactorily and that he or she had enough time to think about participating. Furthermore, it is agreed on that all data collected, including biomaterials, will be stored anonymously for ten years, and destroyed after this time span. The analysis of the biomaterial

is conducted strictly on an anonymous basis, and consequently, results cannot be provided. The participant confirmed to have received and read a copy of each, the IFp and CFp. In case of queries the participant may be contacted by telephone. The CFp was dated with the date of its creation, which was June 18th, 2017.

Additionally, there was the possibility for the child to sign on a specially designed patient assent form. Here too, a distinction was made between children under and over 12 years of age. The information herein is slimmed down compared to the CFp and formulated in a child-friendly way. They only meant to give the child the feeling of active participation. This should appeal mainly to the older children. A missing written assent by the underage participant was not legally binding. Analogue to the IFu12 and IFo12, the text was composed in a way that primarily a child having glaucoma would feel addressed. Just like with all other documents, no alternative forms had been created for glaucoma suspects or the control group.

As mentioned above, legal guardians and interested youngsters were to be informed about the details of the study not just in writing but also in personal conversation. The designated study physicians Prof. [redacted], Prof. [redacted], and MD [redacted] were responsible for oral briefing on the pilot study so only their signature was legally binding. All consent and assent forms included a field for the study physician's name and signature who had undertaken the oral briefing. However, it was allowed to delegate the information consultation task to another non-physician study team member. View Addendum 7.2.4. for the CFp. The Patient informed Assent Form under 12 years (AFu12), named "Einwilligungserklärung für Kinder (bis 12 Jahre)" in German, is presented in Addendum 7.2.5 and the Patient informed Assent Form over 12 years (AFo12), named "Einwilligungserklärung für Kinder (>12 Jahre)" in German, in Addendum 7.2.6.

3.3.3 Data collection tools

To collect the desired data about the participants in a systematic and comparable way, Prof. [redacted] and Prof. [redacted] designed one Examination Under Anaesthesia form (EUAF) and two questionnaires. In addition, the KINDL^R was selected as PROM for the pilot study.

As the name already suggests, the EUAF was designed to record information collected during an EUA. This was to be filled in by the ophthalmologist who performed the EUA. Regarding the questionnaires, one served to mainly enquire the medical history and the other the familial background, birth, and pregnancy history of the participant. However, it was allowed to delegate the process of data collection using these questionnaires to another non-physician study team member, which in every case was the author of this dissertation.

3.3.3.1 Medical History Questionnaire (MQ)

This questionnaire consisted of only one unilaterally printed page and had the German name "ReKiG-Stationsbogen v1.0". The Medical History Questionnaire was designed with the

understanding that it was preferably filled out under supervision of a study member or in an interview-style, as some questions might not be easily understood by laypersons. Parents were permitted to refer to any documents they brought along for assistance or to provide the necessary information later. They were not required to rely solely on their memory.

At first the questionnaire required the entry of the patient's pseudonymisation code, the date and name of the clinic and the name of the doctor filling in this form or assisting the parents to complete it. Next was general information about the child namely date of birth, gender, country of origin and five-digit postcode of the place of residence. The option "Germany" (in German: "Deutschland") was pointed out while the alternative was "foreign country" (in German: "Ausland") with some space behind to elaborate. The following questions specifically dealt with the child's glaucoma disease: Date of suspected diagnosis and which specialty (paediatrician or ophthalmologist) or clinic made it; date of initial presentation to an ophthalmologist; affected eye side (explicitly to be mentioned by the parents only) and treated eye side if applicable; which or if any therapy has been received since the suspected diagnosis ("eye drops", "operation including laser" or "none" could be marked); the active ingredient and frequency of possible eye drops; and name, date and clinic of any possible eye operations including laser treatments. Lastly, non-ophthalmological diseases of the child and medications taken were to be listed. The responses on this form were to be provided in various formats depending on the question: either in free-text gaps, as a date in the format dd/mm/yyyy, or by selecting yes-no checkboxes or checkboxes with other answers. There were no specifications regarding a minimum or maximum number of checkboxes to be marked. The MQ is presented in the original German version in Addendum 7.2.7.

3.3.3.2 Gestational and Family History Questionnaire (GFQ)

The Gestational and Family History Questionnaire was comprised of a single one-sided printed page and was to be completed by at least one parent. Supervision by a study team member was not mandatory. But one could be consulted in case of any ambiguity regarding questions or answers. The German name of this questionnaire was "ReKiG-Auskunftsbogen v3.0".

The GFQ mainly required data about the mother's pregnancy and the familial background including the occurrence of childhood glaucoma diseases. First, the patient's pseudonymisation code and the completion date needed to be entered. Then the birth years of mother and father were enquired and whether both are related and if yes in which relation, e.g., cousin-cousin. Then the number and gender of other mutual children was requested and whether there is knowledge of any relative who went blind or developed glaucoma as a minor. In addition, a few facts about the delivery of the patient were of interest, namely hight, weight and week of pregnancy at birth, as well as the punctuality. Regarding the time of pregnancy, the questionnaire asked about the mother's possible daily habit of smoking cigarettes and weekly amount of alcohol and drug abuse. The questionnaire also enquired whether the

conception was natural or artificial. If the GFQ was filled in by the mother, it was a self-report and a third-party report if only the father completed the questionnaire. Since there are differences in perception, depending on whether it is a self-report or proxy-reported, according to Prof. [redacted] one should be able to relate to the interviewee when interpreting the data. For this reason, the questionnaire also asked whether the mother or father was giving the answers. The responses on this form had to be provided in varying formats, like in the Medical History Questionnaire, either as free-text, in year format (yyyy), or by selecting yes-no or other checkboxes. Again, there were no specific requirements regarding the minimum or maximum number of checkboxes to be chosen.

Addendum 7.2.8 presents the GFQ as conceptualized by Prof. [redacted] and Prof. [redacted].

3.3.3.3 Patient-reported outcome measure (PROM)

The KINDL^R was selected as a PROM for the pilot study to determine the patients' HR-QoL. See chapter 2.6.3 for further details to this PROM. According to Prof. [redacted], as stated in the expert interview, he chose this one as the best validated means in the German-speaking region for measuring quality of life in children. The generic main instruments and the additional "Disease" scales were exclusively downloaded in German free of charge from the official website https://www.kindl.org/ and printed as paper-pencil version. Instruments in other languages than German were not included in the pilot study. The age-appropriate versions were to be distributed to the parents and the child. The questionnaire was meant to be used according to the attached manual which could also be downloaded from the official website free of charge. View Addendum 7.2.10, including subchapters, to see the five age-adapted self- and proxy-reported KINDL^R questionnaires and their pertaining sub-scales as downloadable from https://www.kindl.org/contacts/german/ in German (172). These were all utilized in this pilot study. The official English translations can be found and downloaded under https://www.kindl.org/contacts/english/ (173).

No KINDL^R existed for children aged 0 to 2 years. Probands aged 4 to 17 years were asked to complete their age adapted KINDL^R plus the subscale "Disease", which involved 5 pages per child. A 4- to 6-year-old therefore had 18 questions and children in the age groups 7-13 and 14-17 years had 30 questions in total to complete. Parents of children aged 3-6 years needed to deal with 6 pages meaning a total of 46 questions, while in the age group 7-17 years, five pages and 30 questions were the standard.

3.3.3.4 Examination Under Anaesthesia Form (EUAF)

This form, in German named "ReKiG-NKU-Bogen v2.0", consisted of two pages and was to be filled out by or under supervision of the examiner who conducted the patient's EUA. The examiner needed to confirm the correctness of the data by signing both pages. Values were recorded separately for each eye and measuring device names were noted whenever in use.

The protocol was based on the standard EUA procedure on children with glaucoma at the Childhood Glaucoma Center of Mainz University Medical Center. Possible responding options consisted of free-text gaps and boxes, yes-no checkboxes, and checkboxes with other answers. The form is presented under Addendum 7.2.9.

The following information was recorded on the form, along with the date and the pseudonymisation code: the IOP in mmHg, its assessment method (either Perkins, Schiötz or “other”) and point in time after the induction of anaesthesia, including stating the type of anaesthesia. The form included details on refraction and keratometry measurements, vertical and horizontal corneal diameters, axial length and pachymetry, including the number of values used to calculate the mean CCT as provided by the device. When it came to the examination of the anterior segment, the examiner was asked to indicate whether any of the following preselected conditions were present: megalocornea, Haab's striae, stromal corneal opacity, endothelial opacity, embryotoxon posterior, ectropion uveae, iris defects and cataract. In the free text field, any additional abnormalities could be noted. The second page dealt with the examination of the fundus and iridocorneal angle. One should note if the fundus was visible and whether a papillary photo was taken. The investigator was invited to tick either yes or no when the optic disc appears glaucomatous and if there was an abnormal macular wall reflex. There was also a free text area for additional observations and the examiner was asked to estimate the horizontal and vertical CDR. During gonioscopy, the investigator should indicate whether the angle was clearly visible and if it appeared dysgenetic. It should also be noted whether goniosynechiae were visible, and any other abnormalities in the free text field. The form asked to indicate if the child already had a known glaucoma diagnosis or even underwent operations before this examination date. Finally, the form demanded to tick the appropriate diagnosis for each eye separately from a selection of options, including PCG and the succeeding subtypes of SCG: aphakia, uveitis, ocular trauma, aniridia, Axenfeld-Rieger anomaly, PA, Sclerocornea, SWS, Neurofibromatosis type 1, Lowe syndrome and posterior anomalies e.g., Persistent fetal vasculature, ROP, and Familial Exsudative Vitreoretinopathy (FEVR). If all these diagnoses were not applicable, there was the possibility to choose "other" and make specifying notes in the subsequent free-text field.

As previously stated, the examiner was instructed to observe specific preselected conditions during the examination of the anterior segment, fundoscopy, and gonioscopy. Depending on whether the condition was present in the eye, a checkmark had to be placed next to either "yes" or "no". Prof. [redacted] implemented this method in the EUAF to ensure unambiguous evaluation, as the absence of a checkmark does not automatically imply a "yes" or "no" response but rather indicates missing information. However, there was no requirement to provide a reason for this omission.

3.3.4 Genetics

As mentioned in the IFp, the founding study team originally planned to anonymously send saliva and excess blood samples from the child and 18ml blood samples from the parents to the Department of Human Genetics at the University Medical Centre Mainz for storage and whole exome sequencing. This testing would not have provided any immediate, treatment-altering insights for the patient or parents. However, the Human Genetics Department stated that a saliva sample was insufficient for molecular genetic analysis and whole exome sequencing. Therefore, a blood sample must also be taken from the child. And instead of collecting samples for pseudonymised whole exome sequencing, this pilot study was redesigned as an opportunity to catalyse the process of testing for known genetic mutations associated with childhood glaucoma as part of normal patient care. Conducting these tests is a service covered by German statutory health insurers, as it can be crucial for treatment decisions and future reproductive choices. With the shift in focus from pure research, adherence to the GenDG became necessary. The child's blood sample, and if applicable, the samples from both parents, needed to stay identifiable for the analysis in the Human Genetics department. Genetic analysis became an optional component of the pilot study, but it was implied that any genetic results may be pseudonymously integrated into the probands' dataset. To address the new deviation from the provided information in the IFp, further discussion during the verbal briefing with the parents and written adjustments on the information forms were necessary.

3.4 Methods of testing study material, study logistics and data collection

Prior to approaching the first proband, the author of this dissertation consulted Prof. [redacted] from the Human Genetics Department of the University Medical Center Mainz. During this exchange, all necessary information was provided to ensure that the genetic analyses would be in accordance with clinic internal procedures, the German statutory health insurers and the GenDG. Details regarding the blood sample collection were conveyed, as well as the requirement for additional documents, e.g., specific official referral slips that needed to be obtained from either the child's paediatrician in private practice or from the parents' primary care physician. These referral slips were necessary to ensure that the procedure was covered by the statutory health insurance. Further elaboration on the genetic aspect of the pilot study can be found in chapter 4.3.5.

If it was possible to initially contact the potential participant's mother or father through a phone call, this opportunity was utilized to deliver an initial oral explanation of the study. No information material was to be handed out to the parents beforehand neither via email nor postal service. Thus, the only request to the interested parent(s) on the phone was to bring any up-to-date medical documents and either the child’s medical examination booklet (“U-Heft” in German), the maternity certificate or discharge documents from the hospital after birth to the

next appointment. Additionally, the parents in the experimental group were advised that, if interested in a genetic examination, a referral slip from the family physician and/or paediatrician would be required, enabling them to make necessary arrangements.

Aside from the requirements that the study materials should not be provided to parents prior to their initial in-person appointment, paying attention to the in- and exclusion criteria, and ensuring that the procedure does not have an adverse effect on the patient's treatment and the normal clinical routine, there were no specific guidelines or limitations concerning the testing of the study material, study logistics including adjustments made to the genetical aspect of the study and the data collection process. The feasibility of the study material, study logistics, and data collection relied on achieving the established time targets, ensuring data completeness, and confirming the usability of the study material even if adjustments were necessary during the process. However, significant changes were to be avoided, and any such changes needed to be discussed with Prof. [redacted] beforehand. However, the focus was on observing how data collection in the experimental group could be integrated into the daily clinical operations of the Department of Ophthalmology and Human Genetics Department at Mainz University Medical Center in a future database or registry. Nonetheless, it was important to keep in mind that the author of this dissertation had the status of a medical student during the implementation and therefore could not perform tasks strictly assigned to a physician. For these tasks either a medical study team member or any other medical staff at the Eye Clinic needed to assist.

3.5 Pseudonymisation technique and method of data processing and storing

Due to the data collection material being paper-based and the dataset of 40 planned cases rather small, “counter” was selected as first-level pseudonymisation technique. A paper document (mapping table) was created to record the assignment of pseudonymisation codes to each participant. The data was to always stay pseudonymised. A personal reference was to be merely possible if the mapping table were used. This table was to be kept in a safe place in the Childhood Glaucoma Center located in the Department of Ophthalmology at Mainz University Medical Center and only accessed by study team members.

Regarding data processing and storage, no specific instructions were provided, except for the requirement that, for data protection reasons, the study materials carrying personal data must always remain in the Department of Ophthalmology. And no later than 10 years from the start or in the event of an earlier termination of the pilot study, all collected data has to be destroyed.

4 Results

This chapter provides partial pilot study outcomes regarding the feasibility of first-level pseudonymisation of data, proband recruitment, testing of study logistics and data collection, testing and primary adaptation of original study material as well as in- and exclusion criteria, and proportional study outcome analysis using descriptive analysis and provides analysis using qualitative methods.

4.1 Adaptation of inclusion criteria

During the recruitment phase, it became evident that the inclusion criteria listed in chapter 3.1 needed to be expanded. The additional criteria arose due to observations and challenges encountered during the recruitment phase. The criteria A, parts of B and G already existed at the beginning of the pilot study. All criteria in Table 9 applied to all included probands in both groups, however this meant that one or the other subject was no longer considered a potential subject or subsequently excluded from the study.

Table 9: Adapted inclusion criteria for probands of the pilot phase. The underlined criteria emerged as necessary during the pilot phase and were therefore added while the remaining criteria have been left unchanged from the beginning of the pilot study.

	Experimental group (glaucoma)	**Control group (other eye disease)**
A	Age <18 years at the date of inclusion	
B	At least one eye either diagnosed with glaucoma (according to CGRN criteria) or glaucoma suspected (according to CGRN criteria)	No glaucoma diagnosis and at least one eye with other diagnosed eye disease
C	At least one appointment in the Department of Ophthalmology at Mainz University Medical Center during data collection period	
D	Permanent residency in Germany	
E	Possibility to communicate with at least one present legal guardian in German, English or via interpreter	
F	At least one biological parent of the proband takes part in the study	
G	Written consent from all legal guardians	

CGRN= Childhood Glaucoma Research Network

Criterion B in the experimental group was extended by glaucoma suspects according to the CGRN criteria and cases very likely of having glaucoma. In many cases, a definite determination of glaucoma or glaucoma suspicion according to the CGRN criteria was only possible during the EUA. But parents had to have consented to participate in the pilot study before the results of the EUA could be included. Thus, if at the moment of obtaining consent

the probands were not yet diagnosed with glaucoma, it was at least suspected or very likely. If a glaucoma diagnosis or glaucoma suspicion could be ruled out through clinical evaluation, these cases were excluded from the experimental group. All other cases remained in the experimental group, labelled as suspects, as they might transition into glaucoma cases later in their lives.

Criterion C, that at least one visit to the Department of Ophthalmology at Mainz University Medical Center would be needed during the data collection period, was implied in the monocentric study design and due to the fact, that all hardcopy documents needed to be handed over to the parents in person.

The necessity of introducing criterion D came with its pros and cons. The decisive factors for introducing criterion D were that these patients would only be accessible for the study and a future registry within a limited timeframe due to their short stay in Germany only for an operation, and that a genetic examination in the pilot study would not be feasible due to the lack of cost coverage. Furthermore, there was a consideration regarding whether children living abroad should be included in a future German childhood glaucoma registry and consequently in the pilot study. For this pilot study, this question was answered with a "no" during the recruitment phase, thus these cases were subsequently excluded from the pilot study or not approached in the first place after finding out about their residency through the HIS.

Criterion E also emerged during the recruitment phase. The reason for this was quite straightforward – without being able to communicate in German, English or via interpreter, exchange with the parents would have been practically impossible.

Criterion F was introduced during the recruitment phase due to the occurrence of two cases. In these instances, the legal guardians were not the biological parents, and the latter had no contact with the child. The initial consideration for excluding patients who did not have at least one biological parent present to take part in the study was that in such cases, the GFQ or Revised GFQ would remain unanswered from the outset, as neither the mother nor the father could complete the questionnaire, and some questions could not be answered on their behalf. Consequently, testing the GFQ within the pilot study would have been impossible in these cases. In hindsight, the introduction of this inclusion criterion would not have been deemed necessary, as these patients should have a place in a future childhood glaucoma registry, just like those with biological parents as legal guardians.

The exclusion criterion of the pilot study remained unchanged, namely when any of the inclusion criteria were not fulfilled.

4.2 Proband enrolment

Due to the sole responsibility for recruiting subjects and testing study material, there were unavoidable interruptions in the continuous patient recruitment process. Furthermore, each participant, especially in the experimental group, implied a considerable expenditure of time. This resulted in the inability to reach out to all potential participants at the Childhood Glaucoma Center during the recruitment phase, especially in the case of patients who were only present for a short outpatient appointment at the clinic.

The recruitment process for both patient groups typically followed the scheme as illustrated in Figure 4. However, there were few exceptions that were recruited through different means due to adjustments of the in- and exclusion criteria or on special request of other study members.

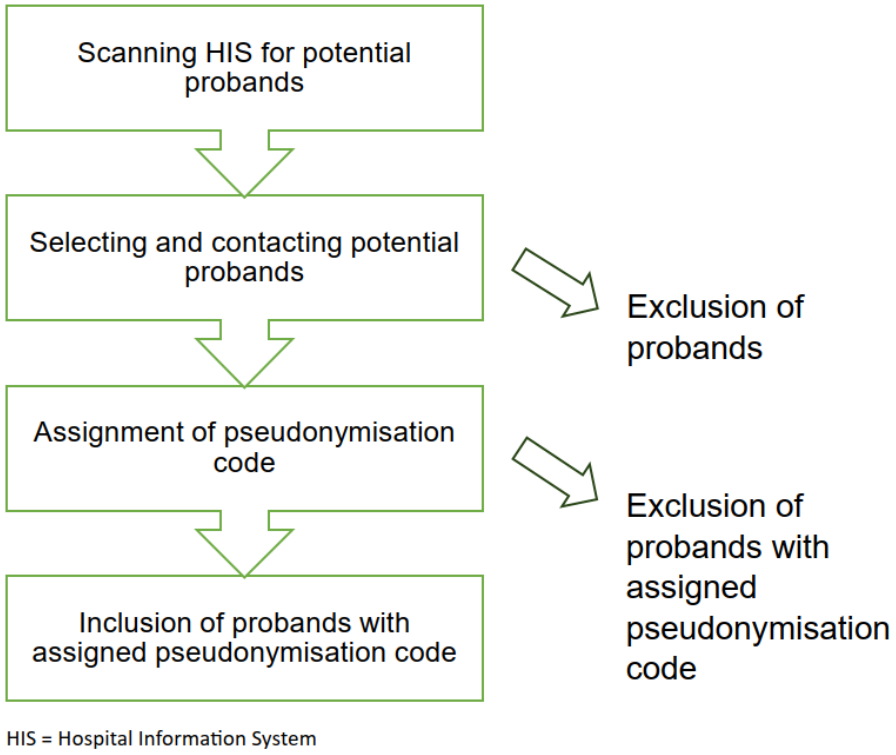


Figure 4: Typical scheme of proband recruitment process

At first, the hospital information system (HIS) was utilized at regular intervals, usually weekly, to screen eligibility of potential subjects for both groups. The term "potential" implied that, at the very least, based on the notes in the HIS, the subjects did not present any exclusion criteria from the outset. The focus was directed towards those weekdays and times during which the potential subjects were most likely to be present at the clinic. This varied between both groups and will be further explained. For this purpose, the author of this dissertation received an independent reading access to the HIS of the eye clinic. This was coordinated with the clinic's in-house data protection department. The selection of potential probands was constantly subject to adjustments of the inclusion and exclusion criteria during the recruitment phase. Refer to chapter 4.1 for further details on these adjustments.

4.2.1 Experimental group

Typically, children suspected or diagnosed with glaucoma visited the Childhood Glaucoma Center at Mainz University Center on specific weekdays. Tuesdays were designated for EUA and eye surgeries and patients usually arrived on the day before. On arrival, the child and one parent were admitted as inpatients to a specific ward in the Department of Ophthalmology dedicated to the Childhood Glaucoma Center. An anaesthesia consultation with an anaesthesiologist was arranged for the same day if permanent consent for anaesthesia hadn't been obtained. Furthermore, the patient was scheduled to visit the orthoptics department on the same day. Then the ward physician and senior physician responsible for the eye procedure conducted an orientating eye exam. Accompanying parents were informed about the upcoming procedure if not yet discussed in a prior outpatient appointment. It had been internally agreed that infants under the age of one year who needed to stay overnight would be accommodated in the paediatric clinic, just a few minutes' walk from the Childhood Glaucoma Center. These young patients were then brought to the Childhood Glaucoma Center for eye and orthoptistic exams and any necessary surgical procedures. Usually, a number between zero and up to four children with (suspected) childhood glaucoma was planned for the operation room on Tuesdays. Usually, a higher number of children attended outpatient consultations on Wednesdays where they underwent an orthoptic examination as a standard procedure before the consultation appointment.

The schedule of the operating room and of the outpatient department were regularly scanned via HIS to find out which underage patients with a confirmed, suspected or very likely glaucoma diagnosis would be visiting the Childhood Glaucoma Center soon for EUA, surgery, or outpatient consultation. The confirmation or likelihood of glaucoma or glaucoma suspicion was mainly assessed through the HIS or, if the HIS did not provide enough details, through oral questioning of the parents during the first approach. Likelihood of glaucoma diagnosis or at least suspicion increased especially when the patient was referred to the Childhood Glaucoma Center in Mainz from an ophthalmologist or other eye clinic. Probands were selected for being contacted based on the following considerations: At the beginning of the recruitment phase, it became apparent that it was unrealistic to include more than two probands on the same day. The reason for this was the time required for each proband and the inability to handle more than one family at a time in compliance with data protection regulations. Further explanations to this point can be found in subchapter 4.3.6. Therefore, when more than two potential probands were available on a given day, one or at the most two temporally compatible probands were selected.

Figure 5 provides visual representation of the recruitment process outcome of the experimental group. It was necessary to approach a larger quantity of subjects due to a higher number of exclusions, and it proved more challenging to obtain complete data sets from 20 probands

than in the control group. Exclusion of participants occurred at two points in time: either immediately after the approach but before assigning a pseudonymisation code, or after a pseudonymisation code had been allotted, forms were distributed, and exclusion was subsequently necessary. Participants in the experimental group were excluded before the assignment of pseudonymisation codes due to issues with verbal communication (3 cases), the absence of biological parents (2 cases), study refusal (1 case), or missing out on the planned appointment in the Department of Ophthalmology at Mainz University (1 case). These factors were observable during the (missing) initial encounter. Exclusion after pseudonymisation code assignment occurred due to switching groups (2 cases; explained further below in this chapter), the absence of written consent from all legal guardians (2 cases), or exclusion due to residence outside Germany (1 case). There were no dropouts after written consent from all legal guardians had been obtained.

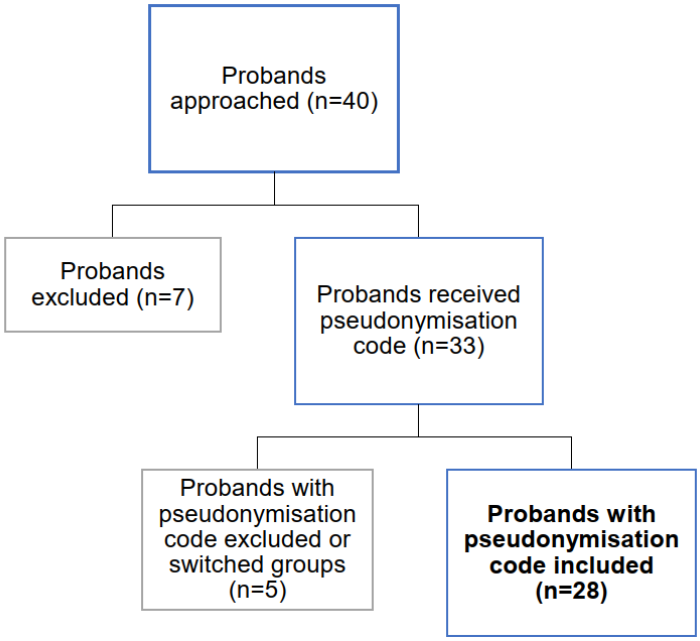
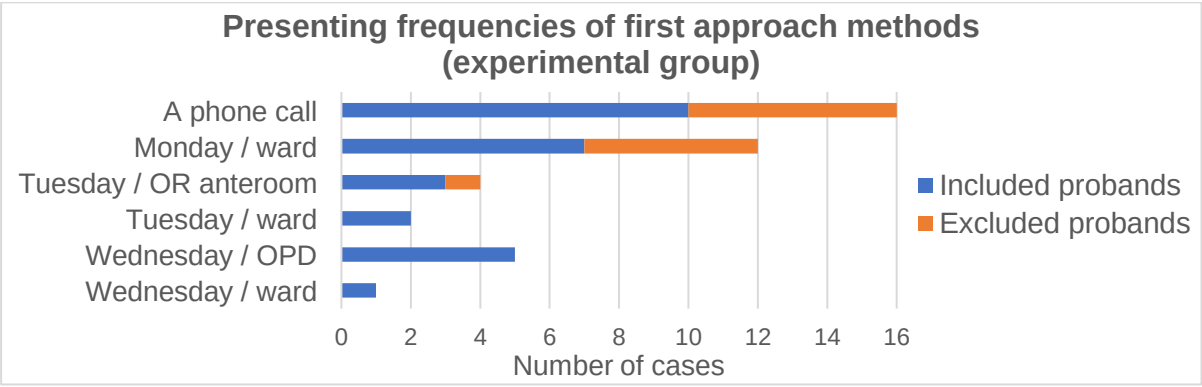


Figure 5: Diagram showing participant flow for the experimental group.

The proband recruitment process for the experimental group started on 14th of May 2018 and was concluded on 3rd of June 2019. Total proband recruitment in the experimental group therefore took just over one year. Within the first 6 months of patient enrolment for the experimental group, until 13th November 2018, 21 subjects received a pseudonymisation code. However, three of them had to be subsequently excluded, with two of them being allowed to switch to the control group, meaning in the first 6 month 18 probands were included in the study. The 20th subject, who remained included, agreed in participating in the pilot study on December 3rd in 2018. More than the initially planned 20 subjects had to be included because it turned out that obtaining a complete dataset was not always possible, mainly due to missing scheduled EUA during the recruitment phase. Including a larger number of subjects was intended to ensure 20 subjects with complete datasets. However, the remaining 8 probands in

the experimental group were gradually included in the second half of the recruitment phase, at a slower pace, with continuous consideration of whether any already included proband would still receive an EUA. Ultimately, 27 included probands would have sufficed. However, the last two were siblings, which is why they were both included together in the study.

In the first month of the recruitment phase, the focus was initially on inpatients scheduled for surgery on Tuesdays. Subsequently, patients with outpatient appointments on Wednesdays were also considered. The primary contact method with the parent(s) was either a face-to-face conversation at different instants at the Childhood Glaucoma Center or a phone call few days prior to the scheduled appointment at the Center. The first face-to-face conversations with the parent(s) incorporated the formal oral briefing on the nature, significance, risks, and scope of the registry. Parents who had been previously contacted by phone also received a formal, but usually less elaborate, oral briefing during their initial in-person meeting at the clinic, since, they had received preliminary and comprehensive information about the pilot study beforehand. The downside of this approach was the need for a two-part time commitment. However, the advantages included the fact that parents could already contemplate their participation and an optional genetic examination, as well as make any necessary preparations, such as bringing any required documents. The approach via phone call was only possible if the necessary contact information was already recorded in the HIS. However, this also implied that the opportunity to participate in the pilot study was reduced if potential participants' phone numbers were not recorded in the HIS or parents did not pick up the phone after a certain number of attempts at various points in time or dates. Figure 6 details the occurrences of both approaches - contacting probands via phone calls and through face-to-face conversations - applied for engaging with participants in the experimental group. Regarding the latter method, the specific weekdays and locations inside the Childhood Glaucoma Center are provided.



OPD = outpatient department, OR = Operating room

Figure 6: Diagram representing methods employed for the initial contact with parents of approached probands. Blue bars represent the 28 probands who remained enrolled in the study until the end, while orange bars represent those 12 probands who were excluded.

The following special cases during patient enrolment are to be highlighted: In one case in the experimental group (pseudonymisation code 0017), childhood glaucoma could be ruled out during the study, not after clinical evaluation but lastly through genetic testing which confirmed an X-linked megalocornea. Though, this child remained in the experimental group, due to its longer history as glaucoma suspect. All other probands, that were included in the experimental group were confirmed during the study of having glaucoma in at least one eye. In two other cases, the probands switched from the experimental group to the control group after a pseudonymisation code had been assigned and written consent obtained. In the first case the proband (pseudonymisation code c0009) had congenital cataract and was a sibling of a child with secondary childhood glaucoma following cataract surgery, who was included and remained in the experimental group. The proband with pseudonymisation code c0009 was initially placed in the experimental group because it was assumed that a secondary glaucoma was also present, but this was ruled out during the completion of the questionnaires. Therefore, after obtaining oral consent from the mother, this proband switched to the control group as a child with an eye condition other than glaucoma. In the second case, the proband (pseudonymisation code c0010) was referred to the Childhood Glaucoma Center in Mainz due to suspicion of childhood glaucoma. The legal guardians had consented to participate in the study; however, it was discovered during the initial ophthalmic examination in the hospital that the proband had retinoblastoma, ruling out the presence of glaucoma. In this situation, the parents expressed their willingness to continue participating in the study as control subjects.

4.2.2 Control group

The process of selecting and reaching out to potential participants for the control group was conducted in a manner comparable to the experimental group. The knowledge acquired from the patient recruitment process for the experimental group was applied to improve the efficiency of recruiting the control group. The delay in starting was to allow to establish a preliminary estimate of the average age in the experimental group before recruiting the control group. Most parents were informed about the study through a phone call a few days before their scheduled appointment at the eye clinic, only few were not contacted in advance and arrived unprepared for their appointment. Nonetheless, similar benefits and drawbacks related to missed phone calls or unavailable phone numbers in the HIS were observed, mirroring those in the experimental group. Regarding the enrolment of patients for the control group, there were more possibilities as it encompasses all other eye conditions. As a result, there were various days of the week where potential control patients were present in the Department of Ophthalmology. For instance, outpatients attending the orthoptics department, e.g., for follow-up visits, such as after strabismus surgery or children being admitted as inpatients for an operation other than childhood glaucoma, which typically occurred on any day of the week except Tuesdays.

The enrolment took place during waiting time for check-up appointments in the orthoptic department, in the patient room or in the waiting area on the ward after being admitted as inpatients for an operation.

Due to the smaller dataset and therefore quicker data acquisition, a more predictable calculation allowed for the inclusion of exactly 20 subjects here. 19 of 20 probands were included or had received their pseudonymisation codes within approximately three and a half months. All control probands were enrolled from 20th December 2018 until 9th July 2019, which was roughly 6 and ¾ months. The time extension was necessary because the final participant was approached three months later than the second-to-last participant. This delay occurred because another proband needed to be excluded from the study at a later stage due to lack of written consent from both legal guardians, despite having been given ample time for consideration. Exclusion after pseudonymisation code assignment occurred solely due to the absence of written consent from all legal guardians. There were no dropouts after written consent had been obtained.

Figure 7 visualizes the participant flow in the control group.

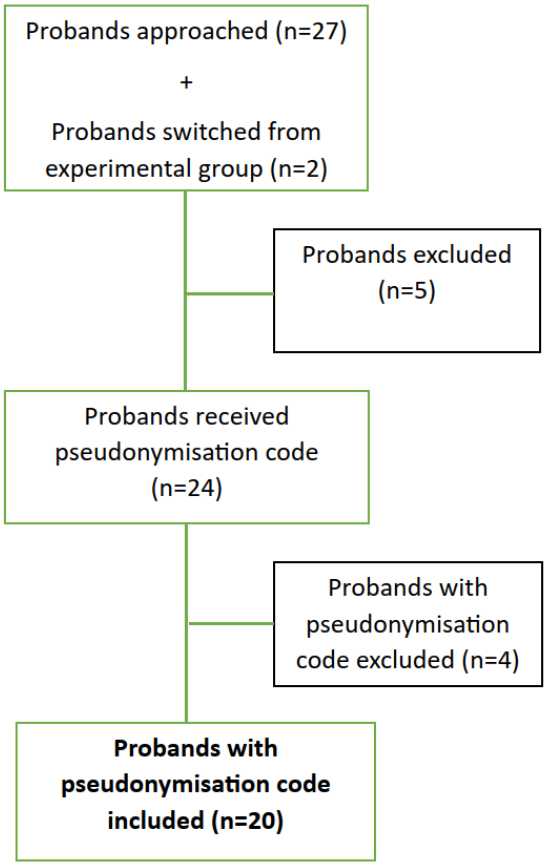


Figure 7: Diagram showing participant flow for the control group.

Even though these were parents and children unrelated to glaucoma, most of them were willing to invest some time and contribute to the study. Like in the experimental group, participants were excluded at two different junctures: either right after the initial contact but before assigning

a pseudonymization code, or later, after a pseudonymization code had been assigned, forms had been distributed, and it became necessary to exclude them. Participants in the control group were excluded before the assignment of pseudonymisation codes due to absence of biological parents (2 cases), study refusal (2 case), or due to the announcement beforehand, that there are no official birth records available (1 case). However, excluding the latter proband was a mistake because the exclusion criteria were not met. Exclusion after pseudonymisation code assignment occurred due to absence of written consent from all legal guardians (3 cases), or exclusion due to communication issues (1 case). There were no dropouts after written consent from all legal guardians had been obtained.

4.2.3 Results concerning both groups

It became evident that the initial phone communication with parents was feasible only if they were proficient in either German or English. In cases requiring an interpreter, parents were unable to understand initial preliminary study information beforehand via phone call. However, this fact could not necessarily be extracted in advance from the HIS and only became apparent during the phone call. At times, only one parent could communicate in German or English, so a second call or some waiting time was necessary to be able to speak with that parent. In both groups, parents exhibited a sense of preparedness when they arrived for their appointment after a prior phone conversation. They had a rough idea of what to expect, appeared less stressed, and had fewer questions about the study during the in-person meeting. This allowed for a smoother continuation with the paperwork. In the experimental group, some parents even already brought along the referral slip for the child to the first meeting as they were highly interested in a genetic examination.

4.3 Testing and adapting of study material, study logistics and data collection

Figure 8 and Figure 9 represent all the documents that constituted the dataset for an individual patient in the experimental and control cohorts, respectively, after adaptation. The precise adjustments will be explained in the following subsections.

The documents and materials in the experimental group could be organized in five categories which are colour contrasted from each other. In the control group, the categories remained at three. Genetic reports were anonymously incorporated into the data set. Inclusion of all documents marked with an asterisk (*) was necessary to deem a patient's dataset to be complete.

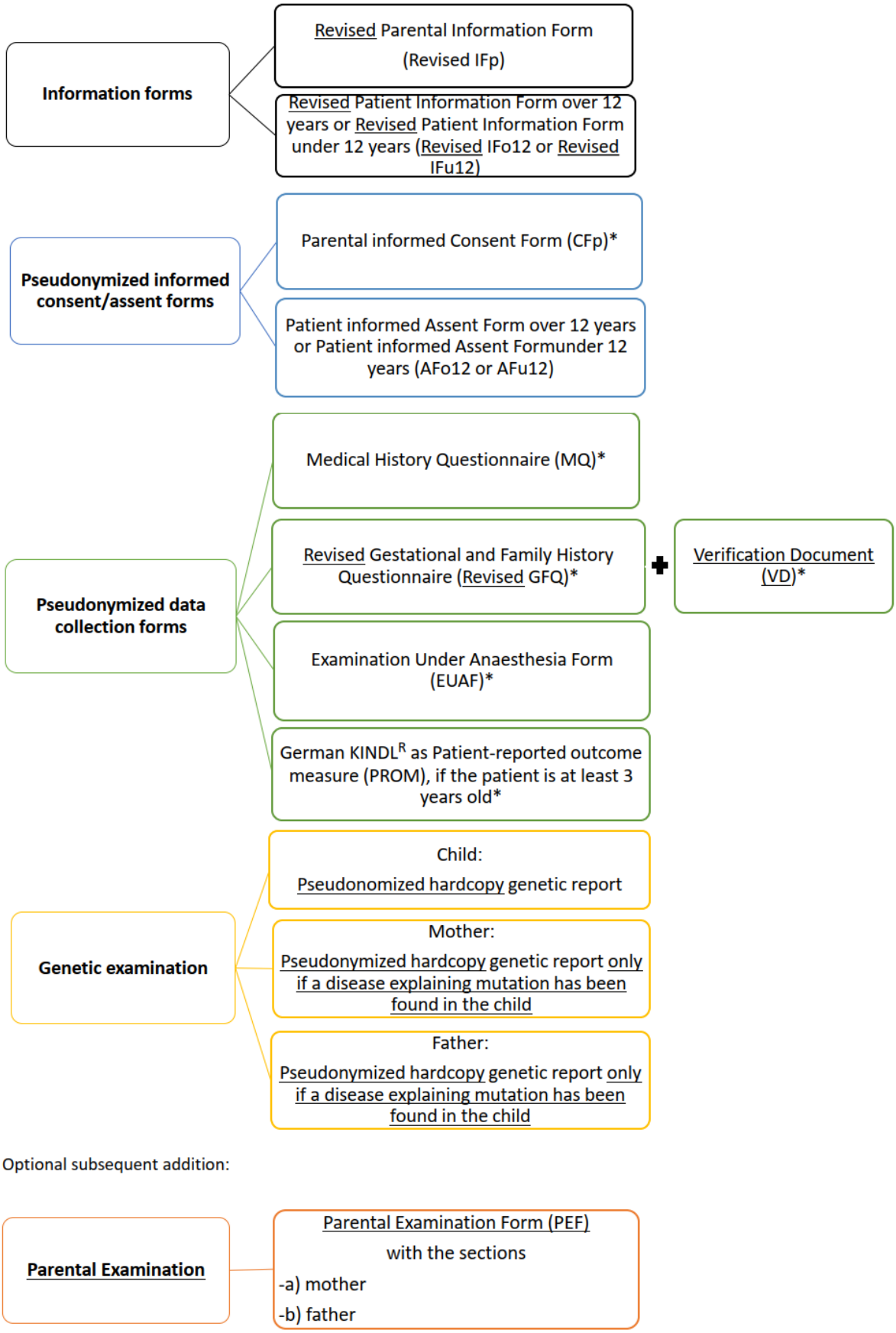


Figure 8: Display of all documents and samples that comprised the data set for an individual patient within the experimental cohort after being modified before and during the recruitment phase. Changes, compared to Figure 2, are highlighted by underlining.

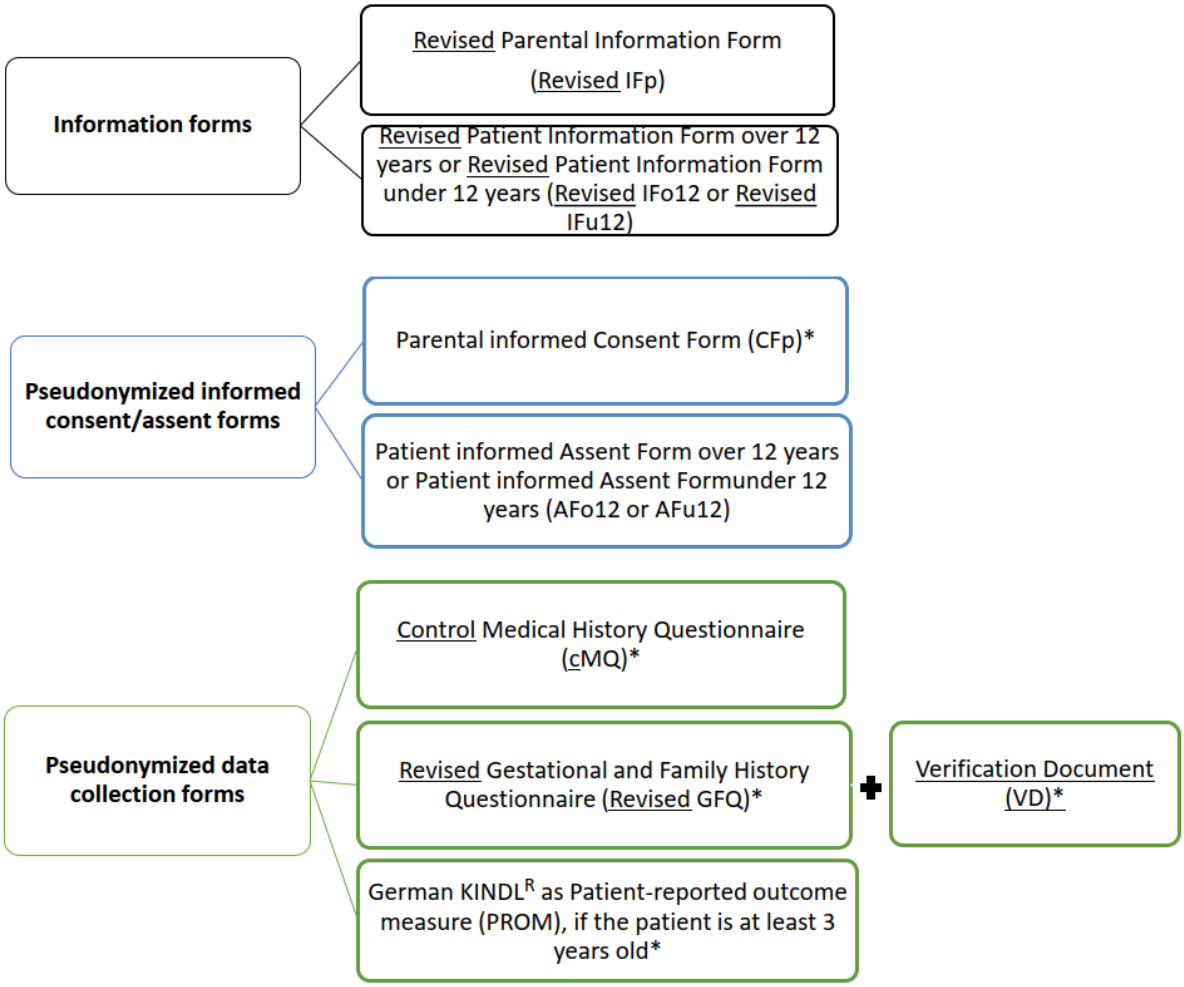


Figure 9: Display of all documents and samples that comprised the data set for an individual patient within the control cohort after being slightly modified during the recruitment phase. Changes, compared to Figure 3, are highlighted by underlining.

4.3.1 Information forms

As a result of rescheduling related to the human genetic testing in the experimental group, minor modifications were made to the text on the IFp, IFo12, and IFu12 to rectify inaccuracies without eliminating the original text approved by the Ethics committee. The new versions of the Information forms were named Revised Parental information form (Revised IFp), Revised Patient information form <12 years (Revised IFu12) and Revised Patient information form >12 years (Revised IFo12). The Revised IFp features five changes when compared to the original. At first, the information mentioning the 18 ml-blood-sample from the parents was visibly crossed out. However, an error occurred in this process of correction, as instead of altering to the appropriate 5-10 ml for adults, it was mistakenly revised to 2-3 ml. This is the required quantity for newborns. Secondly, the term "saliva" from "saliva sample" (in German: “Speichel” from “Speichelprobe”) was crossed out and the German word for blood was written above it. In the last three cases, there were only cross-outs made without any corrections. Specifically, two sentences were crossed out completely, stating that only blood obtained during the routine

diagnostics before the operation/EUA of the child would be used, meaning no additional blood sampling of the child would be required for the study. The fifth instance involved a partial sentence that contained the term "saliva sample" once more. The Revised IFp is attached to this document in chapter 7.3.1. In both patient information forms, only the term "saliva" (in German "Speichel") was visibly crossed out and replaced with the German word for blood. The modifications were also verbally explained, and any inquiries were resolved. The Revised Patient information form <12 years (Revised IFu12) and the-Revised Patient information form >12 years (Revised IFo12) can be found in chapter 7.3.2 and 7.3.3 respectively. It can certainly be argued whether more adjustments in all three forms would have been necessary to fully correct the statements and create individual forms for the control group.

During the initial individual meetings with participants and parents of both, the experimental and control group, the Revised IFp was given as primary information document. No significant comprehension issues were reported by the parents in the experimental group, except for the obvious revisions and their resulting consequences which required further explanations. Parents in the control group were requested to disregard the sections pertaining to genetic examinations on the Revised IFp. There were few instances where questions arose about why the form was dated in the past. The Revised IFo12 or Revised IFu12, however, were only distributed in the experimental group. The rationale for excluding it in the control group was as follows: The design of both the revised and unrevised versions of the IFu12 and IFo12 was clearly intended for children affected by glaucoma. It did not cater to other children. However, only written parental consent was required for study inclusion. Keeping the dataset in this group smaller also reduced the parents' potential reluctance to participate in the study due to being confronted by a larger number of forms.

Due to the age distribution of the recruited probands in the experimental group, the Revised IFo12 was not needed at all. All probands were younger than 12 years of age. In the control group, the Revised IFo12 would have merely been required in 2 cases. However, during the personal encounter at the clinic, the Revised IFu12 remained largely disregarded by the young patients. Potential explanations are lack of curiosity, inability to read caused by visual impairment or being in preschool age. Furthermore, there was no inquiry regarding whether the forms received attention from the children at home or if the content was verbally explained to them by the parents.

4.3.2 Informed consent and assent forms

After the parents showed interest in participating in the study, they were given the CFp and literate interested children in the experimental group were given either the AFo12 or AFu12. No significant comprehension issues were reported by the parents in either group. The child-friendly informed assent forms were omitted in the control group for the same reasons as the

information forms. Because the CFp still mentioned the statement about anonymized analysis of biomaterial, the parents in the experimental group were explicitly reminded of the adjustments made in the IFp, while parents in the control group were informed about the insignificance of this matter. A written modification was not made on the CFp, unlike the IFp, as it was decided to stick with verbal communication for this aspect. However, it can certainly be discussed whether adjustments in the text would have been necessary to rectify the statements in writing and, in addition, create a modified version for the control group. If all legal guardians of a child were present, signing could be done directly after the oral briefing, resulting in an immediate return of the document. However, it was not unusual for only one legal guardian to be present, in which case the CFp was retained and returned during a subsequent meeting or through postal service. For this purpose, pre-stamped envelopes were provided. No second oral briefing for the absent legal guardian was requested. Written informed assent of the under-age child in the experimental group was optional and not enforced.

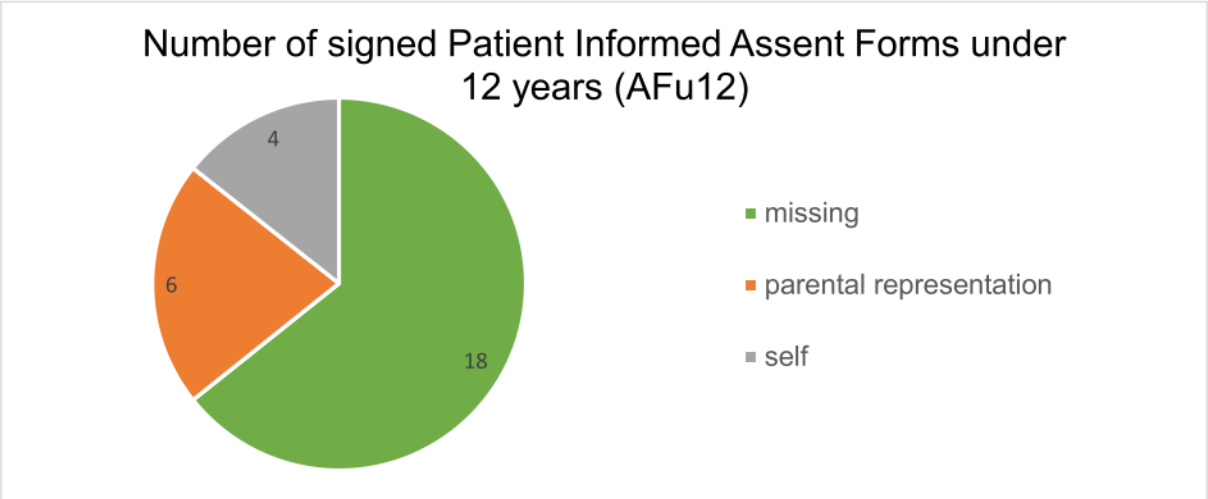


Figure 10: Diagram pointing out the frequency of written informed assent by the patients in the experimental group.

The results related to the children's tendency to largely ignore the AFu12 were similar to those of the information forms. This resulted in only 4 signatures from the children themselves, 6 forms being signed by a parent on behalf of the child and 18 completely missing forms, as depicted in Figure 10. Potential explanations are lack of curiosity, inability to read and write caused by visual impairment or being in preschool age. Since written informed consent from all legal guardians was an inclusion criterion, the CFp was always complete in both groups.

On each signed informed consent and assent form, the name and the signature of the informing study physician were required. As the oral briefing was mainly delegated to the author of this thesis, who was a non-physician at that time, the signature of the responsible study physician, typically MD [redacted], was obtained afterwards. The date of

consent on the CFp was considered as inclusion date in the pilot study. Therefore, to maintain the prospective nature of the study, only data generated on or after that day were included.

4.3.3 Data collection forms

After obtaining written consent from at least one legal guardian, ensuring the child's participation in the study was highly likely, the next step involved answering the data collection forms, ideally on-site under supervision of a study member to be able to observe and immediately address any issues.

4.3.3.1 Medical History Questionnaire

All parents in the experimental group received the MQ in its unaltered original form. However, it was specifically tailored to children with glaucoma and no separate questionnaire for the control group had been created. Thus, before enrolling control probands, the author of this dissertation designed a version for the control group by making four minor but necessary adjustments and named it “Control Medical History Questionnaire” (cMQ). Initial experiences from the testing phase with the experimental group have been considered for the modifications. The section with the physician’s name was replaced by the term of the patient's eye condition (referred to as "Augenerkrankung" in German). At two other points in the questionnaire, the focus was on the date of suspected glaucoma diagnosis as well as the eye side with the glaucoma diagnosis. In the cMQ, the terms for glaucoma ("Glaukom" in German) were removed from this section without replacement. Lastly, beneath the question which or if any therapy had been received since the suspected diagnosis, another response option, namely “other” (“andere” in German), was integrated. No other changes were made to maintain comparability and the questionnaire remained single-sided. The cMQ is attached to this document under Addendum 7.3.4. The only exceptions in the control group that received the original MQ were parents of two probands who were included in the experimental group as glaucoma suspects at first but reclassified and switched to the control group afterwards.

As the MQ and cMQ were not designed to be easily understood by laypersons, answering the questions in an interview-style approach was preferred. This meant that the questions, and if applicable, the predetermined answers, were read aloud to the parent(s), and their responses manually recorded by the author of this dissertation. Alternatively, parents read the questionnaire themselves and provided handwritten answers independently while being supervised to address any potential questions they had while completing the questionnaire. However, if strongly preferred by the parent(s), it was possible for individuals to fill in the MQ or cMQ unsupervised and return it during a subsequent meeting or through postal service.

Where necessary, follow-up questions were answered either in person or by telephone in order to fill in any gaps. In all cases, the questionnaire was completed. When filling in the questionnaire, parents were allowed to refer to any medical documents at any time or complete the relevant information at a later point. They were not obligated to write purely from memory.

Table 10: Execution method of completing the MQ in the experimental group and the cMQ in the control group.

Group	**Experimental group**	**Control group**
Interview-style	14	5
Independently, follow-up questions necessary or gaps left	10	8
Independently, *no* follow-up questions necessary and *no* gaps left	4	7

Table 10 illustrates the modalities in which the MQ or cMQ was completed. “Interview-style” means, that the responses of the parents were manually filled in by the author of this dissertation. “Independently” implies, that parents read the questionnaire themselves and answered in own handwriting. However, a distinction is made based on whether follow-up questions were necessary afterwards or if gaps were left. 50% of parents in the experimental group filled in the questionnaire independently while 75% in the control group. Potential explanations for this phenomenon may include the greater tendency among parents in the control group to take the questionnaires home, primarily due to the limited time available during their short stay in the orthoptic department. Additionally, a larger proportion of German-speaking parents was observed in the control group. Parents in the experimental group usually had a longer inpatient stay in the clinic or longer waiting time in the OPD, resulting in more time to complete the questionnaire in the clinic. They also appeared to be more distracted by their child and any accompanying siblings, potentially leading to less independent questionnaire completion. However, in 24 of 28 (86%) completed MQs, the involvement of a study team member was necessary. This was also the case in 13 of 20 (65%) cMQs. One potential explanation for the rather high percentage in the experimental group could be the typically more complex medical history of children with glaucoma, which necessitated parents to provide more extensive and detailed information. The higher frequency of omitted responses or the need for follow-up questions in both groups may partly be attributed to the fact that the questionnaire was not explicitly designed to be easily understood by laypersons.

The following are specific aspects of the MQ that commonly lacked clarity not only to parents but also to the author of this dissertation due to ambiguous wording, were frequently left

unanswered or would have required more space for elaboration. Aspects that are not explicitly addressed here did not exhibit any significant conspicuity during testing.

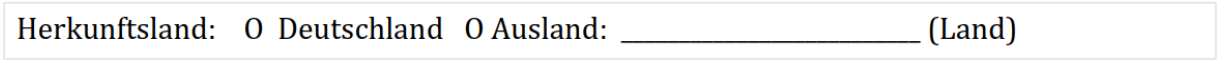


Figure 11: Excerpt from the Medical History Questionnaire and Control Medical History Questionnaire. Content: country of origin (in German: "Herkunftsland")

Figure 11 presents an excerpt from the MQ or cMQ. The term "country of origin" occasionally posed challenges in interpretation, particularly when the child's ethnic or genetic origin differed from the country they or the parents identified with. Thus, the child could either be born abroad but the parents identify it as of German origin due to having grown up in Germany, or, conversely, be born in Germany but recognized as of foreign origin. Apart from that, the designated space for specifying the country was often too narrow.

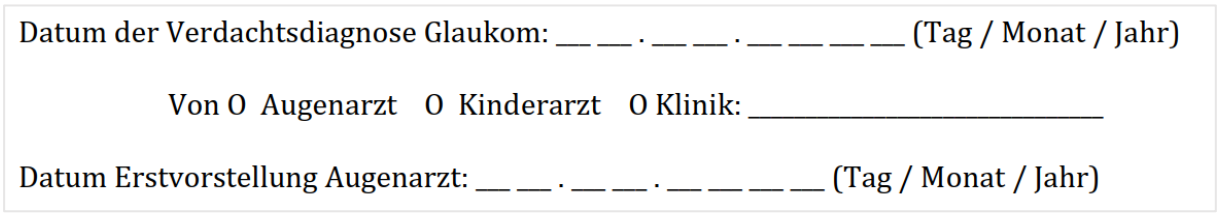


Figure 12: Excerpt from the Medical History Questionnaire. Content: Date of suspected diagnosis and which specialty (paediatrician or ophthalmologist) or clinic made it; date of first presentation to an ophthalmologist. Requested format dd/mm/yyyy.

Figure 12 presents a cut-out from the MQ, which requires a date in the format dd/mm/yyyy. The first date requested is when glaucoma was first suspected, with additional options to specify which specialty or clinic raised the suspicion. The second date pertains to the child's initial presentation to an eye doctor. Regarding the information about who made the glaucoma suspicion diagnosis, here are some comments and suggestions: It was noticeable that the questionnaire only asks for the name of the clinic that voiced the suspicion, but not for the names or locations if an eye doctor or paediatrician voiced the suspicion. It might be worth considering whether more detailed information could be useful for the future registry. Additionally, in some cases, parents only provided the general name of the clinic without specifying which department expressed the suspicion (e.g., paediatric clinic or eye clinic). Furthermore, in some instances, more space would have been needed to record the clinic's name. The term "initial presentation to an ophthalmologist" (in German: "Erstvorstellung Augenarzt") occasionally raised questions about which information should be derived from it. The question could mean when the child had its very first appointment with an eye doctor in its entire life, even before glaucoma suspicion, or at/after the suspicion of glaucoma diagnosis.

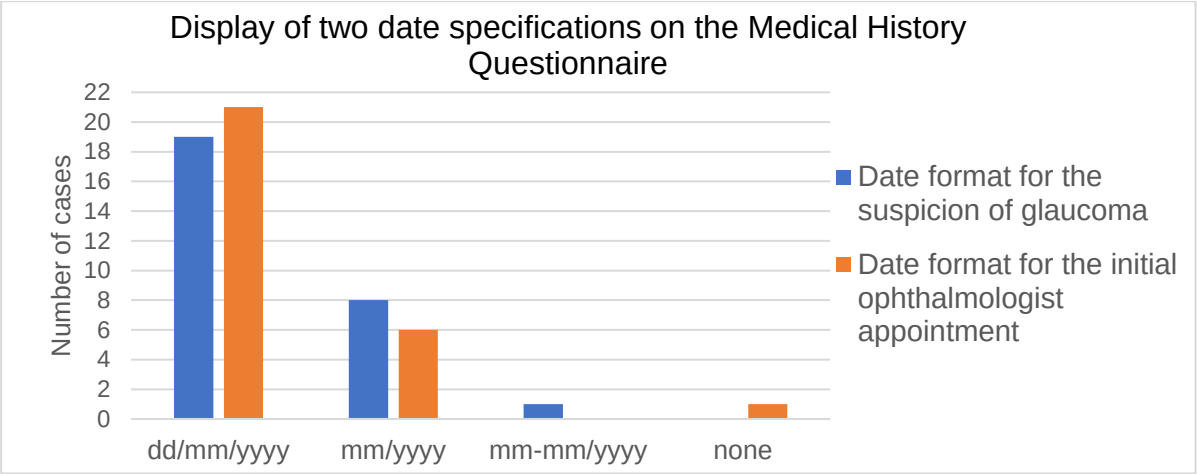


Figure 13: Date specifications provided by the parents in the experimental group on the Medical History Questionnaire concerning the date of glaucoma suspicion and date of initial consultation of an ophthalmologist.

As shown in Figure 13, a commonly observed phenomenon was that parents could in nearly all cases recall the month and year of the suspected diagnosis and first presentation to an ophthalmologist quite well. However, specifying the exact day of the month sometimes proved challenging. Additionally, parents typically couldn't locate or retrieve the precise date from their documents. Consequently, this information was mostly provided based on their memory alone, making verification difficult.

Therapie seit Erstdiagnose: O mit Augentropfen O keine O Operation (inkl. Laser)

Falls Augentropfen: Wirkstoffart und Häufigkeit: A _____

Augenseite mit Therapie: O rechtes Auge O linkes Auge

Falls Operation: wo, wann und welche wurde durchgeführt:

_____

B

_____

_____

_____

Figure 14: Excerpt from the Medical History Questionnaire. Content: Therapy received since suspected diagnosis; name and frequency of possible eye drops; treated eye side if applicable; where and when have which possible eye operations been performed. The blue letters A and B represent the corresponding blanks.

Figure 14 displays another excerpt from the MQ, focusing on the child's previous therapy for its glaucoma condition. It became evident that in this segment, the questions or desired responses were either not sufficiently clear, or the allocated space proved to be inadequate. Starting from the top, it enquired about the methods that have been used for therapy so far (in German: “Therapie seit Erstdiagnose”). Appropriate checkboxes were to be marked accordingly. However, oral pressure-lowering medication was not selectable. Given that multiple responses could be marked, this point was initially understandable. However, if more than one checkbox was selected, it would be difficult to determine which eye the selected therapy would be related to. If this was indeed intentional, the question arises whether this crucial additional information should be collected in the future. The question below that deals with the potential use of eye drops in the child's previous glaucoma therapy, including the type of active ingredient and frequency (in German: “Falls Augentropfen: Wirkstoffart und Häufigkeit”). If this was the intention, it would encompass any eye drops that the child had received throughout its life as part of its glaucoma therapy. Especially, for children whose diagnosis was made a long time ago, parents found it challenging to recall this information. Ultimately, parents were requested to only mention or record the current therapy, if they had any doubts. Furthermore, some parents had difficulty distinguishing between eye drops containing pressure-lowering agents and those that are purely lubricating. Parents typically recognize the brand names of the products. In such cases, it would be the interviewer's responsibility to be familiar with the corresponding active ingredient and deduce it. In the third line in Figure 14, it was asked which eye side had received therapy, but it remains unclear, which type of therapy is referred to. When in doubt, parents were asked to mention the eye having received any kind of therapy. In the fourth line, information about potential eye surgeries is requested, including details on where, when, and which surgery was performed. In contrast to the selection option provided above, it is again not specified whether laser treatments are included. Yet, which eye received the respective operation is again not enquired. In some cases, parents were not aware of the exact date or the technical term for the operation. Assistance could be provided through medical documents. However, not all cases were resolved this way, as these documents were not always brought along.

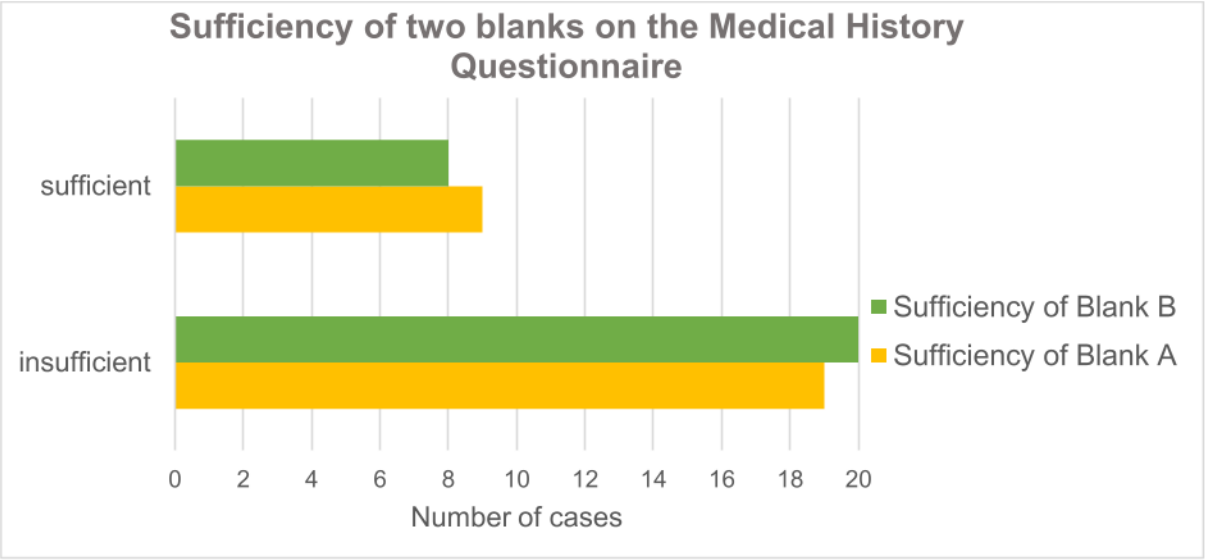


Figure 15: Diagram pointing out (in)sufficiency of blanks in the Medical History Questionnaire as defined in Figure 14.

Figure 15 points out, how often the given blanks in Figure 14, A and B, were too little and thus insufficient or adequate and consequently sufficient. "Insufficient" was counted as soon as even a single character, such as a letter, had to be written below or beside the line, due to lack of space above the line. "Sufficient" when everything fit within the provided lines. As can be seen, “insufficient” is more numerous.

4.3.3.2 Gestational and Family History Questionnaire

Following the completion of the MQ or cMQ, the process continued with the Gestational and Family History Questionnaire. Upon the inclusion of the first child in the experimental group, minor modifications to the GFQ were made based on a recommendation from this child's mother, who was also a physician. She suggested adding one more question to the GFQ, specifically inquiring whether the mother had undergone folic acid prophylaxis during pregnancy. After consultation with Prof. [redacted], the GFQ was modified. Ultimately, the Revised GFQ corresponded to the original GFQ, with the addition of three new questions at the bottom of the document and some wording editions. It was formatted in a way that allowed it to remain single-sided. The first additional question enquired whether the mother had used any medications while pregnant (in German: “Hat die Mutter Ihres Kindes in der Schwangerschaft Medikamente eingenommen?”) and required a selection of either “yes” or “no” (in German “ja” “nein”). If the answer was “yes”, the questionnaire asked for details in free-text format on which medications were taken and during which week of pregnancy (in German: “Falls ja, welche Medikamente und in welcher Schwangerschaftswoche?”). The third question was another yes-no question inquiring whether the mother had utilized folic acid prophylaxis during her pregnancy (in German: “Hat die Mutter Ihres Kindes vor bzw. während der Schwangerschaft eine Folsäure-Prophylaxe durchgeführt?”). The questions

about the intake or use of noxious substances were originally worded in such a way as to assume that the mother would complete the questionnaire. Instead of starting the respective questions with "Did you..." (in German: “Haben Sie…”) the revised GFQ contained "Did the mother of your child..." (in German: “Hat die Mutter Ihres Kindes…”) so that fathers completing the questionnaire would also feel addressed. View Addendum 7.3.5 for the Revised GFQ. Until the new version was finalized and included in the standard document set of the experimental group, the additional questions were posed orally, and both the question and the answer were manually added at the bottom of the GFQ. Patients with pseudonymisation codes 0001, 0002, and 0004 (0003 was excluded) still received the original questionnaire. All subsequent probands and the whole control group received the Revised GFQ.

If responses were given on-site, the procedure was carried out either in an interview-style approach, by parents completing the questionnaires independently, or a combination of both. Alternatively, individuals had the option to complete the forms unsupervised and return them during a subsequent meeting or via postal service. When filling in the questionnaire, parents were allowed to refer to official medical birth documents, if brought along, at any time or complete the relevant information at a later point. As with the MQ or CMQ, they were not obligated to write purely from memory. Whether the answering process started with an interview-style approach or parents initially filled out the questionnaires on their own depended on several factors. The following aspects favoured the independent completion: both parents were present, allowing the respondent to be less distracted while the other parent attended to the child and any potential siblings; at least one parent was capable of reading in German, or there was an interpreter present; the parents favoured taking the questionnaires home and answering them at their convenience instead of hurriedly completing them during an outpatient appointment. The reasons for adopting an interview approach were as follows: participants had limited or basic German language skills without the presence of an interpreter, leading to the need for more explanations or an English translation; when the responding parent was frequently distracted, making verbal responses easier; and when this approach was preferred by the parents. If oral translation into English or the use of an interpreter was necessary, it was documented on the forms.

Table 11: Execution method of completing the (Revised) Gestational and Family History Questionnaire in both groups. The additional questions introduced in the revised version that had to be asked orally in three instances are not considered follow-up questions.

Group	**Experimental group**	**Control group**
Interview-style	8	3
Independently, follow-up questions necessary or gaps left	3	4
Independently, *no* follow-up questions necessary and *no* gaps left	17	13

According to Table 11, in the control group, it was rather common for the legal guardians to independently fill out the questionnaire, while in the experimental group the interview-style was also a frequent option. Possible reasons for this could be the more frequent practice of taking the questionnaires home and a higher proportion of German-speaking parents in the control group, whereas in the experimental group, parents tended to be more distracted by their child and any accompanying siblings. Nevertheless, it sometimes occurred in both groups that, upon completing the questionnaires independently, certain sections on the form remained incomplete and follow-up questions were necessary either in person or over the phone to complete the missing information. However, the study team required fewer follow-up questions when parents completed this form on their own, compared to the Medical History Questionnaires. It seems, that the questions in the GFQ and Revised GFQ proved to be more understandable for parents compared to those in the MQ or cMQ.

The following are specific aspects of the Revised GFQ where some issues were observed. Aspects not explicitly mentioned here did not show any significant problems during testing.

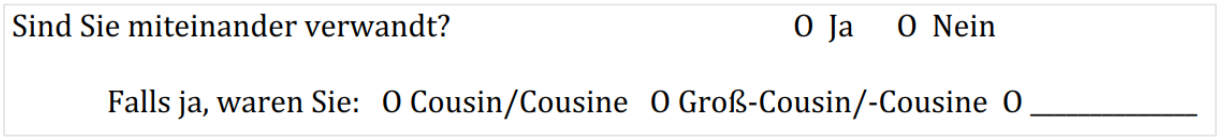
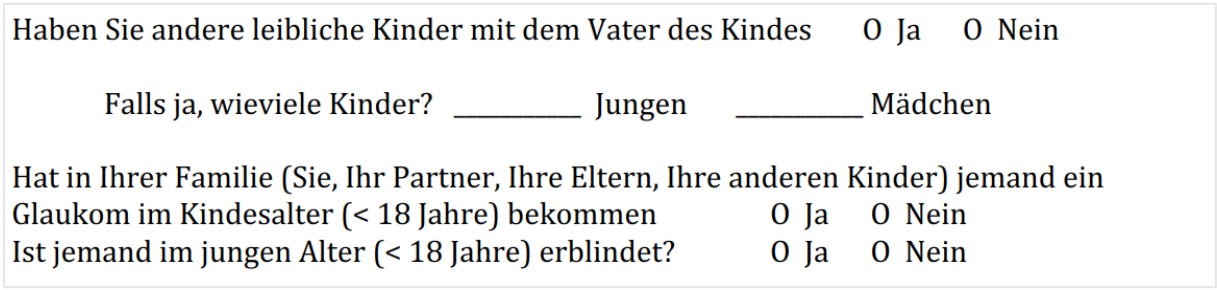


Figure 16: Excerpt from the Revised Gestational and Family History Questionnaire. Content: Relation of the parents

Figure 16 displays a segment from the Revised GFQ concerning whether the parents are related. Some parents sought clarification on how to interpret this question. Ultimately, it makes sense to refer to blood relation, which could be highlighted more clearly in the wording. Additionally, respondents are asked about their specific relationship, in case of

blood relation, such as being cousins. There is a phrasing in the past tense here (in German: “Falls ja, waren Sie:…”), likely unintentional, but not quite appropriate.

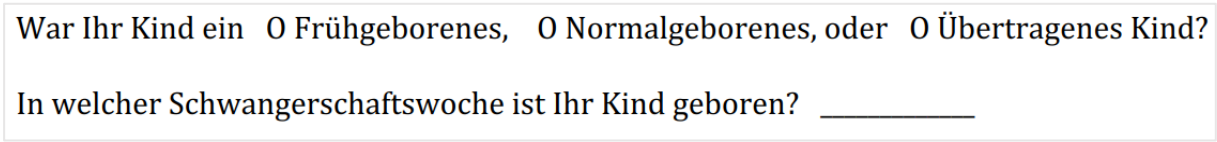

Haben Sie andere leibliche Kinder mit dem Vater des Kindes O Ja O Nein

Falls ja, wieviele Kinder? _____ Jungen _____ Mädchen

Hat in Ihrer Familie (Sie, Ihr Partner, Ihre Eltern, Ihre anderen Kinder) jemand ein
Glaukom im Kindesalter (< 18 Jahre) bekommen O Ja O Nein
Ist jemand im jungen Alter (< 18 Jahre) erblindet? O Ja O Nein

Figure 17: Excerpt from the Revised Gestational and Family History Questionnaire. Content: Number and gender of other mutual children and whether there is knowledge of any relative who went blind or developed glaucoma as a minor

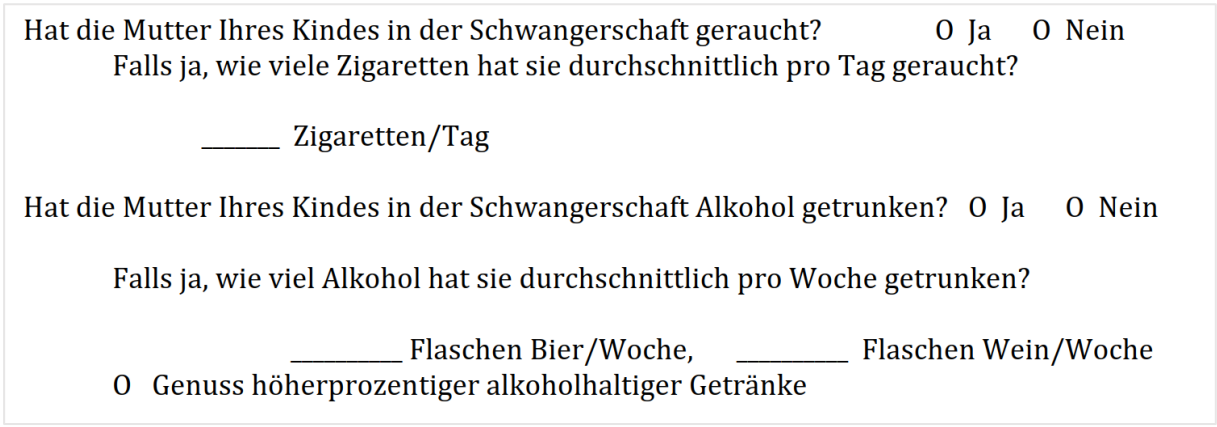
Figure 17 illustrates another segment from the Revised GFQ where parents are asked how many more sons and daughters they have together. However, during testing, two issues were noticed. Firstly, the phrasing in German asks how many more biological children the respondent of the questionnaire has with the child's father, implying that the mother is filling out the form. This might not always be the case, so the wording needs adjustment. Secondly, parents sometimes enquired whether the proband should be included in the count. It is possible that parents overlooked the term "other biological children” (in German: “andere leibliche Kinder”), so the phrasing may be made even clearer in this regard. However, since only the mutual children are being asked about, any other potential children are not considered. Below, it is enquired whether relatives in the family (which could be specified more precisely as "blood relatives of the participant") have developed childhood glaucoma or become blind under the age of 18. In some cases, parents voluntarily provided additional details about which relative was affected. Systematically collecting this information might be of interest.


War Ihr Kind ein O Frühgeborenes, O Normalgeborenes, oder O Übertragenes Kind?

In welcher Schwangerschaftswoche ist Ihr Kind geboren? _____

Figure 18: Excerpt from the Revised Gestational and Family History Questionnaire. Content: Punctuality of birth

The segment in Figure 18 addresses questions about the birth of the proband, firstly inquiring whether the child was born prematurely, at full term, or overdue. Subsequently, the gestational week in which the child was born is enquired. In terms of content, asking about the punctuality of birth doesn't provide additional value if the gestational week is mentioned. However, the sequence of questions could be reversed, and the specification of punctuality used as an additional question if the exact gestational week cannot be recalled.


Hat die Mutter Ihres Kindes in der Schwangerschaft geraucht? O Ja O Nein

Falls ja, wie viele Zigaretten hat sie durchschnittlich pro Tag geraucht?

_____ Zigaretten/Tag

Hat die Mutter Ihres Kindes in der Schwangerschaft Alkohol getrunken? O Ja O Nein

Falls ja, wie viel Alkohol hat sie durchschnittlich pro Woche getrunken?

_____ Flaschen Bier/Woche, _____ Flaschen Wein/Woche

O Genuss höherprozentiger alkoholhaltiger Getränke

Figure 19: Excerpt from the Revised Gestational and Family History Questionnaire. Content: Mother's possible daily habit of smoking cigarettes and weekly amount of alcohol and drug abuse

Figure 19 addresses the noxious substances the child might have been exposed to during pregnancy. The questionnaire enquires about the exact potential number of cigarettes consumed by the mother per day, and bottles of beer and wine consumed per week. The precise number was difficult for parents to retrieve, also because the consumption was usually not consistent throughout the pregnancy.

4.3.3.3 Patient-reported outcome measure

Lastly, parents were asked to complete the PROM. However, this only applied to cases where the child was at least three years old at inclusion. In cases in which the proband was younger than three years at inclusion, completion of the PROM was omitted without replacement. Children of at least four years of age on the day of inclusion were requested to complete a PROM as well. In this regard, it was highly beneficial to know the exact age of the participant from the HIS before the first meeting, allowing for the preparation of the appropriate versions of the German KINDL^{R}. As mentioned in chapter 2.6.3, it was particularly important to ensure that both the child and the parents filled out their respective PROMs independently and without mutual influence. However, assistance was certainly permitted for younger and therefore illiterate or visually impaired children.

In the KINDL^{R}, questions always focused on assessing the past week. For this reason, the following consideration by the author of this thesis played a role in determining when parents and children were asked to complete the PROM: Specific uncommon occurrences had the potential to significantly impact the mood of both the child and the parents over the past week. One such factor that could affect the comparability of completion conditions would be an EUA or surgery that occurred during this period. With this in mind, participants and parents were asked to complete the questionnaire either on the day before the event or with an appropriate time interval thereafter. This could ensure comparable conditions while filling in the PROMs.

Alternatively, the PROM would be filled in during an outpatient appointment at the Childhood Glaucoma Center or while conducting a telephone interview.

While completing the KINDL^R, care was taken to adhere to the instructions provided in the manual. If both, parents, and child required assistance while completing the PROMs, it automatically meant a prolonged time investment. When the forms were filled out on-site at the eye or children's clinic in the presence of the author of this thesis, it was usually possible to create appropriate conditions according to the manual. Nonetheless, especially when the questionnaires were completed in the occasionally bustling waiting areas at the Childhood Glaucoma Center, where free treatment rooms were scarce, and patients/parents needed to be attentive to being called into a treatment room, children and parents were often interrupted when completing the PROMs. Additionally, the children were easily distracted. Yet, it was impossible to govern appropriate conditions when parents took the KINDL^R home, and the completion occurred without the observation of a study member. This was regularly the case in the control group. After being independently completed on-site, the PROM could be promptly reviewed by the author of this dissertation to identify any unanswered sections, which were then resumed with either the child or the parent or left unanswered if not possible. However, in the case of self-completion at home, this was not feasible due to the altered assessment period when the documents had been returned to a study member. Individuals were asked to complete the questionnaire either on the day before the event or with an appropriate time interval thereafter. However, both procedures had disadvantages. The downside of the first approach was that it didn't guarantee the prevention of mood influence linked to the anticipation of an approaching EUA or surgery. The drawback of the latter approach was that, usually, the inpatient stay would typically be over by then, and the completion would occur without supervision at home, which often resulted in forgetting. One alternative was to process the PROM during the next outpatient appointment at the Childhood Glaucoma Center; however, there was uncertainty whether this appointment would still occur within the pilot phase or take place at the Childhood Glaucoma Center in Mainz at all. The alternative option of conducting a telephone interview format occurred in one case with the mother of a participant in the experimental group. This approach was of course most time consuming.

In conclusion, it was not simple to create optimal conditions in the clinic for both the child and the parents to complete their PROMs without interruption, without influencing each other, and at the right time in relation to a potential date of surgery. The most uninterrupted moment likely occurred at home; however, the completion conditions couldn't be controlled and realisation with parents or older children over the phone was very time-consuming from the outset.

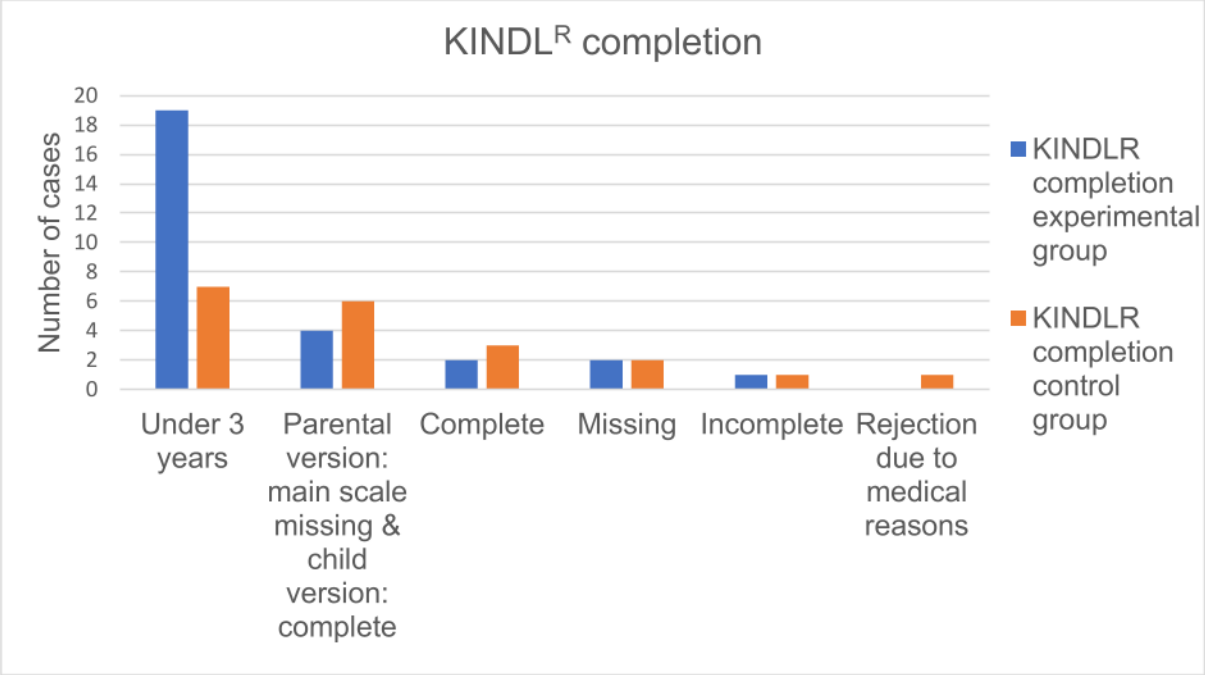


Figure 20: Application of the KINDL[R] in both groups

There was an error in distributing the main-scale for parents of 7-17-year-olds, however, only the additional sub-scale "Disease" was handed out. Consequently, in this age group, "parental version: main-scale missing & child version: complete" is recorded in Figure 20. Nevertheless, the sub-scale in this age group was consistently filled out in its entirety in both groups. Only two participants or parents per group were not offered a PROM to fill out, recorded as “missing” in Figure 20. In all other cases, either the PROM provided was edited (categories: “Complete” and “Incomplete”), probands were too young (“Under 3 years”), or completion was rejected due to impossibility resulting from the probands mental illness. The majority of probands in the experimental group (19 of 28 cases) was younger than 3 years of age on the day of inclusion.

4.3.3.4 Examination Under Anaesthesia Form

During the recruitment phase, the EUA were solely conducted by two different ophthalmologists at the Childhood Glaucoma Center, one being Prof. [redacted] and the other Senior Prof. [redacted], with frequent assistance of the third individual, MD [redacted]. If it was the patient's initial EUA at the Childhood Glaucoma Center, a comprehensive examination was typically performed following an internal procedure, which remained unaltered during testing of the EUAF. Less comprehensive examinations were conducted before emergency interventions or when the previous EUA had been performed recently. In such instances, EUAFs could only be partially completed as well. Keeping the data in the official patient record always took precedence over the pilot study. For this purpose, it was a weekly routine for the surgical staff to manually record the determined values during the

EUA on a blank sheet in the hospital's internal medical record of the patient. The examiner either conveyed the values verbally or a printout of the measuring device was attached for documentation. It was found to be necessary to have a person involved in the pilot study present in the operating theatre for separate data collection on the EUAF. This individual, always the author of this dissertation, would record the data announced by the examiner simultaneously with the surgical staff. This ensured that the EUA's duration was not unnecessarily extended to allow for additional time for data collection. Furthermore, this approach largely enabled independent data collection autonomously from the hospital's internal patient record, thus minimizing the risk of transmission errors.

However, due to time limitations, it was customary for the examiner to only dictate noteworthy characteristics observed during the patient's examination. Unremarkable normal findings were not explicitly emphasized, contrary to what was desired on the EUAF. Therefore, it was not uncommon for the EUAF to have a few unticked blanks at the end of the examination. Other predominantly missing values included the type of anaesthesia and the timing of intraocular pressure measurement following anaesthesia induction. The type of anaesthesia was not a characteristic that was routinely collected within the internal protocol of the EUA. In most cases, it was impossible to establish one specific point in time of IOP measurement due to being conducted multiple times in succession using two different measurement methods. The reason for this procedure was another concurrent study focused on IOP before and after anaesthesia induction. Therefore, the data collection procedure for these values for the other study took priority. Usually, the EUA process smoothly transitioned into the patient's surgery, leaving no time for the examiner's final review of the EUAF and signature for completeness until afterwards. However, even after the surgery, due to time constraints in the operating room schedule, the signature was often provided with only a limited window for accuracy review and completeness check. In certain instances, completions were required and occurred few days after the examination. Some sections of the form were left unfilled if they could not be reconstructed from the clinic's internal patient records or the examiner's memory. Additionally, some sections were deliberately left incomplete because the measurement of certain values was unnecessary for further treatment, e.g., before an emergency intervention, and thus omitted. Some patients with exceptionally uncommon eye characteristics had digital screen captures taken during the EUA. However, due to the lack of designated space on the EUAF, it was not feasible to transfer these captures, along with ultrasound images or every single value listed on the printouts. Consequently, only the values explicitly intended on the form were recorded, and other values seldomly included. Images, however, were never incorporated.

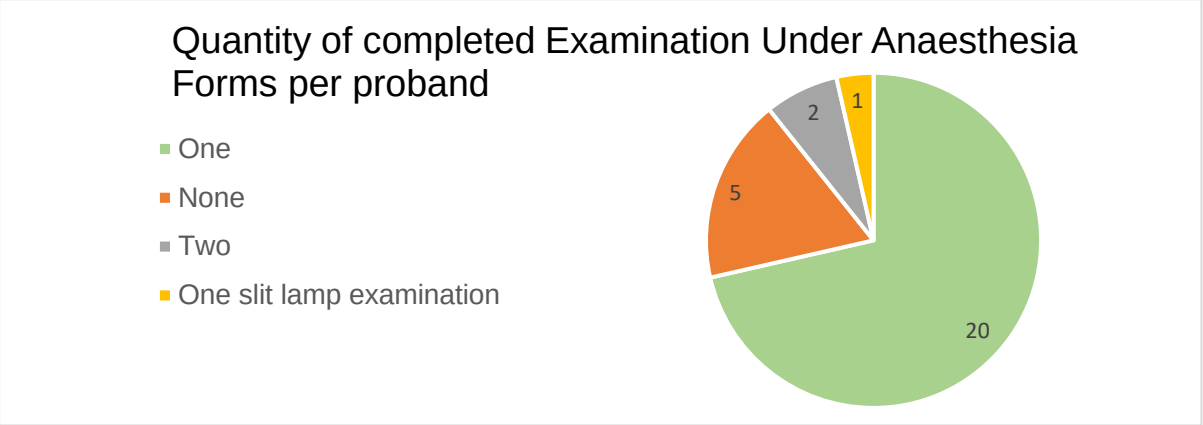


Figure 21: Diagram illustrating the quantity of completed Examination Under Anaesthesia Forms per proband in the experimental group.

All in all, 24 EUA and one slit lamp examination were documented. As illustrated in Figure 21, five probands did not receive an EUA at the Department of Ophthalmology at Mainz University Medical Center during the testing phase. Two even needed to undergo two EUA and 20 had just one. One proband did not receive an EUA but was old enough to be examined at the slit lamp. Nevertheless, the information was documented in the EUAF due to the absence of a suitable form.

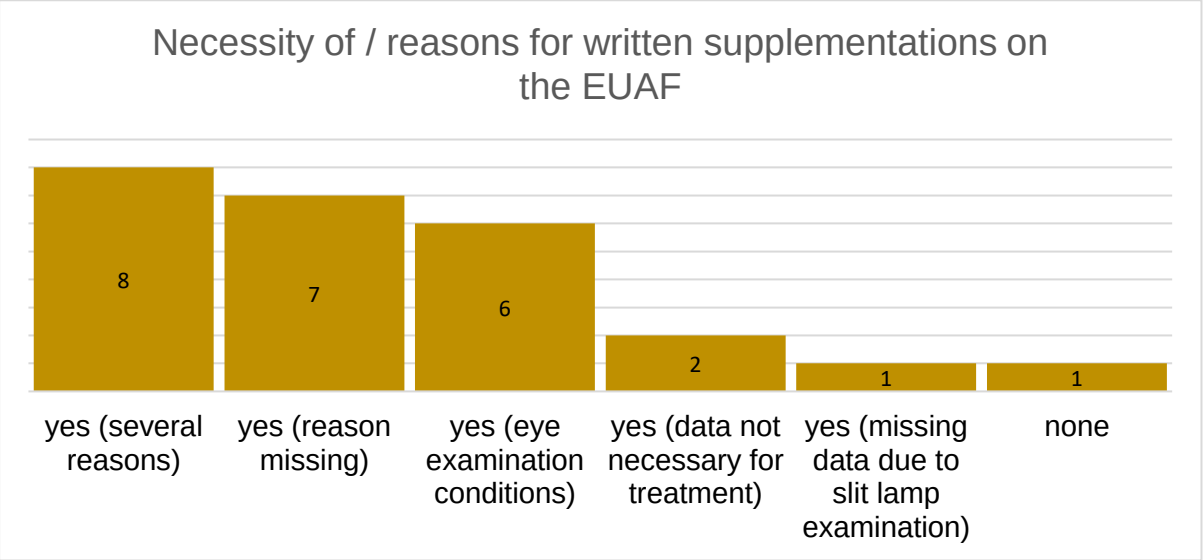


Figure 22: Diagram illustrating necessity of and reasons for written supplementations on the 25 completed EUAFs.

Figure 22 displays whether additional information in writing was added during or after the completion of the EUAF. This was the case in 24 out of 25 forms. The reasons for these additions are indicated in the diagram. However, no specific space was allocated for specifying the reason for missing data, although it could be an essential data analysis category. "Several reasons" implies that more than one cause for missing data was apparent on an EUAF, including factors such as challenging eye examination conditions (e.g., corneal opacity),

technical problems with measurement devices, lack of necessity for the child's treatment, and occasionally, the reason was not stated. The latter was typically the absence of an optic disc photo, which is requested on the second page of the EUAF.

In the following passage, additional observations during the testing will be explained.

Intraokulardruck in mmHg: OD: _____ OS: _____ Zeitpunkt: _____ min nach Narkoseeinleitung

Methode: O Perkins O Schiötz O andere _____

Figure 23: Excerpt from the Examination Under Anaesthesia Form. Content: IOP in mmHg, its assessment method and point in time after the induction of anaesthesia

In Figure 23, the first segment of the EUAF concerns the recording of IOP. One value for each eye is required, along with the measurement method below. The preselected options are Perkins and Schiötz. It was notable that IOP was always measured using two methods during testing phase, namely PAT and iCare™ PRO. Consequently, there were not enough designated spaces on the form to enter more than one value per eye. Considering that Schiötz, as a method, has largely been abandoned according to the literature, it might be advisable to replace it as a preselected option.

Keratometrie: O Retinomax O anderes Gerät: _____

OD: _____ mm / _____ mm / _____° Achse

OS: _____ mm / _____ mm / _____° Achse

Pachymetrie: Mittelwert aus O 1-3 O 4-6 O 7-9 O ≥10 O Gerät: _____

OD: _____ µm OS: _____ µm

Figure 24: Excerpts from the Examination Under Anaesthesia Form. Content: Details on keratometry and pachymetry measurements, including the number of values used to calculate the mean CCT as provided by the device.

In the segments depicted in Figure 24, the focus is on keratometry and pachymetry measurements. Concerning keratometry, the form requests two radii of curvature for each eye separately but only one axis. However, the measuring device consistently provided the second axis, for which no space was provided on the form. Regarding pachymetry, it enquires about the number of values from which the device calculated the mean thickness. However, it can vary for each eye how many values were utilized. The form lacks the necessary space to distinguish them.

Diagnose:

OD:	**OS:**
O Primäres kongenitales Glaukom	O Primäres kongenitales Glaukom
O Sekundäres Glaukom bei	O Sekundäres Glaukom bei:
O Aphakie	O Aphakie
O Uveitis	O Uveitis
O Okuläres Trauma	O Okuläres Trauma
O Aniridie	O Aniridie
O Axenfeld-Rieger Anomalie	O Axenfeld-Rieger-Anomalie
O Peters-Anomalie	O Peters-Anomalie
O Sclerocornea	O Sclerocornea
O Sturge-Weber	O Sturge-Weber
O Neurofibromatose 1	O Neurofibromatose 1
O Lowe-Syndrom	O Lowe-Syndrom
O Posteriore Anomalien (PFV, ROP, FEVR)	O Posteriore Anomlien
O andere:	O andere:

Figure 25: Excerpt from the Examination Under Anaesthesia Form. Content: Demand to tick the appropriate diagnosis for each eye separately from a selection of options. If no preselected diagnosis is applicable, there is the possibility to choose "other" (in German: "andere") and make specifying notes.

The lower section of the second page, as depicted in Figure 25, concerns the diagnosis concluded from the examination. It requires specifying the glaucoma type for each eye. However, this section does not account for glaucoma suspects, the exclusion of glaucoma in at least one eye, or potential uncertainties in diagnosis, nor does it consider the recommendation for a genetic analysis to aid clarification. JOAG also is not mentioned as a possible selection option.

One final observation not to be overlooked is that due to the lack of digitalization or insufficient space on the form, any visual materials, whether ultrasound images or digital photos of the eye, could not be included.

4.3.3.5 Parent Examination Form (PEF)

During the patient recruitment process, the idea arose of offering parents in the experimental group an optional slit lamp examination focusing on glaucoma signs, with the request to incorporate these pseudonymously under the child's ID number into the study. Both the parents and the future childhood glaucoma registry could benefit from the insights gained from this, as the parents would receive a free eye examination as part of their child's appointment, and potential phenotypic similarities between the child and the parent could be identified. The author of this dissertation developed a corresponding form in November 2018 to systematically note the examination results for interested parents. This form was named "Parent Examination

Form” (PEF), in German "Untersuchung der Eltern an der Spaltlampe". Once the form was prepared for use, parents were verbally notified about this choice whenever circumstances allowed for the examination to take place within the available timeframe. The slit lamp examination was usually conducted by MD [redacted] himself, who either had been attending to the child during the outpatient appointment or could spontaneously fit in the examination at short notice.

The form was structured as follows: In the top right corner, like most other forms, the patient ID of the participating child was recorded. Then came section “a) mother”, in German a) Mutter”, which was the area for notes regarding the mother's examination, followed by section “b) father”, in German “b) Vater” for the father's examination. These two sections were structured identically and consisted of the date of the examination and four questions, one for each of the following examination steps: anterior segment, fundus, intraocular pressure, and gonioscopy. Apart from noting the IOP in mmHg in a provided free-text box, the other three examination sections enquired about any abnormalities, deviations from a normal finding. For each of these, checkboxes were provided: the checkbox for "no", in German “nein”, indicating the absence of abnormalities, and the checkbox for "yes, the following", in German “ja, folgende”, indicating the presence of abnormalities and the request to describe them in the free-text field below. At the very bottom, the complete name and signature of the examining physician should be provided, allowing the information to be reviewed before potential integration into the database or registry, like the process with the EUAF, and enabling further clarification in case of any questions. The PEF can be found under Addendum 7.3.6.

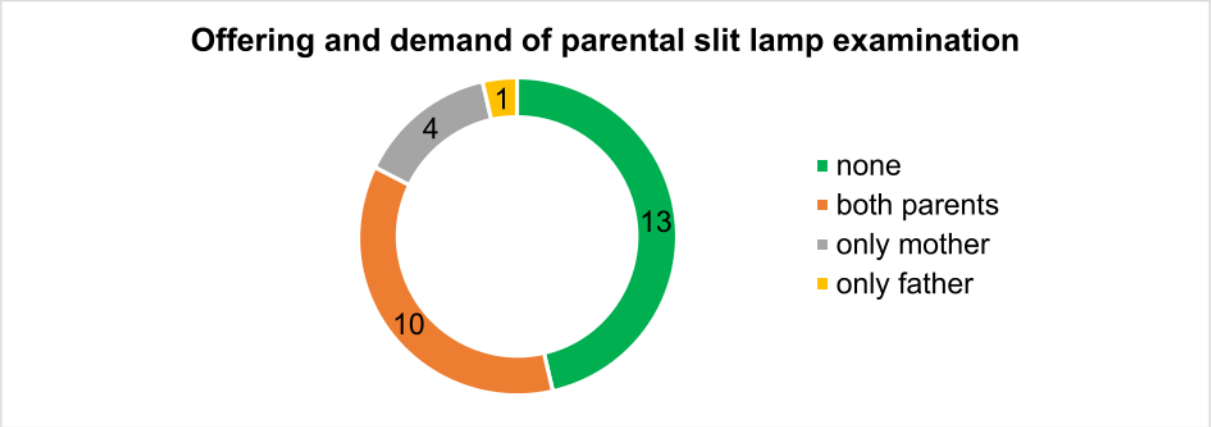


Figure 26: Diagram illustrating the demand of a parental slit lamp examinations in the experimental group.

All parents who were offered a slit-lamp examination willingly accepted it. It was not an issue for these examinations to be recorded under the child's pseudonym. Due to the delayed implementation of this offering, 13 couples were not able to receive the examination, as illustrated in Figure 26. In 5 cases, one parent was absent. In three instances the PEF was not yet ready for use, so the examination was documented on a blank paper sheet instead.

4.3.4 Process of acquiring information for data quality verification

According to Prof. [redacted] the incorporation of a control group was deemed crucial to provide insights into validating the quality of parental statements. There might be a divergence in the information given by parents of children with glaucoma when compared to parents of children without. Some data elements, especially concerning the time of pregnancy, are answered through self-disclosure and the responses are not verifiable due to lack of default recording. One of the objectives of the pilot study was to gain an initial insight into any potential reduction in data quality within the responses provided by parents of children with glaucoma, as compared to other parents and, thus, minimize erroneous data for the future database and nation-wide registry. Therefore, the control group was incorporated in the study.

Hence, Prof. [redacted] identified three birth parameters suitable for exemplary verification of data quality in both groups. These parameters, weight, height, and week of pregnancy at delivery, are also routinely recorded in official medical birth records in Germany. Parents in the control group were to be asked to complete the same set of questionnaires to ensure that they do not pay special attention to the three validation items, thus ensuring that data collection conditions are consistent across both groups. The values from official medical birth documents served as a reference for validating the quality of parental information in both groups. The information provided by the parents in both groups should be compared with official medical birth documents such as the child medical examination booklet (“U-Heft”), the maternity certificate or discharge documents from the hospital after birth. Therefore, parents were asked to provide one of these documents to a member of the study team who then noted the official values on an extra sheet. For this purpose, an exact copy of either the GFQ or Revised GFQ was utilized, termed Verification Document (VD). If the parents had neglected to bring the official medical birth documents, this task had to be carried out during a subsequent appointment. In occasional instances, parents, who filled in the data collection forms at home and returned them via postal service, were requested to enclose a copy of the relevant page from an official medical birth document.

Figure 27 illustrates that official birth documents were available for verification purpose in most cases. Nevertheless, there were situations where transferring data to the VD was impossible because the legal guardians had misplaced all official medical birth documents, for instance, during a relocation. In these instances, the relevant sections in the VD were left empty, with a note explaining the situation. However, it was observed in 4 cases in the experimental group and 2 cases in the control group that the official birth documents were incomplete, with the gestational week at birth as the most common missing information.

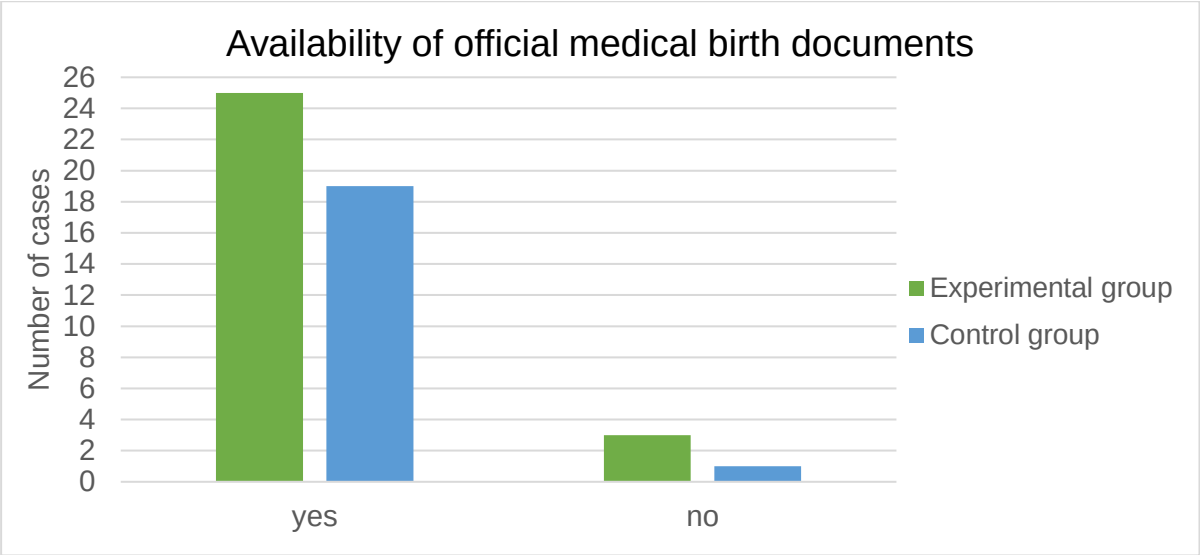


Figure 27: Illustration of the availability of official medical birth documents or data verification in both groups despite their completeness or incompleteness.

Analysis of data quality was not within the scope of this dissertation and will, therefore, not be elaborated further.

4.3.5 Genetics

Since this step is exclusively to be carried out by a physician, according to the GenDG, the ophthalmologist currently overseeing the child's care in the outpatient department or during its hospital stay was required for the information session regarding the genetic examination. For each person, whose blood was to be analysed, it was required to provide a specific official referral slip as mentioned in chapter 3.4 and to sign a general request form for genetical analyses within the clinic, referred to as “Human Genetic Request Form”. These referral slips were necessary to ensure that the procedure was covered by the statutory health insurance. Once completed and signed, the Human Genetic Request Form served as evidence that the patient or one legal guardian had given informed consent for genetic testing in accordance with the regulations of the GenDG. This form needed to include information about the cost carrier, indication, request, timing of sample collection, and any other remarks regarding the patient's medical history. The Human Genetics Department started conducting molecular genetic analysis as soon as they received at least the blood sample of the child, its human genetics request form and its referral slip.

After obtaining written consent, the samples were scheduled to be taken during appointments at the Childhood Glaucoma Center, in case of young children conveniently when anaesthetized and unconscious for the EUA or eye surgery. A blood sample of 2–3 ml for new-borns and 5-10 ml for all other ages, with the addition of ethylenediaminetetraacetic acid (EDTA), was considered appropriate by the Human Genetics department. The samples could be sent to the

Human Genetics department without refrigeration and with a time delay of approximately one day after collection. In three exceptional cases, blood samples were taken outside an operating room of the University Hospital in Mainz, as there were no upcoming scheduled EUAs or surgeries for the child. Despite this, the parents maintained their interest in the genetic results. One blood sample was taken at the outpatient department of the paediatric clinic at University Hospital Mainz, while another one was obtained at a private paediatrician's practice. The parents then sent the blood sample directly to the Human Genetics Department in Mainz by post. In the third case, the child received further treatment and genetic testing at another hospital in Germany. Thanks to her special interest in the pilot study, we received the genetic report from the mother via mail.

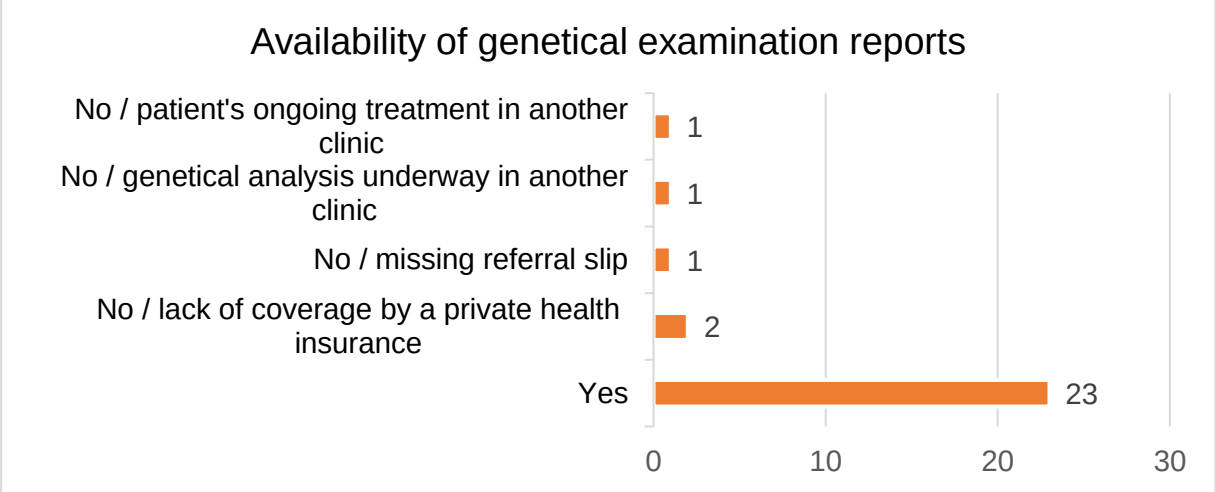


Figure 28: Illustration of the collection of genetical reports in the experimental group. If no genetic result was obtained, the reason is clarified.

Due to various reasons illustrated in Figure 28 it was not possible to obtain a blood sample or to ensure that it was tested for genetic mutations from 5 children in the experimental group. Several factors contributed to this scenario, including the legal guardians' failure to provide a referral slip despite repeated reminders, a genetic analysis underway in another clinic prior to the appointment at the Childhood Glaucoma Center in Mainz, the patient's ongoing treatment in another clinic before the possibility of obtaining a blood sample in Mainz, and the participant's private health insurance not covering the expenses. A cost estimate was issued by the Department of Human Genetics for privately insured children. Statutory health insurers always provided coverage for the costs. The absence of genetic results due to a fundamental rejection of genetic analysis by the parents or unusable material was never the case. Genetic results were available in 23 of 28 cases.

The collection of blood samples of children within the experimental group was usually carried out by the assigned anaesthesiologist in the operating room. It was important to have a labelled

blood tube ready and written consent for genetic testing on file. To ensure a seamless process for sample collection and transfer to the Department of Human Genetics, the ward physician, the ward nurses, and the responsible anaesthesiologist needed to be informed. Most times, the author of this thesis closely monitored each step of the process and personally handled all critical aspects of informing and transportation, ensuring that the documents and tube could not be lost. As the study advanced, the process grew more efficient, and ultimately, by the conclusion of the study, informing the ward physician after previous instruction was enough to commence the sampling and transportation process. However, the inclusion of genetic analyses in the clinic's internal protocol for all childhood glaucoma patients had not yet become standard practice which meant it was offered only as part of the pilot study. Blood samples from the consenting parents were taken in various treatment rooms, and if none was available, in the patient's room. It is important to note that genetic analyses could only be conducted on blood samples from parents who were present at the clinic. However, the sample from the parents was of secondary importance, as the blood of the participant was naturally the primary focus. In some cases, the parents' blood had been unnecessarily collected, as no known mutation was found in the child. Consequently, the analysis of parental blood was omitted. However, the Human Genetics Department in Mainz preferred that blood samples from both the child and parents be submitted within close proximity in time to enable a seamless analysis of parental blood without delay in case a mutation was found in the child. For the Human Genetics Department, it was not a big issue if parents had only submitted a referral slip for their child and not for themselves. However, if the referral slip for the child was missing, no analysis was conducted at all until it was provided. Nonetheless, all submitted blood samples were processed and frozen in the interim by the Human Genetics Department to allow the material to be further processed at any time.

Finalization of genetic results usually took a few weeks and was contingent on the availability of the referral slip. Parents were able to submit referral slips through various methods: they either brought them to the first in-person meeting after being informed about the requirement over the phone with enough lead time for them to arrange it, or they sent them by mail to the Childhood Glaucoma Center, together with other outstanding study material, for the author of this dissertation to redirect them to the Human Genetics Department, or parents directly mailed them there. After the analysis was conducted, the Human Genetics Department would provide a hardcopy genetic report on the blood samples. These documents delivered standardized information about the type of examination conducted on the blood sample, the genes that were examined, any identified disease-causing mutations along with a scientific classification of the results. The medical reports about the parents’ samples contained details about the child's mutation and whether it was also found in either of the parents. In case no mutation was detected in the child, the samples of the parents were not examined, and no report was

generated for them. All genetic reports were sent to the requesting ophthalmologist in charge, conformant with the GenDG, who then forwarded a copy of them to the author of this dissertation for the inclusion of a pseudonymized copy to the study data.

4.3.6 General observations and further descriptive statistics

This chapter includes general comments and descriptive statistics that complement the observations and procedures outlined in each of the documents mentioned above.

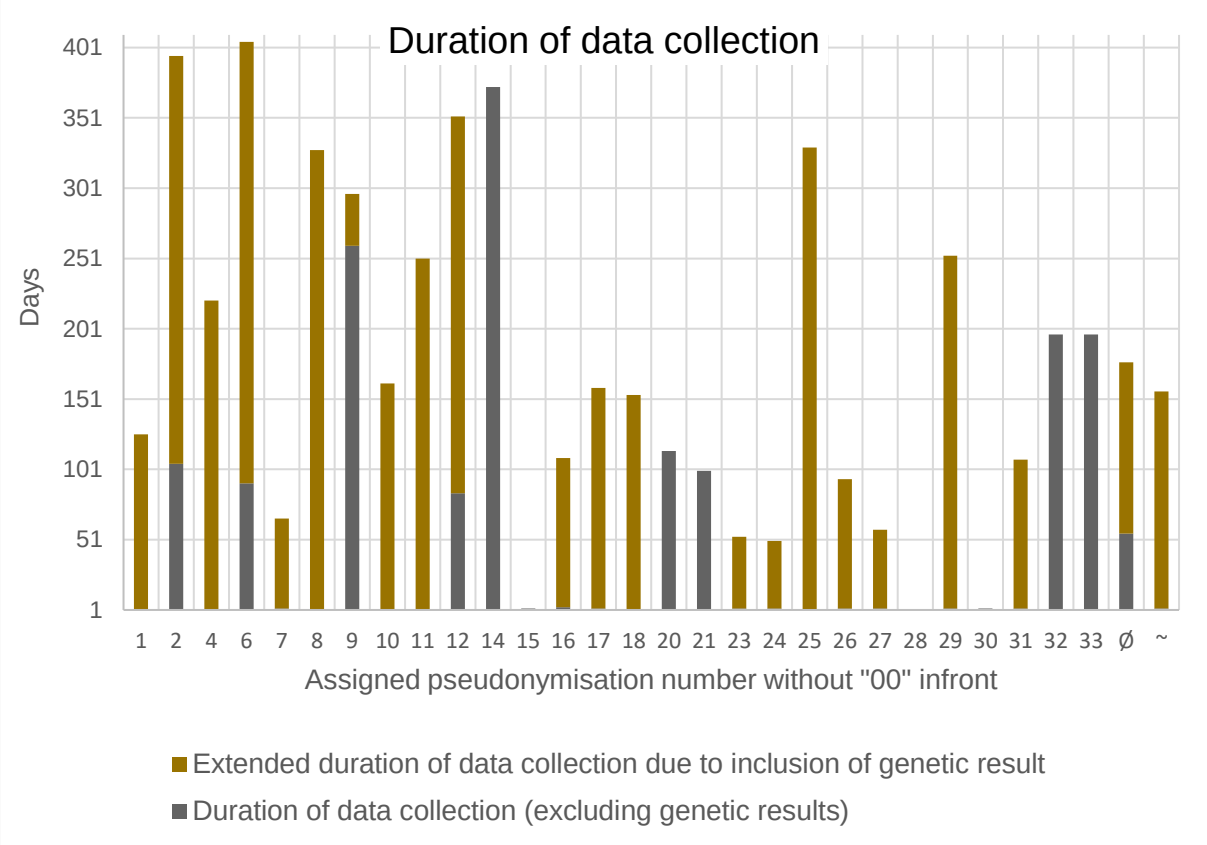
For the most part, timing, and location for the in-person oral briefing, addressing all questions from the parents, studying information forms, signing consent and assent forms, completing questionnaires along with the PROM, and the whole genetical procedure could barely be standardized. Each proband, especially in the experimental group, implied a considerable expenditure of time which altered significantly from case to case due to various factors. These factors included whether the child was affiliated to the experimental or control group and thus the number of forms to be completed, the need to overcome language barriers either through an interpreter or English communication, the need to explain the questionnaires, potential distractions parents faced by their child and/or siblings, and the availability of the patient and parent(s) during inpatient stays or before and after outpatient appointments. Finding a suitable and free treatment room each time was also a hurdle and a time factor. After all, the study ran alongside the usual daily routine at the clinic. The paperwork was mostly done in the waiting area, often alongside other waiting patients, or in the inpatient room which frequently accommodated two or more patients and their parents. One was rarely undisturbed in the process but rather constantly interrupted due to the concurrent appointments of the proband in the hospital. Concerning the experimental group, multiple sessions were often necessary to complete everything, as it could not be finished in just one session. For this the parents needed to spare quite some time. Often, in the experimental cohort as well as in the control group, uncompleted paperwork was taken home and returned via postal service, particularly when only one parent was present at the clinic and hence the other parent’s signature missing on the CFp.

In general, the feedback from participating parents in the experimental group was consistently positive. They support research in this area and the establishment of a registry. The parents of two participants were so interested that they would like to receive the final study results of the pilot study.

4.3.6.1 Duration of data collection

In the experimental cohort it wasn't until 10th December in 2019 that the final data, a pending genetical report, was incorporated into the study data. Figure 29 shows the duration of data collection of each proband in the experimental group. On average, it took 176 days from the written informed consent to the inclusion of the last document of a proband. In 20 out of 28

cases (71%), this last document was the genetic result. Genetic analysis itself typically took several weeks and in addition its initiation was dependent on when the blood sample, human genetic request form, and referral slip were submitted. The latter, in turn, highly relied on the parents´ attention to obtaining it from their family doctor or paediatrician. Excluding the time needed for the inclusion of genetic results, the mean duration of data collection of a proband was 55 days whereas median duration was 2 days.



Ø = arithmetic average proband, ˜ = median proband

Figure 29: Diagram illustrating the duration in days between written informed consent and inclusion of the last document of an experimental group probands data set. In most cases inclusion of genetic results significantly extended the data collection period.

In the control cohort, the date of including the last proband also marked the conclusion of data collection for this group.

4.3.6.2 Data set completeness

28 probands were included in the experimental group of which 21 had a complete data set, meaning all documents marked with an asterisk in Figure 8 were obtained. Data was either incomplete due to missing EUAF (5 cases), missing PROM (1 case) or both (1 case). The Medical History Questionnaire, the Gestational and Family History Questionnaire and the Verification Document was filled out in 100% of cases, either in a revised or unrevised version.

From 23 of 28 probands genetic results could be included in the data set. In the control group, all included 20 probands had a complete data set according to Figure 9.

4.4 Pseudonymisation and data processing and storing

The allocation of a pseudonymisation code resulted from the order of approaching the participants, starting with “0001” in the experimental group and “c0001” in the control group. As soon as approached legal guardians verbally agreed to consider participation, a pseudonymisation code was assigned to the proband and noted on each page of every document before being handed over to the parents. In the event of study withdrawal or exclusion, e.g., due to missing written consent of both legal guardians on the CFp, the pseudonymisation code was not reassigned.

While certain forms provided specific areas for the code, others, such as the CFp, AFo12, AFu12, the second page of the EUAF, and all pages of the PROMs, did not include such designated spaces. A unique aspect were the genetic results, which, after being received in paper form, needed to be pseudonymized before they could be added to the dataset. To do this, specific sections on the received copies of all pages of the reports were obscured as much as possible using black markers (excluding information already collected in one of the other questionnaires, such as postal codes). These blackened documents were then copied once again to ensure that the printed text underneath the black marker couldn't be seen. These final versions were provided with the pseudonymisation code of the proband on every single page including the parental genetic reports and then added to the dataset. To be able to assign ambiguous reports to either the child or a parent, they were additionally marked with the German word for either child (“Kind”), mother (“Mutter”) or father (“Vater”). All other copies were discarded in the clinic's data disposal.

The mapping tables, one each for the experimental and control group, were stored in a locked cabinet within the eye clinic to which only the author of this thesis had access. In the event of study withdrawal or missing written consent, all data collected by then was destroyed.

All pseudonymized documents were filed in paper format and stored in folders at the Department of Ophthalmology, separate from the mapping tables. To keep track of the available, missing, or pending documents for each participant, a spreadsheet was maintained and regularly updated during the recruitment phases. Refer to Table 12 as sample excerpt from the spreadsheet for illustration. The upper table, with a larger portion cut off, was for the experimental group, while the lower one was for the control group. The latter was notably smaller, as fewer documents were collected and thus fewer steps required. Analyses were conducted using successive versions of this and additional Microsoft Excel spreadsheets. After the recruitment phase was completed, all pseudonymized documents were scanned at the

Department of Ophthalmology, and the scans saved on a USB stick. This was stored along with the hardcopy documents and primarily utilized for the analysis.

An initial step towards digitization entailed capturing the gathered raw data of the experimental group, which were the information from the questionnaires, the EUAF, and the genetic results of the experimental group, using IBM SPSS as a preliminary systematic approach. Additionally, the spreadsheets were converted to Microsoft Excel to enable the utilization of both software programs. In this regard, the question arose as to how one could sensibly digitize the data, making it comparable without losing information. This proved to be particularly challenging and time-consuming, especially when digitizing non-numeric data for example information provided in the free-text fields.

Table 12: Spreadsheet maintained in German during the recruitment phase. This excerpt provides a snapshot during the recruitment phase and was not utilized for analyses.

Code	Einwilligung Eltern	Einwill. Kind	Anamnesebogen	Auskunftsbogen	Auskunftsb. valid.	Einwilligung Humangenetik			Blut be
						Kind	Mutter	Vater	Kind
/0001	15.05.2018	15.05.2018 (stellv.)	15.05.2018			25.06.2018	25.06.2018	25.06.2018	26.06.201
/0002	05.06.2018	05.06.2018	05.06.2018		off. Doku. unvollst.	18.09.2018	18.09.2018	war n.a.	18.09.201
X0003	XXX	05.06.2018	05.06.2018		XXX	XXX	XXX	XXX	XXX
/0004	05.06.2018	05.06.2018	05.06.2018		keine Dokumente	12.12.2018	12.12.2018	12.12.2018	12.12.201
X0005	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
/0006	20.06.2018	20.06.2018 (stellv.)	20.06.2018		off. Doku unvollst.	17.09.2018	17.09.2018	17.09.2018	18.09.201
/0007	23.07.2018	fehlt	23.07.2018			24.07.2018	24.07.2018	06.11.2018	24.07.201
/0008	25.07.2018	fehlt	25.07.2018			20.03.2019	20.03.2019	20.03.2019	20.03.201
/0009	31.07.2018	fehlt	16.04.2019			31.07.2018	13.02.2019	13.02.2019	31.07.201
/0010	31.07.2018	fehlt	31.07.2018			30.07.2018	30.07.2018	30.07.2018	31.07.201
/0011	01.08.2018	01.08.2018	01.08.2018		off. Doku unvollst.	01.08.2018	01.08.2018	01.08.2018	
/0012	01.08.2018	fehlt	22.10.2018			22.10.2018	22.10.2018	22.10.2018	24.10.201
/0013	08.10.2018	fehlt	08.10.2018		off. Doku unvollst.	08.10.2018	XXX	XXX	09.10.201
/0014	08.10.2018	08.10.2018	08.10.2018			08.10.2018	08.10.2018	n.a.	09.10.201
/0015	15.10.2018	15.10.2018 (stellv.)	15.10.2018			15.10.2018	15.10.2018	15.10.2018	16.10.201
/0016	22.10.2018	fehlt	24.10.2018			22.10.2018	22.10.2018	22.10.2018	
/0017	22.10.2018	22.10.2018 (stellv.)	22.10.2018			22.10.2018	22.10.2018	22.10.2018	23.10.201
/0018	06.11.2018	fehlt	06.11.2018			06.11.2018	06.11.2018	06.11.2018	08.11.201
X0019	Patient als c0009 in Kontrollgruppe					05.11.2018	s. /0020	05.11.2018	06.11.201
/0020	10.12.2018	10.12.2018 (stellv.)	10.12.2018			19.12.2018	10.12.2018	s. /0019	19.12.201
/0021	13.11.2018	fehlt	20.02.2019			13.11.2018	13.11.2018	13.11.2018	13.11.201
X0022	Patient als c0010 in Kontrollgruppe					XXX	XXX	XXX	XXX
/0023	03.12.2018	fehlt	03.12.2018			03.12.2018	03.12.2018	03.12.2018	04.12.201
/0024	03.12.2018	03.12.2018	03.12.2018			03.12.2018	03.12.2018	03.12.2018	05.12.201
/0025	17.12.2018	fehlt	17.12.2018			17.12.2018	17.12.2018	17.12.2018	Düsseldo
/0026	15.01.2019	fehlt	16.01.2019			15.01.2019	15.01.2019	15.01.2019	15.01.201
/0027	04.03.2019	fehlt	24.07.2019			04.03.2019	n.a.	04.03.2019	05.03.201
/0028	11.03.2019	fehlt	11.03.2019			11.03.2019	11.03.2019	11.03.2019	
/0029	02.04.2019	fehlt	02.04.2019		off. Doku unvollst.	02.04.2019	03.04.2019	XX.10.2019	04.04.201
/0030	20.05.2019	fehlt	20.05.2019			Humangenetische Untersuchun			
/0031	03.06.2019	fehlt	03.06.2019			03.06.2019	03.06.2019	n.a.	04.06.201
/0032	08.05.2019	fehlt	08.05.2019		keine Dokumente	08.05.2019	08.05.2019	s. /0033	20.08.201
/0033	08.05.2019	fehlt	08.05.2019		keine Dokumente	08.05.2019	s. /0032	08.05.2019	20.08.201

Code	Einwilligung Eltern	Einwilligung Kind	Anamnesebogen	Auskunftsbogen	Auskunftsb. valid.	KINDL (Eltern und Kind)	Anmerkung
c0001	20.12.2018	fehlt	20.12.2018			zu jung	
c0002	15.01.2019	fehlt	15.01.2019			15.01.19 (1 Tag vor OP)	
Xc0003	XXX	XXX	XXX	XXX	XXX	XXX	keine Rückm.
c0004	19.03.2019	fehlt	19.03.2019	unvollst.	off. Doku unvollst.	nicht möglich	
c0005	13.03.2019	fehlt	13.03.2019			13.03.2019	
c0006	13.03.2019	fehlt	13.03.2019			zu jung	
c0007	31.03.2019	fehlt	31.03.2019			31.03.2019	
Xc0008	XXX	XXX	XXX	XXX	XXX	XXX	
c0009	05.11.2018	fehlt	05.11.2018			05.11.18 (1 Tag vor OP)	
c0010	12.11.2018	fehlt	12.11.2018		off. Doku unvollst.	zu jung	
c0011	09.04.2019	fehlt	09.04.2019			09.04.2019	
c0012	19.03.2019	fehlt	20.03.2019			20.03.2019	
Xc0013	XXX	XXX	XXX	XXX	XXX	XXX	keine Rückm.
c0014	26.03.2019	fehlt	26.03.2019			zu jung	
c0015	27.03.2019	fehlt	27.03.2019			25.03.2019	OPA1
c0016	27.03.2019	fehlt	27.03.2019			27.03.2019	OPA1
c0017	17.04.2019	fehlt	17.04.2019			17.04.2019	
c0018	26.03.2019	fehlt	26.03.2019			26.03.2019	
Xc0019	XXX	XXX	XXX	XXX	XXX	XXX	
c0020	01.04.2019	fehlt	01.04.2019			fehlt	
c0021	04.04.2019	fehlt	04.04.2019			fehlt	
c0022	01.04.2019	fehlt	01.04.2019			zu jung	
c0023	09.04.2019	fehlt	09.04.2019			zu jung	
c0024	09.07.2019	fehlt	09.07.2019			zu jung	

5 Discussion

This chapter solely deals with considerations, suggestions of improvement, and thought-provoking impulses based on results achieved in the experimental group.

5.1 In- and exclusion criteria

When considering the establishment of a future database or registry for Childhood Glaucoma, the adapted inclusion and exclusion criteria, as outlined in Table 9, can be adopted as they are or subject to further adjustments.

Potential alterations might involve modifying criterion A by either lowering the age limit for inclusion to 16 years or removing it altogether. There are arguments both in favour and against this. On one hand, the definition of a child in Europe and by UNICEF is age up to 16 years. However, this could mean potentially excluding some eligible participants. On the other hand, including all individuals who developed glaucoma during childhood, regardless of their current age, has its merits. For instance, there could be patients who develop JOAG after they have officially transitioned out of childhood, but they would not be part of the future database or registry under these circumstances.

Regarding criterion B, it is necessary to contemplate whether glaucoma suspects should be incorporated into the same future database or registry, perhaps receive a separate domain, or be completely excluded until glaucoma is diagnosed in at least one eye.

As the registry extends its coverage across all of Germany, it's evident that criterion C will require adaptation. Nevertheless, until the database or registry encompasses patients from beyond the Department of Ophthalmology at Mainz University Medical Center, there is room to consider relaxing this criterion by exploring alternative methods for document exchange and providing oral briefing.

Regarding criterion D, it's fundamentally important to contemplate which patient clientele should be incorporated into the future database and registry. Should it include any child diagnosed or treated in Germany or only those born or permanently resident in Germany, or yet another subset? Once a decision has been reached on this matter, the criterion may need to be adjusted accordingly.

Criterion E was introduced primarily because in some cases communication with the parents was impossible since there was no common language. Since the author of this dissertation was able to provide comprehensive information in German and English, these were embedded in the criterion. The inclusion of additional languages would depend on the future study team.

Criterion F can certainly be challenged, as it was already questionable during this pilot study, as explained in Chapter 4.1, and such children should also have their place in a future database or registry.

Regarding criterion G, the premise could be that participation is also possible if only one legal guardian gives written consent. This would save a considerable amount of logistical work, as often only one parent was present at the clinic, and therefore, the CFp had to be taken home for the other parent's signature. In cases where adult participants are involved, they will have the autonomy to provide their own written consent.

5.2 Proband enrolment

It can be advantageous to inform prospective parents in advance about the study, either orally or in writing, e.g. with the help of an informing study brochure. The questionnaires could also be sent in advance before the first face-to-face meeting. Parents who are better organized and more relaxed can improve and expedite the entire data collection process. Theoretically, any doctor in the department who admits patients can conduct patient recruitment for the study. However, this process entails additional time, particularly if integrated into the standard clinical workflow. To prevent delays for other unrelated matters and to avoid duplicating participant enrolments, there must be personnel dedicated to conducting and coordinating patient recruitment. A similarly effective alternative to consulting the HIS for potential subjects is not currently foreseeable. Perhaps recruitment could occur at the level of the local eye doctors. However, for this to happen, the study needs to be made accessible to a larger number of ophthalmologists first.

5.3 Study material, study logistics and data collection

A fundamental consideration regarding any study materials that participants are expected to read is that they should be offered in other languages, but at the very least in English. If the inclusion of control patients continues to be necessary in the future, efforts should be made to adapt the forms to this target group so that they feel addressed.

5.3.1 Information and informed consent/assent forms

Only a few suggestions for improvement can be made. One is to allow participation in the study with the written consent of just one parent. In the pilot study, this would have eliminated the need for the form to be taken home for the second signature and then returned. A solution devised for this would simplify and speed up data collection. Information forms and written consent forms should be kept up to date, also in terms of content. Some parents were confused by the past date in the forms. This could be omitted in a revision. Everything else appeared to have been clearly articulated to the parents and does not require any adjustments.

The forms intended for younger children could include a minimum age requirement, for example 6 years, since they frequently showed diminished interest in comprehending the study or were simply too young.

5.3.2 Data collection forms

In broad terms, it is crucial to reassess at this juncture what information should be gathered with which questionnaire or form, the purpose behind it, and how the related questions should be formulated. It might be necessary to either fine-tune the wording of the question or add additional space, but in some cases, it may also be essential to reorganize the inquiries. For larger open-text sections, it may be possible to provide a tabular format for more structure and, thus, facilitate document analysis. To further enhance clarity on the questionnaires, questions can be numbered or organized in a clear manner. Additionally, during the analysis, it should be clear whether gaps were intentionally left or were accidental omissions. It could be incorporated that for each question, at least one response, even if negative, is necessary, or a reason for potential missing data entry. Instructions for parents on the forms can indicate whether multiple or only single choices are allowed, and which documents may be consulted when seeking information. When creating or modifying a questionnaire, it may also be essential to keep in mind the potential for digitizing the collected data. Free-text fields can generally be particularly cumbersome in this regard.

Regarding the MQ, it is particularly important that it is always certain which eye the response pertains to. This should be adjusted on the form. Furthermore, it may be beneficial to allocate more space or consider providing a table for the answers in certain sections. Concerning Figure 12, a suggestion would be not only to ask for the name of the clinic but also enquire about the specific department if such data would be relevant for the registry. It also may be worth considering designing the MQ in such a way that it does not require medical personnel, allowing participants or parents to understand and independently complete the questionnaire. As stated in the results chapter 4.3.3.1, half of the parents in the experimental group and three quarters in the control group completed the MQ independently rather than in an interview-style approach. This indicates that this method was preferred by the parents in the pilot study and can be a way to save human resources. But this approach should involve asking as few technical terms as possible, as left-over gaps still require a study member’s intervening. However, if these technical terms are essential for the later database or registry, the questionnaire can be divided into two parts: one to be filled out exclusively by a study member, as it requires expertise, and another one that parents can complete on their own as laypersons.

As to the GFQ, its usefulness and comprehensibility for parents are already practical. Minor adjustments to the revised version may be sufficient. Regarding Figure 17 it may be worth exploring how to enquire about additional blood-related children of both parents, and blood relatives of the same generation as the proband. Concerning Figure 19, the query could

potentially be adjusted to either enquire more specifically about the timing of consumption during pregnancy or merely enquire about the fact of consumption. Moreover, it is a sensitive topic, and parents might answer dishonestly, with or without the presence of a study team member. The reliability of the data might therefore not be ensured.

Regarding the when, where and how the PROMs are to be completed, additional contemplation and strategic planning are essential to determine the most feasible approach. For a future database or registry, it might be worth considering conducting the Quality of Life assessment once the child reaches three years of age during participation, rather than just if the child was at least three years on the day of inclusion. Additionally, conducting the assessment at defined regular intervals could help gather longitudinal data in this regard. However, this would require a significant additional effort. Using other PROMs measuring HR-QoL in German language, like the PedsQLTM 4.0 Generic Core Scales or the EU-funded KIDSCREEN could also be explored. However, no glaucoma related sub-scales are available up to date. The German version of the Children's Visual Function Questionnaire (CVFQ), the "Fragebogen zum Kindlichen Sehvermögen" (FKS) can be considered to assess VR-QoL in children with glaucoma aged 7 years and younger.

Concerning the EUAF, keratometry is not listed as a recommended measurement by the CGRN. It could potentially be entirely omitted from the EUAF. Regarding Figure 25, one could alternatively list the classification of childhood glaucoma according to CGRN, thus bringing about an even more systematic approach. A digital or analogue extension of the EUAF is required to include image material such as ultrasound images or photographs in the dataset. Currently, there is no adequate method to document a slit lamp examination of older children. Potentially, another form could be designed for this purpose. If the data collection is to be extended to the probands' local ophthalmologists in private practice, this new form could also be sent to them. During the pilot study, no system was in place for collecting surgery-specific data. Another form could potentially be developed for this purpose.

Encouraging feedback was received regarding the parental examination, indicating that this opportunity was gladly accepted in the pilot study. Gathering parental phenotypic data could be valuable for a future database or registry. To enhance systematic data collection, the Parental Examination Form could be further refined by replacing open-text fields. Additional elaboration on the information forms should highlight this possibility.

5.3.3 Genetics

The opportunity for optional genetic testing on already known disease-causing genes was frequently utilized by the parents. In some cases, this allowed for the confirmation of the proband's glaucoma diagnosis, discovery of a new gene variant related to secondary

glaucoma, and exclusion of a glaucoma suspect. However, the analysis faced issues in two cases due to financing constraints. A solution might need to be explored for this. Furthermore, considering the GenDG, this specific aspect of the study must be assigned to a physician. Alternatively, or additionally, funding is required for the original idea of pseudonymized whole exome sequencing. Furthermore, in the discussion with the Department of Human Genetics, it was clarified that saliva samples would not be useful for genetic purposes. Therefore, it is mandatory to collect blood samples. The study demonstrated that these collections can be standardized within clinic sample logistics. However, to include genetic data in a proband's dataset, coordination and oversight are essential. The option for a genetic analysis can be provided more to parents and children independently of a future database or registry.

5.4 Pseudonymisation and data processing and storing

Employing the "counter" technique demonstrated its simplicity and suitability for a small database. However, it is worth noting that the sequence of inclusion can still be discerned. As the volume of data grows, a different, potentially stronger pseudonymisation method may become necessary. In this regard, the "Mainzelliste" as referenced in the literature review, presents itself as a viable option. Existing data from this pilot study can subsequently be integrated into the future database/registry under a fresh pseudonym. This process involves modifying the current pseudonymisation code into a new one.

Processing and storing data for the future database or registry will necessitate additional considerations, particularly regarding digitalization efforts. Apart from an initial test of data digitalization in IBM SPSS or Microsoft Excel, no further progress has been made. Following the example of other childhood glaucoma registries mentioned in the literature section, this should be pursued further. This can then also facilitate the incorporation of digital image materials.

5.5 Overall considerations

Not all probands were included in the study due to various time-related circumstances, which means that the sample is not entirely representative or randomly selected. Therefore, it is essential to acknowledge the potential limitations and biases associated with convenience sampling when interpreting the results.

During the pilot study, it became evident that a seamless integration of the study into the daily routine of the clinic was not, or only partially, possible. This challenge was particularly notable in the patient recruitment process, data collection for the EUAF, and the overall aggregation of data due to its time-intensive nature. An active study coordinator is essential to oversee the process, initiate necessary steps, and a suitable treatment room needs to be available for constant use.

The failure to include the distribution of a main scale of the PROM indicates that one can easily lose track due to the multitude of paper sheets and documents. Digitization, aimed at improving logistical organization, such as intelligently suggesting appropriate forms for individual participants or reminding about missing documents, could be beneficial. If thought further, every piece of information collected analogously requires digitalization in a subsequent step and then inclusion into a database. To bypass this, data collection would need to be digital from the start. There could be various approaches to this which need to be clarified in terms of data privacy. Data could be entered into forms on a digital device, such as a tablet or desktop computer, and then transferred to the database, perhaps automatically.

Based on insights gained during literature research, to keep a long-term data collection process efficient in a rare disease registry, patients or parents could also be granted access to a selection of the registry's data and actively contribute to it. This might be a consideration for the future.

Potential steps might involve officially registering the future registry on the EU Rare Disease Platform and to collaborate with the existing international childhood glaucoma registry.

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7 Addendum

7.1 Expert interviews transcripts

7.1.1 Prof. [redacted]

Expert interview with **Prof. MD** [redacted] 3rd February 2021

H. Diel: Dear Prof. [redacted], many thanks for participating in this expert interview and for your permission to use its content in my dissertation.

Prof. [redacted]: *My pleasure. Thank you for the invitation.*

H. Diel: In summary, in today's interview I would like to find out more about the development of the pilot study on the nationwide registry for congenital glaucoma in Germany. So, my first question is: When and for which reason did you have the idea of initiating the registry? Where you perhaps inspired by a certain incidence?

Prof. [redacted]: *The Department of Ophthalmology has a long history of treating glaucoma patients from all over the country. The emphasis on the treatment of childhood glaucoma patients is part of our glaucoma centre for, let´s say, about 20 years. Therefore, we have a special interest and a high expertise in the management and treatment of these kids.*
Since congenital glaucoma is a rare disease there are not many cases in Germany and worldwide. However, we don´t know exact numbers in Germany. Treatment is mainly performed at specialized centres, but we don´t know this in detail. Therefore, it was our idea to set up a registry, meaning a clinical and epidemiological database to "count" the patients with congenital glaucoma across Germany.

H. Diel: As an expert in the diagnosis and treatment of childhood glaucoma, what are you hoping for from establishing a nationwide registry for congenital glaucoma in Germany?

Prof. [redacted]: *First of all, we will have insight into the actual numbers of babies and children with congenital glaucoma in Germany. We will learn about diagnostics and treatment strategies. By setting up a database, we will be able to perform extensive research on childhood glaucoma that is not available due to missing data up to now.*

H. Diel: Did you receive help from other colleagues to start the project?

Prof. [redacted]: *To set up a registry is not a "one-woman-show". You will need a team of researchers, clinicians, students, data manager and so on to start with such a project. It is greatly interdisciplinary, which makes such a project very interesting. And you will need money that has to be applied for recently. Yes, it´s teamwork, and everybody is important.*

H. Diel: My next and last question is about the medical history form that you and Dr. [redacted] have developed. Why is it important for the registry whether and of which amount and gender the parents had any other children together apart from the child included in the study?

Prof. [redacted]: *The answers from the parents can provide information if there may be any other children with the same disease or other healthy siblings. So, it is for genetic reasons. Perhaps gender may play a role in the disease expression.*

H. Diel: Dear Prof. [redacted], thank you very much for your time!

7.1.2 Prof. [redacted]

Expert interview with **Prof. MD** [redacted] 11th February 2021

H. Diel: Dear Prof. [redacted], many thanks for participating in this expert interview and for your permission to use its content in my dissertation.

Prof. [redacted]: *No problem. Thanks for having me.*

H. Diel: As a cofounder of the pilot study, you were very much involved in the process of developing the forms which serve to systematically collect data for the registry. Among other things you designed one medical history form and one patient's gestational history questionnaire which were to be filled in by the parents, and one form documenting the examination of the child under general anaesthesia. The development of the medical history form and the patient's gestational history questionnaire was to be validated by including 20 children with glaucoma and 20 children with other eye disorders as control group. The form documenting the examination of the child under general anaesthesia was to be tested in one examination per glaucoma patient with a total of 20 children. Now here is my first question: In contrast to the form documenting the examination of the child under general anaesthesia, for which probably no reasonable or ethically justifiable control group exists, why was a control group needed for validating the developed medical history form and patient's gestational history questionnaire?

Prof. [redacted]: *We saw the possibility that the information provided by the parents of children with glaucoma could differ significantly from the information provided by other parents. Since you cannot assess this deviation if you only include the group of people to be examined in the study, we needed a comparison group. In this way, one can examine the variance in the data and thus determine that, for example, certain statements from parents only accumulate in the glaucoma group.*

H. Diel: As the statistician of the study, could you perhaps explain in a simple way why it had to be at least 20 children per group?

Prof. [redacted]: *We supposed that a number of 20 children might be enough to assume variance in the data. There was no statistical calculation that could be used here. We estimated how many children with glaucoma we treat in our clinic and made the number dependent on it. So, we came up with a number of 20 children who could be included in the pilot study within about half a year.*

H. Diel: While using the questionnaires I noticed something. Was there a particular reason why you decide to create two separate forms to collect the medical and gestational information provided by the parents?

Prof. [redacted]: *When developing the patient's gestational history questionnaire, we were guided by the "Mainzer Modell" birth register. It is used for the standardized recording of congenital malformations in new-borns and foetuses. All neonates born in birth clinics in Mainz are included. Since a patient's gestational history questionnaire is also used here, we have partly adopted the content of it. The parents should answer this questionnaire only once in our pilot study. We kept the medical history form separate so that it may be filled in more often than the gestational history questionnaire, since the child's therapy changes again and again.*

H. Diel: To continue with the gestational questionnaire: which intention did you have on recording which parent (mother, father, or both) filled in this questionnaire?

Prof. [redacted]: *The gestational history questionnaire mainly asks questions about the mother and her pregnancy and birth with her child. It is a self-report if the mother fills it in herself and a third-party report if only the father fills in the form. Since there are differences depending on whether it is external or self-reported, one should be able to retrace this when evaluating the data.*

H. Diel: I can imagine that exact medical data is of high importance to keep a registry as error-free as possible. In some cases, the parents may not know exactly about the current and previous treatments of their child. For which reason did you prefer the parents to provide the medical history concerning the eyes themselves instead of simply asking for permission to collect the data from the hospital information system (SAP) or doctor´s letters?

Prof. [redacted]: *In Germany, when a child is referred from an ophthalmologist to our glaucoma department, medical data is rarely transferred. When we first encounter the child and parents, we are very much dependent on the anamnesis. Even if the parents bring their child's previous physician's letters with them, one cannot be sure that the medical history is complete and correct. Sometimes, data is transferred from one letter to the next without checking for gaps. Thus, for the first time a child is entered in the registry, we would like to include the information from the parents that is believed to be as true as possible. As soon as the child is included in the registry, the prospectively collected data should automatically flow into the registry.*

H. Diel: Adding on to my last question: To validate the correctness of the information provided by the parents, the details on weight and height at birth and week of pregnancy at birth were to be compared with either maternity record, child medical examination booklet ("U-Heft") or discharge documents from hospital after birth. Why did you choose these three parameters of all to validate the correctness?

Prof. [redacted]: *Ultimately, most questions about pregnancy cannot be validated because they are not collected by default. So, we have to trust the self-disclosure. The few documented data contain these three parameters. At the end of the pilot study, we would like to find out how much data of birth stated by the parents differ from the official data. If it turns out that the information hardly differs from one another, we do not have to ask all parents to bring the official documents with them to answer the questionnaire and to validate the parents' information.*

H. Diel: The interview is now drawing to a close. I have one final question. To investigate the children´s health-related quality of life you intended to resort to already existing questionnaires provided by the Office of Quality of Life Measures at the University Medical Center Hamburg-Eppendorf. These questionnaires called "KINDLR" were designed by Ulrike Ravens-Sieberer and Monika Bullinger and revised in the year 2000. It is imaginable that the health-related quality of life of the young glaucoma patients is an important point that cannot be neglected. Why did you decide to investigate it by using the KINDL^R?

Prof. [redacted]: *In the German speaking area, the KINDL^R is simply the best validated questionnaire on the quality of life in children. So, we found it appropriate to use this one.*

H. Diel: Dear Prof. [redacted], thank you very much for this interview and your time!

7.2 Original study material

7.2.1 Parental Information Form (IFp), two pages

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Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Elterninformation

Sehr geehrte Eltern,

wir möchten Sie fragen, ob Sie an der nachfolgend beschriebenen Registerstudie teilnehmen möchten.

Studienhintergrund:
Eine Glaukomerkrankung bei Kindern ist selten. Aufgrund der Seltenheit der Erkrankung gibt es nur wenige Untersuchungen dazu, die meisten wissenschaftlichen Arbeiten berichten über einzelne Fälle und fassen Fälle im Nachhinein zusammen. Gründe für das Auftreten der Erkrankung sind bisher nur wenige bekannt: so wurden beispielsweise verschiedene Gene diskutiert. Die Standardtherapie für die Behandlung eines angeborenen Glaukoms ist die chirurgische Eröffnung der Kammerwinkelstrukturen. Wichtig ist eine Nachuntersuchung. Im Rahmen dieser Pilotstudie sollen Fragebögen für ein deutschlandweites Glaukomregister vorbereitet werden und erste Untersuchungen auf Zusammenhänge von Risikofaktoren in der Schwangerschaft und das Auftreten eines Glaukoms bei Ihrem Kind erfolgen.

Untersuchungen:
Wir werden Sie zur Schwangerschaft mit Ihrem Kind, sowie Ihren Familienerkrankungen befragen. Die Ergebnisse der Untersuchung Ihres Kindes werden bereits im Rahmen der medizinischen Behandlung standardisiert protokolliert und wenn Sie an der Studie teilnehmen im Rahmen der Studie ausgewertet einschließlich der Kontrolluntersuchungen. Die Befragung wird ca.15 Minuten beanspruchen. Bei der nächsten Kontrolluntersuchung beim niedergelassenen Augenarzt (bei Kindern in höherem Alter) wird dem Augenarzt hierfür ein standardisierter Untersuchungsbogen zugesandt. Zudem möchten wir Ihnen als Eltern gerne eine kleine Menge Blut (18 ml) abnehmen, sowie bei Ihrem Kind eine Speichelprobe entnehmen. Bei dem Register sollen mit den Proben genetische Untersuchungen bis hin zu genomweiten Analysen des Erbgutes erfolgen. Im Rahmen dieser Pilotstudie möchten wir nur feststellen, ob die so gewonnenen Proben für solche Untersuchungen ausreichend sind. Bei genomweiten Analysen werden alle Abschnitte des Erbguts untersucht, da sich die krankheitsrelevanten Veränderungen im gesamten Erbgut befinden können. Diese Analysen und Vergleiche mit dem Erbgut gesunder Menschen bieten eine einzigartige Möglichkeit, die Rolle und den Beitrag genetische Faktoren zu Gesundheit und Krankheit genauer zu verstehen. Davon erhoffen wir uns ein besseres Verständnis der Vererbungsvorgänge bei dieser seltenen Erkrankung. Von Ihrem Kind wird nur Blut verwendet, welches im Rahmen der üblichen Diagnostik vor der Operation/Narkoseuntersuchung anfällt. Für dieses Register wird also keine zusätzliche Blutentnahme von Ihrem Kind notwendig.

Genetische Untersuchungen werden nur anonymisiert durchgeführt, das heißt, dass eine Zuordnung zu Ihnen und Ihrem Kind nicht möglich sein wird. Hierbei beabsichtigen wir nach bisher noch nicht bekannten Krankheitsgenen mittels genomweiter Analysen zu suchen, die bisher nicht bekannt sind. Daher werden für Sie keine Zusatzbefunde durch diese genomweiten Untersuchungen entstehen.

Studienteilnahme:
Durch die Teilnahme an dieser Untersuchung entsteht kein unmittelbarer individueller Gesundheitsnutzen für Ihr Kind. Es findet keine Aufwandsentschädigung oder Fahrtkostenerstattung statt. Die erhobenen Daten werden in Papier- und elektronischer Form pseudonymisiert, d.h. codiert ohne Angabe von Name, Adresse oder Ähnlichem erhoben und auf einem gesicherten Server der Universitätsmedizin Mainz gespeichert. Eine Weitergabe von Daten an Dritte, einschließlich Publikation wird nur in anonymisierter Form erfolgen. Erhobene Daten und Biomaterial wird nach Beendigung der Studie, spätestens nach 10 Jahren gelöscht werden, oder zum Zeitpunkt des Widerrufs.

Ein Widerruf der Studienteilnahme ist durch Sie jederzeit mündlich oder schriftlich ohne Angabe von Gründen und ohne jegliche Nachteile möglich, für diesen Fall werden die erhobenen Daten anonymisiert werden. Das entnommene Blut der Eltern und der Speichel wird, sofern noch nicht verbraucht oder anonymisiert, im Falle Ihres Widerrufs vernichtet.

Vorsorglich werden Sie darauf hingewiesen, dass eine Versicherung für nicht schuldhaft verursachte Schäden, die im Zusammenhang mit der Studie auftreten können, nicht abgeschlossen wurde. Ein Versicherungsschutz besteht damit nur, wenn den Arzt oder einen anderen Mitarbeiter der Prüfstelle der Vorwurf eines schuldhaften Fehlverhaltens trifft. Zugunsten des Studienteilnehmers können dabei in bestimmten Fällen Beweiserleichterungen eintreten (Bürgerliches Gesetzbuch, § 630h: zur Beweislast bei Haftung für Aufklärungs- oder Behandlungsfehler). Wegeunfälle sind ebenfalls nicht versichert.

Nachfragen:
Bei Fragen zu dieser Studie wenden Sie sich bitte unter kinderglaukomregister@unimedizin-mainz.de oder 06131-17-2119 an uns.

7.2.2 Patient Information Form under 12 years (IFu12)

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Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Patienteninformation für Kinder

Hallo,

wir möchten dich fragen, ob du an der folgenden Studie teilnehmen möchtest.

Warum wir die Studie durchführen:
Um die Glaukomerkrankung, wie du sie hast, noch besser verstehen und behandeln zu können, sollen Daten vieler Patienten in einem Register gesammelt und wissenschaftlich ausgewertet werden.

Untersuchungen:
Wir werden deine Eltern einige Fragen bezogen auf die Krankheit kurz befragen. Die Befragung wird ca. 15 Minuten beanspruchen. Später sollen auch andere Ärzte, die den Verlauf der Krankheit jedes Jahr untersuchen, jeweils zu deiner Gesundheit befragt werden. Zudem möchten wir bei dir eine Speichelprobe entnehmen, um genetische Untersuchungen durchzuführen. Wir werden von dir nur Blut verwendet, welches dir für deine Behandlung bereits entnommen wurde.

Studienteilnahme:
Wenn du an dieser Studie teilnehmen möchtest, wirst du genauso behandelt wie wenn du nicht teilnimmst. Die erhobenen Daten werden auf Papier und elektronisch gespeichert, ohne dass dein Namen oder Ähnliches hierbei vermerkt wird. Alle Daten und Proben bei dieser Studie werden spätestens nach 10 Jahren gelöscht.
Solltest du an dieser Studie später nicht mehr teilnehmen mögen, kannst du jederzeit durch einen Anruf oder schriftlich (Brief oder Email) die Studie für dich beenden.

Nachfragen:
Bei Fragen zu dieser Studie wende dich bitte unter **kinderglaukomregister@unimedizin-mainz.de** oder unter 06131-17-2119 an uns.

7.2.3 Patient Information Form over 12 years (IFo12)

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Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Patienteninformation für Jugendliche ab 12 Jahre

Hallo,

wir möchten dich fragen, ob du an der folgenden Studie teilnehmen möchtest.

Warum wir die Studie durchführen:
Eine Glaukomerkrankung, wie du eine hast, ist bei Kindern und Jugendlichen selten. Deshalb gibt es nur wenige Untersuchungen dazu. Gründe für das Auftreten der Erkrankung sind bisher nur wenige bekannt: so werden zum Beispiel verschiedene Gene diskutiert. Die Standardtherapie für die Behandlung eines angeborenen Glaukoms ist eine Operation. Wichtig ist auch eine regelmäßige Nachuntersuchung. Im Rahmen dieser Studie sollen Fragebögen für ein deutschlandweites Glaukomregister vorbereitet werden und erste Untersuchungen auf Zusammenhänge von Risikofaktoren für das Auftreten eines Glaukoms erfolgen.

Untersuchungen:
Wir werden deine Eltern zur Schwangerschaft mit dir, sowie zu Familienerkrankungen befragen. Die Befragung wird ca.15 Minuten beanspruchen. Bei der nächsten Kontrolluntersuchung beim niedergelassenen Augenarzt wird dem Augenarzt hierfür ein standardisierter Untersuchungsbogen zugesandt. Zudem möchten wir bei dir eine Speichelprobe entnehmen, um genetische Untersuchungen durchzuführen. Mittels dieser Untersuchungen wird dein Erbgut (DNA) daraufhin untersucht, ob es dort einen Grund für das Auftreten deiner Krankheit gibt. Davon erhoffen wir uns ein besseres Verständnis der Vererbungsvorgänge bei dieser seltenen Erkrankung. Da wir diese Untersuchungen nur anonymisiert durchführen, wird eine Zuordnung zu dir selbst nicht möglich sein. Daher werden sich hierfür für dich keine Zusatzbefunde ergeben.

Studienteilnahme:
Durch die Teilnahme an dieser Untersuchung entsteht kein unmittelbarer Nutzen für dich: wenn du an dieser Studie teilnehmen möchtest, wirst du genauso behandelt wie wenn du nicht teilnimmst. Die erhobenen Daten werden auf Papier und elektronisch gespeichert, ohne dass dein Name oder Ähnliches hierbei vermerkt wird. Eine Weitergabe von Daten an Dritte wird nur so erfolgen. Alle Daten und Proben werden spätestens nach 10 Jahren gelöscht. Du kannst aber auch vorher es uns mitteilen, wenn du die Teilnahme an der Studie nicht mehr willst, dann werden die Daten und Proben gelöscht.

Nachfragen:
Bei Fragen zu dieser Studie wende dich bitte unter **kinderglaukomregister@unimedizin-mainz.de** oder unter 06131-17 2119 an uns.

7.2.4 Parental informed Consent Form (CFp)

UNIVERSITÄTSmedizin. MAINZ

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Mainz, 18.06.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Einwilligungserklärung

Ich erkläre für mich und mein Kind an dem o. g. Register freiwillig teilzunehmen. Mir ist bekannt, dass ich jederzeit und ohne Angabe von Gründen von der Teilnahme an dem Register zurücktreten kann (mündlich oder schriftlich), ohne dass mir oder meinem Kind daraus Nachteile entstehen.
Ich bin in einem persönlichen Gespräch ausführlich und verständlich über Wesen, Bedeutung, Risiken und Tragweite des Registers aufgeklärt worden. Ich hatte die Gelegenheit zu einem Beratungsgespräch. Alle meine Fragen wurden zu meiner Zufriedenheit beantwortet, ich kann jederzeit neue Fragen stellen. Ich habe darüber hinaus den Text der Aufklärung gelesen und verstanden. Ich hatte ausreichend Bedenkzeit, mich zu entscheiden.
Ich habe verstanden und bin damit einverstanden, dass die studienbezogenen Gesundheitsdaten pseudonymisiert (d.h. kodiert ohne Angabe von Namen, Anschrift, Initialen oder Ähnliches) erhoben, auf gesicherten Datenträgern der Universitätsmedizin Mainz gespeichert und ausgewertet werden. Die Daten werden 10 Jahre gespeichert und anschließend gelöscht. Die Weitergabe an Dritte einschließlich Publikation erfolgt ausschließlich in anonymer Form, d.h. kann nicht meiner Person oder meinem Kind zugeordnet werden. Biomaterial wird anonym gewonnen und anonym in der Universitätsmedizin bis zu 10 Jahre gelagert werden. Die Analyse des Biomaterials erfolgt ausschließlich anonymisiert, sodass hierdurch keine Zusatzbefunde entstehen und mitgeteilt werden können.
Ich stimme zu, dass ich bei Rückfragen telefonisch kontaktiert werden darf.
Für den Fall, dass ich die Teilnahme widerrufe, werden bereits erhobenen personenbezogenen Daten von mir oder meinem Kind zum frühestmöglichen Zeitpunkt anonymisiert.

Eine Kopie der Patienteninformation und Einwilligungserklärung habe ich erhalten, diese gelesen und verstanden.

_____ _____

Ort, Datum *Unterschrift beider Eltern/gesetzlicher Vertreter*

_____

Name des aufklärenden Arztes in Druckbuchstaben und Unterschrift

7.2.5 Patient informed Assent Form under 12 years (AFu12)

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Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Einwilligungserklärung für Kinder (bis 12 Jahre)

„Ich möchte an der Pilotstudie für Kinder mit einem Glaukom freiwillig mitmachen. Ich habe mit einem Arzt darüber länger gesprochen und alle meine Fragen wurden gut beantwortet. Ich kann jederzeit neue Fragen stellen.
Ich möchte bei dieser Untersuchung mitmachen um Erklärungen zu finden, warum Kinder eine solche Erkrankung, wie ich es habe, bekommen. Wenn ich an der Studie nicht mehr teilnehmen möchte, kann ich jederzeit widerrufen, ohne dass Nachteile für mich entstehen.“

Ich habe verstanden und bin damit einverstanden, dass meine Angaben über meine Gesundheit in der Universitätsmedizin gespeichert werden, ohne dass mein Name dabei erscheint. Die Angaben werden danach ausgewertet um Erklärungen zu finden, warum Kinder ein Glaukom bekommen und wie man dies am besten behandelt.
Wenn Angaben meiner Gesundheit anderen mitgeteilt werden, zum Beispiel in einer Zeitschrift, werden keine Namen verwendet, damit niemand erkennen kann, dass ich hierbei mitgemacht habe.

Hiermit bin ich einverstanden.

Ort, Datum, *Unterschrift Patient*

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Teilnehmers eingeholt.

Ort, Datum, *Name des aufklärenden Arztes in Druckbuchstaben und Unterschrift*

7.2.6 Patient informed Assent Form over 12 years (AFo12)

UNIVERSITÄTSmedizin. MAINZ

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Mainz, **24.04.2017**

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Einwilligungserklärung für Kinder (>12 Jahre)

„Ich möchte an der Pilotstudie für Kinder mit einem Glaukom mitwirken, um die Gründe für das Auftreten und die beste Behandlung für meine Erkrankung zu finden. Glaukom ist eine Erkrankung, bei der die Weiterleitung des Sehens an das Gehirn beeinträchtigt ist, dies wird meist durch hohen Augendruck verursacht. Es gibt verschiedene Behandlungsarten, diese unterscheiden sich je nach Erkrankungsart. Dies kann sowohl eine Operation oder auch Augentropfen sein. Ich habe mit einem Arzt darüber länger gesprochen und alle meine Fragen wurden gut beantwortet. Ich kann jederzeit neue Fragen stellen.
Wenn ich an der Studie nicht mehr teilnehmen möchte, kann ich jederzeit widerrufen, ohne dass Nachteile für mich entstehen.“

Ich habe verstanden und bin damit einverstanden, dass meine Angaben über meine Gesundheit in der Universitätsmedizin gespeichert werden, ohne dass mein Name dabei erscheint. Die Angaben werden danach ausgewertet um Erklärungen zu finden, warum Kinder ein Glaukom bekommen und wie man dies am besten behandelt.
Wenn Angaben meiner Gesundheit anderen mitgeteilt werden, zum Beispiel in einer Zeitschrift, werden keine Namen verwendet, damit niemand erkennen kann, dass ich hierbei mitgemacht habe.

Hiermit bin ich einverstanden.

Ort, Datum, *Unterschrift Patient*

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Teilnehmers eingeholt.

Name des aufklärenden Arztes in Druckbuchstaben und Unterschrift

7.2.7 Medical History Questionnaire (MQ)

ReKiG-Stationsbogen v1.0, 14.06.2016

14.06.2016

Anamnese: Datum: __ __ . __ __ . __ __ __ __ (TT/MM/Jahr) **Bogen-ID:** _____

Klinik: _____ Arzt: _____

Geburtsdatum: __ __ . __ __ . __ __ __ __ (Tag / Monat / Jahr)

Geschlecht: O männlich O weiblich

Herkunftsland: O Deutschland O Ausland: _____ (Land)

Postleitzahl des Wohnortes in Deutschland: __ __ __ __ __

Datum der Verdachtsdiagnose Glaukom: __ __ . __ __ . __ __ __ __ (Tag / Monat / Jahr)

Von O Augenarzt O Kinderarzt O Klinik: _____

Datum Erstvorstellung Augenarzt: __ __ . __ __ . __ __ __ __ (Tag / Monat / Jahr)

Augenseite mit Diagnose Glaukom (Elternangabe): O rechtes Auge O linkes Auge

Therapie seit Erstdiagnose: O mit Augentropfen O keine O Operation (inkl. Laser)

Falls Augentropfen: Wirkstoffart und Häufigkeit: _____

Augenseite mit Therapie: O rechtes Auge O linkes Auge

Falls Operation: wo, wann und welche wurde durchgeführt:

_____

_____

_____

_____

Andere Erkrankungen des Kindes (nicht nur am Auge): O nein O ja

Falls ja, welche: _____

_____

Einnahme von Medikamenten (außer Augentropfen): O nein O ja

Falls ja, welche: _____

7.2.8 Gestational and Family History Questionnaire (GFQ) and one version of the Verification Document (VD)

ReKiG-Auskunftsbogen v3.0, 24.04.2017

Wer beantwortet den Bogen O Mutter O Vater des Kindes Bogen-ID: _____

Geburtsdatum Mutter: __ __ __ __ (Jahr)

Geburtsdatum Vater: __ __ __ __ (Jahr)

Sind Sie miteinander verwandt? O Ja O Nein

Falls ja, waren Sie: O Cousin/Cousine O Groß-Cousin/-Cousine O _____

Haben Sie andere leibliche Kinder mit dem Vater des Kindes O Ja O Nein

Falls ja, wieviele Kinder? _____ Jungen _____ Mädchen

Hat in Ihrer Familie (Sie, Ihr Partner, Ihre Eltern, Ihre anderen Kinder) jemand ein
Glaukom im Kindesalter (< 18 Jahre) bekommen O Ja O Nein
Ist jemand im jungen Alter (< 18 Jahre) erblindet? O Ja O Nein

Zur Geburt

War Ihr Kind ein O Frühgeborenes, O Normalgeborenes, oder O Übertragenes Kind?

In welcher Schwangerschaftswoche ist Ihr Kind geboren? _____

Wieviel wog Ihr Kind bei Geburt? _____ Gramm

Wie groß war Ihr Kind bei Geburt? _____ cm

Zur Schwangerschaft

Ist die Schwangerschaft auf
O natürlichem Weg oder O durch künstliche Befruchtung erfolgt?

Haben Sie in der Schwangerschaft geraucht? O Ja O Nein

Falls ja, wie viele Zigaretten haben Sie durchschnittlich pro Tag geraucht?

_____ Zigaretten/Tag

Haben Sie in der Schwangerschaft Alkohol getrunken? O Ja O Nein

Falls ja, wie viel Alkohol haben Sie durchschnittlich pro Woche getrunken?

_____ Flaschen Bier/Woche

_____ Flaschen Wein/Woche

O Genuss von höherprozentigen Alkohol-haltigen Getränken.

Haben Sie in der Schwangerschaft Drogen konsumiert? O Ja O Nein

7.2.9 Examination Under Anaesthesia Form (EUAF), two pages

ReKiG-NKU-Bogen v2.0

Narkoseuntersuchung: Datum __ __. __ __. __ __ __ __ **Bogen-ID:** _____

Klinik: _____

Intraokulardruck in mmHg: OD: _____ OS: _____ Zeitpunkt: _____ min nach Narkoseeinleitung

Methode: O Perkins O Schiötz O andere _____

Narkoseart: O ITN: O Larynxmaske O Gas: _____ ; O Propofol O andere: _____

Refraktionsmessung: O Retinomax O Skiaskopie O anderes Gerät: _____

OD: _____ Dpt. Sphäre / _____ Dpt. Zylinder / _____° Achse

OS: _____ Dpt. Sphäre / _____ Dpt. Zylinder / _____° Achse

Keratometrie: O Retinomax O anderes Gerät: _____

OD: _____ mm / _____ mm / _____° Achse

OS: _____ mm / _____ mm / _____° Achse

Hornhautdurchmesser:

Vertikal OD: _____ mm OS: _____ mm Horizontal OD: _____ mm OS: _____ mm

Pachymetrie: Mittelwert aus O 1-3 O 4-6 O 7-9 O ≥10 O Gerät: _____

OD: _____ µm OS: _____ µm

Achsenlänge: O Tomey-_____ O anderes Gerät: _____

OD: _____ mm OS: _____ mm

Vorderer Augenabschnitt:

	OD:		**OS:**	
Megalocornea	O Ja	O Nein	O Ja	O Nein
Haabsche Leisten	O Ja	O Nein	O Ja	O Nein
Stromale corneale Trübung	O Ja	O Nein	O Ja	O Nein
Endotheliale Trübung	O Ja	O Nein	O Ja	O Nein
Embryotoxon posterior	O Ja	O Nein	O Ja	O Nein
Ektropium uveae	O Ja	O Nein	O Ja	O Nein
Irisdefekte	O Ja	O Nein	O Ja	O Nein
Katarakt	O Ja	O Nein	O Ja	O Nein
Andere Auffälligkeit	O Ja	O Nein	O Ja	O Nein

Arzt-Unterschrift (und lesbarer Name):

Bitte wenden!

Fundus: Untersuchung durchführbar: O OD O OS
Papillenfoto O OD O OS aufgenommen

	OD:		**OS:**	
Glaukomatöse Papille	O Ja	O Nein	O Ja	O Nein
Abnormaler Makulawallreflex	O Ja	O Nein	O Ja	O Nein
Andere Pathologie	O Ja	O Nein	O Ja	O Nein

OD:
CDR: _____ horiz.
CDR: _____ vertikal

OS:
CDR: _____ horizontal
CDR: _____ vertikal

Gonioskopie:

	OD:		OS:	
Kammerwinkel zirkulär beurteilbar	O Ja	O Nein	O Ja	O Nein
Dysgenetischer Kammerwinkel	O Ja	O Nein	O Ja	O Nein
Goniosynechierungen	O Ja	O Nein	O Ja	O Nein
Andere Auffälligkeit	O Ja	O Nein	O Ja	O Nein

Welche:

Kong Glaukom bekannt/vor Ops: **O OD** **O OS**

Diagnose:

OD:
O Primäres kongenitales Glaukom

O Sekundäres Glaukom bei
- O Aphakie
- O Uveitis
- O Okuläres Trauma
- O Aniridie
- O Axenfeld-Rieger Anomalie
- O Peters-Anomalie
- O Sclerocornea
- O Sturge-Weber
- O Neurofibromatose 1
- O Lowe-Syndrom
- O Posteriore Anomalien (PFV, ROP, FEVR)
- O andere:

OS:
O Primäres kongenitales Glaukom

O Sekundäres Glaukom bei:
- O Aphakie
- O Uveitis
- O Okuläres Trauma
- O Aniridie
- O Axenfeld-Rieger-Anomalie
- O Peters-Anomalie
- O Sclerocornea
- O Sturge-Weber
- O Neurofibromatose 1
- O Lowe-Syndrom
- O Posteriore Anomlien
- O andere:

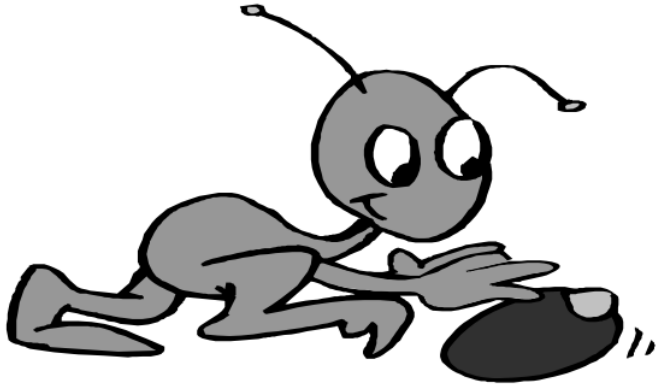
Arzt-Unterschrift (und lesbarer Name):

7.2.10 German KINDL^{R}

7.2.10.1 Kiddy-KINDL^{R} for children aged 4-6 (three pages)

Fragebogen für Kinder

Kiddy-KINDL^{R}



Hallo,

wir möchten gerne wissen, wie es dir zur Zeit geht und wie du dich fühlst. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Ich lese dir jede Frage vor,
- ⇨ Du überlegst, wie es letzte Woche war und
- ⇨ sage mir dann die Antwort, die für dich am besten passt.

Es gibt keine richtigen oder falschen Antworten. Wichtig ist uns deine Meinung.

Bogen ausgefüllt am:

_____

Tag/Monat/Jahr

Bitte sage mir zunächst etwas zu dir

Bist du ein ☐ Mädchen oder ein ☐ Junge?

Wie alt bist du? _____ Jahre

Wie viele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Gehst du in den Kindergarten oder in die Vorschule?
☐ Kindergarten
☐ Vorschule
☐ nichts von beidem

Ich lese dir jetzt ein Beispiel vor:
Wenn du den Satz hörst: „In der letzten Woche habe ich Lust auf Eisessen gehabt",
kannst **du** mir sagen, wie häufig das bei **dir** war?
Es gibt 3 Möglichkeiten zu antworten: **nie, manchmal und ganz oft**.
Also: wie war das bei **dir**?
Würdest **du** sagen: In der letzten Woche habe ich…
nie Lust auf Eisessen gehabt,
habe ich **manchmal** Lust auf Eisessen gehabt oder
habe ich **ganz oft** Lust auf Eisessen gehabt

Antwort des Kindes! Wenn der Eindruck besteht, dass das Kind das Antwortschema verstanden hat weiter mit Frage 1, ansonsten Beispiel wiederholen.

Das machst du sehr gut. Jetzt geht es los.

1. Zuerst möchten wir etwas über deinen Körper wissen, ...

	In der letzten Woche ...	nie	manchmal	ganz oft
1.	... habe ich mich krank gefühlt	☐	☐	☐
2.	... hatte ich Kopfweh oder Bauchweh	☐	☐	☐

2. ... dann etwas darüber, wie du dich fühlst ...

	In der letzten Woche ...	nie	manchmal	ganz oft
1.	... habe ich viel gelacht und Spaß gehabt	☐	☐	☐
2.	... war mir langweilig	☐	☐	☐

3. ... und was du selbst von dir hältst.

In der letzten Woche ...	nie	manchmal	ganz oft
1. ... war ich stolz auf mich	☐	☐	☐
2. ... mochte ich mich selbst leiden	☐	☐	☐

4. In den nächsten Fragen geht es um deine Familie ...

In der letzten Woche ...	nie	manchmal	ganz oft
1. ... habe ich mich gut mit meinen Eltern verstanden	☐	☐	☐
2. ... habe ich mich zu Hause wohl gefühlt	☐	☐	☐

5. ... und danach um Freunde.

In der letzten Woche ...	nie	manchmal	ganz oft
1. ... habe ich mit Freunden gespielt	☐	☐	☐
2. ... habe ich mich mit meinen Freunden gut verstanden	☐	☐	☐

6. Nun möchte ich noch etwas über die Vorschule/den Kindergarten wissen.

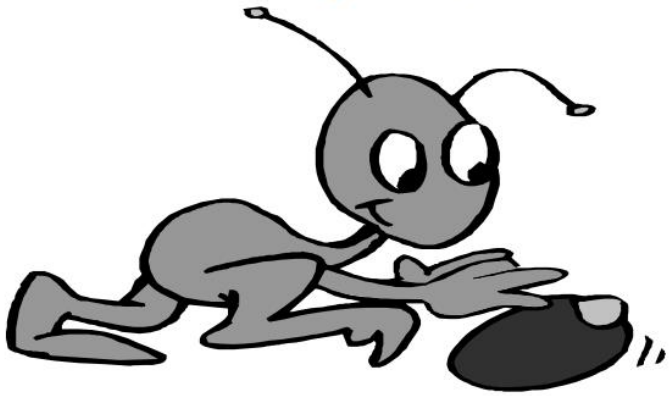
In der letzten Woche, in der ich in der Vorschule/im Kindergarten war, ...	nie	manchmal	ganz oft
1. ... habe ich die Aufgaben in der Vorschule/im Kindergarten gut geschafft	☐	☐	☐
2. ... hat mir die Vorschule/der Kindergarten Spaß gemacht	☐	☐	☐

VIELEN DANK FÜR DEINE MITARBEIT!

7.2.10.2 Kiddy-KINDL^R additional sub-scale “Disease” for children aged 4-6 (two pages)

Fragebogen für Kinder

Kiddy-KINDL^R



Andauernde Erkrankung bzw. längerer Krankenhausaufenthalt

Hallo,

wir möchten gerne wissen, wie es dir zurzeit geht und wie du dich fühlst. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Ich lese dir jede Frage vor,
- ⇨ Du überlegst, wie es letzte Woche war und
- ⇨ sage mir dann die Antwort, die für dich am besten passt.

Es gibt keine richtigen oder falschen Antworten. Wichtig ist uns deine Meinung.

Bogen ausgefüllt am:

_____

Tag/Monat/Jahr

Bitte sage mir zunächst etwas zu dir

Bist du ein ☐ Mädchen oder ein ☐ Junge?

Wie alt bist du? _____ Jahre

Wie viele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Gehst du in den Kindergarten oder in die Vorschule?
☐ Kindergarten
☐ Vorschule
☐ nichts von beidem

Ich lese dir jetzt ein Beispiel vor:
Wenn du den Satz hörst: „In der letzten Woche habe ich Lust auf Eisessen gehabt", kannst **du** mir sagen, wie häufig das bei **dir** war?
Es gibt 3 Möglichkeiten zu antworten: **nie, manchmal und ganz oft**.
Also: wie war das bei **dir**?
Würdest **du** sagen: In der letzten Woche habe ich…
nie Lust auf Eisessen gehabt,
habe ich **manchmal** Lust auf Eisessen gehabt oder
habe ich **ganz oft** Lust auf Eisessen gehabt

Antwort des Kindes! Wenn der Eindruck besteht, dass das Kind das Antwortschema verstanden hat weiter mit Frage 1, ansonsten Beispiel wiederholen.

Das machst du sehr gut. Jetzt geht es los.

In der letzten Woche ...	nie	manchmal	ganz oft
1. ... hatte ich Angst, meine Krankheit könnte schlimmer werden	☐	☐	☐
2. ... war ich wegen meiner Krankheit traurig	☐	☐	☐
3. ... kam ich mit meiner Krankheit gut zurecht	☐	☐	☐
4. ... behandelten mich meine Eltern wegen der Krankheit wie ein Baby	☐	☐	☐
5. ... wollte ich, dass keiner etwas von meiner Krankheit merkt	☐	☐	☐
6. ... habe ich wegen der Krankheit in der Vorschule / dem Kindergarten etwas verpasst	☐	☐	☐

VIELEN DANK FÜR DEINE MITARBEIT!

7.2.10.3 Kiddy-KINDLR for parents of children aged 3-6 (four pages)

ID: __ __ __ __ __

Fragebogen zur Lebensqualität von Kindern

Kiddy-KINDL
3 – 6 Jahre
Elternversion

Sehr geehrte Mutter, sehr geehrter Vater,

vielen Dank, dass Sie sich bereit erklärt haben, diesen Bogen zum Wohlbefinden und zur gesundheitsbezogenen Lebensqualität Ihres Kindes auszufüllen.

Bei den nun folgenden Fragen möchten wir Sie bitten, folgende Instruktionen zu beachten.

- ⇨ Lesen Sie bitte jede Frage genau durch,
- ⇨ überlegen Sie, wie Ihr Kind sich in der letzten Woche gefühlt hat,
- ⇨ kreuzen Sie die Antwort an, die für Ihr Kind am besten zutrifft.

Ein Beispiel:

In der letzten Woche ...

	nie	selten	manch-mal	oft	immer
... hat mein Kind sich wohl gefühlt.	☐	☐	☐	☒	☐

Mein Kind ist ein: Mädchen ☐ Junge ☐ Alter des Kindes: __ __ Jahre

Sie sind: Mutter ☐ Vater ☐ Sonstiges _____?

Ausfülldatum: __ / __ / __ (Tag / Monat / Jahr)

1. Körperliches Wohlbefinden

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind sich krank gefühlt	☐	☐	☐	☐	☐
2. ... hatte mein Kind Kopfschmerzen oder Bauchschmerzen	☐	☐	☐	☐	☐
3. ... war mein Kind müde und schlapp	☐	☐	☐	☐	☐
4. ... hatte mein Kind viel Kraft und Ausdauer	☐	☐	☐	☐	☐

2. Seelisches Wohlbefinden

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind viel gelacht und Spaß gehabt	☐	☐	☐	☐	☐
2. ... hatte mein Kind zu nichts Lust	☐	☐	☐	☐	☐
3. ... hat mein Kind sich allein gefühlt	☐	☐	☐	☐	☐
4. ... hat mein Kind sich ängstlich oder unsicher gefühlt	☐	☐	☐	☐	☐

3. Selbstwert

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... war mein Kind stolz auf sich	☐	☐	☐	☐	☐
2. ... fühlte mein Kind sich wohl in seiner Haut	☐	☐	☐	☐	☐
3. ... mochte mein Kind sich selbst leiden	☐	☐	☐	☐	☐
4. ... hatte mein Kind viele gute Ideen	☐	☐	☐	☐	☐

4. Familie

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind sich gut mit uns als Eltern verstanden	☐	☐	☐	☐	☐
2. ... hat mein Kind sich zu Hause wohl gefühlt	☐	☐	☐	☐	☐
3. ... hatten wir schlimmen Streit zu Hause	☐	☐	☐	☐	☐
4. ... fühlte mein Kind sich durch mich bevormundet	☐	☐	☐	☐	☐

5. Freunde

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind mit Freunden gespielt	☐	☐	☐	☐	☐
2. ... ist mein Kind bei anderen „gut angekommen“	☐	☐	☐	☐	☐
3. ... hat mein Kind sich gut mit seinen Freunden verstanden	☐	☐	☐	☐	☐
4. ... hatte mein Kind das Gefühl, daß es anders ist als die anderen	☐	☐	☐	☐	☐

6. Vorschule / Kindergarten

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind die Aufgaben in der Vorschule/ im Kindergarten gut geschafft	☐	☐	☐	☐	☐
2. ... hat meinem Kind die Vorschule/ der Kindergarten Spaß gemacht	☐	☐	☐	☐	☐
3. ... hat mein Kind sich auf die Vorschule/ den Kindergarten gefreut	☐	☐	☐	☐	☐
4. ... hat mein Kind bei kleineren Aufgaben oder Hausaufgaben viele Fehler gemacht	☐	☐	☐	☐	☐

7. Weitere wichtige Fragen

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... war mein Kind schlecht gelaunt und quengelig	☐	☐	☐	☐	☐
2. ... hat mein Kind mit Appetit gegessen	☐	☐	☐	☐	☐
3. ... konnte ich geduldig und verständnisvoll mit meinem Kind umgehen	☐	☐	☐	☐	☐
4. ... war mein Kind angestrengt	☐	☐	☐	☐	☐
5. ... konnte mein Kind gut schlafen	☐	☐	☐	☐	☐
6. ... ist mein Kind viel herumgetobt und hat sich bewegt	☐	☐	☐	☐	☐
7. ... hat mein Kind schnell geweint	☐	☐	☐	☐	☐
8. ... war mein Kind fröhlich und gut gelaunt	☐	☐	☐	☐	☐
9. ... konnte sich mein Kind gut konzentrieren und war aufmerksam	☐	☐	☐	☐	☐
10. ... ließ sich mein Kind leicht ablenken und war zerstreut	☐	☐	☐	☐	☐
11. ... war mein Kind gern mit anderen Kindern zusammen	☐	☐	☐	☐	☐
12. ... habe ich mit meinem Kind geschimpft	☐	☐	☐	☐	☐
13. ... habe ich mein Kind gelobt	☐	☐	☐	☐	☐
14. ... hatte mein Kind Schwierigkeiten mit Lehrern, Kindergärtnerinnen oder anderen Betreuungspersonen	☐	☐	☐	☐	☐
15. ... war mein Kind nervös und zappelig	☐	☐	☐	☐	☐
16. ... war mein Kind frisch und munter	☐	☐	☐	☐	☐
17. ... hat mein Kind wegen Schmerzen gejammert	☐	☐	☐	☐	☐
18. ... war mein Kind kontaktfreudig	☐	☐	☐	☐	☐
19. ... klappte alles, was mein Kind anfing	☐	☐	☐	☐	☐
20. ... war mein Kind schnell unzufrieden	☐	☐	☐	☐	☐
21. ... hat mein Kind heftig geweint	☐	☐	☐	☐	☐
22. ... wurde mein Kind leicht wütend	☐	☐	☐	☐	☐

Vielen Dank für Ihre Mitarbeit!

7.2.10.4 Kiddy-KINDL^R additional sub-scale “Disease” for parents of children aged 4-6 (two pages)

ID: __ __ __ __ __

Fragebogen zur Lebensqualität von Kindern

Kiddy-KINDL^R
Elternversion

Andauernde Erkrankung bzw. längerer Krankenhausaufenthalt

Sehr geehrte Mutter, sehr geehrter Vater,

vielen Dank, dass Sie sich bereit erklärt haben, diesen Bogen zum Wohlbefinden und zur gesundheitsbezogenen Lebensqualität Ihres Kindes auszufüllen.

Bitte beachten Sie beim Beantworten der Fragen folgende Hinweise:

- ⇨ Lesen Sie bitte jede Frage genau durch,
- ⇨ überlegen Sie, wie Ihr Kind sich in der letzten Woche gefühlt hat,
- ⇨ kreuzen Sie **in jeder Zeile** die Antwort an, die für Ihr Kind am besten zutrifft.

Ein Beispiel:

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
... hat mein Kind gut geschlafen.	☐	☐	☐	☒	☐

Mein Kind ist ein: ☐ Mädchen ☐ Junge

Alter des Kindes: _____ Jahre

Sie sind: ☐ Mutter ☐ Vater ☐ Sonstiges: _____

Ausfülldatum: __ / __ / __ (Tag / Monat / Jahr)

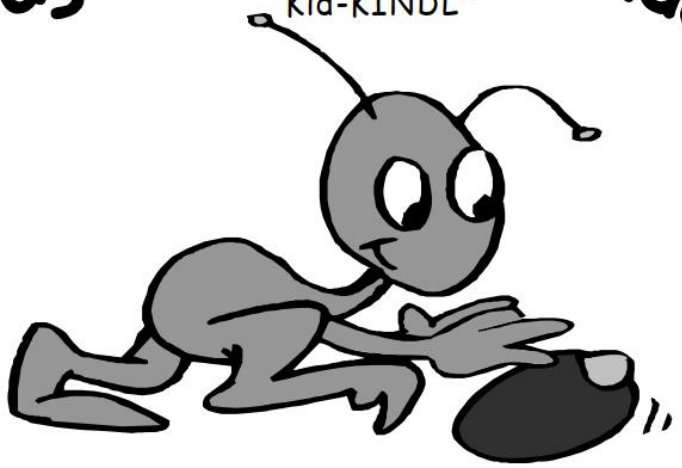
In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hatte mein Kind Angst, die Erkrankung könnte schlimmer werden	☐	☐	☐	☐	☐
2. ... war mein Kind wegen der Erkrankung traurig	☐	☐	☐	☐	☐
3. ... kam mein Kind mit der Erkrankung gut zurecht	☐	☐	☐	☐	☐
4. ... habe ich mein Kind wegen der Erkrankung so behandelt, als ob es jünger wäre	☐	☐	☐	☐	☐
5. ... wollte mein Kind, dass keiner etwas von der Erkrankung merkt	☐	☐	☐	☐	☐
6. ... hat mein Kind wegen der Erkrankung in der Vorschule/ im Kindergarten etwas verpasst	☐	☐	☐	☐	☐

Vielen Dank für Ihre Mitarbeit

7.2.10.5 Kid-KINDL^{R} for children aged 7-13 (three pages)

Fragebogen für Kinder

Kid-KINDL^{R}



Hallo,

wir möchten gerne wissen, wie es dir zur Zeit geht. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Lies bitte jede Frage durch,
- ⇨ überlege, wie es in der letzten Woche war,
- ⇨ kreuze **in jeder Zeile** die Antwort an, die am besten zu dir passt.

Es gibt keine richtigen oder falschen Antworten.
Wichtig ist uns deine Meinung.

Ein Beispiel:	nie	selten	manch-mal	oft	Immer
In der letzten Woche habe ich gerne Musik gehört	☐	☐	☐	☒	☐

Bogen ausgefüllt am:

_____
Tag/Monat/Jahr

Bitte sage uns zunächst etwas zu dir. Kreuze an oder trage ein !

Ich bin ein ☐ Mädchen ☐ Junge

Ich bin _____ Jahre alt

Wieviele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Welche Schule besuchst du? ☐ Grundschule ☐ Hauptschule ☐ Realschule ☐ Gesamtschule ☐ Gymnasium ☐ Sonderschule ☐ privater Unterricht

1. Zuerst möchten wir etwas über deinen Körper wissen, ...

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich mich krank gefühlt	☐	☐	☐	☐	☐
2. ... hatte ich Kopfschmerzen oder Bauchschmerzen	☐	☐	☐	☐	☐
3. ... war ich müde und schlapp	☐	☐	☐	☐	☐
4. ... hatte ich viel Kraft und Ausdauer	☐	☐	☐	☐	☐

2. ... dann etwas darüber, wie du dich fühlst ...

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich viel gelacht und Spaß gehabt	☐	☐	☐	☐	☐
2. ... war mir langweilig	☐	☐	☐	☐	☐
3. ... habe ich mich allein gefühlt	☐	☐	☐	☐	☐
4. ... habe ich Angst gehabt	☐	☐	☐	☐	☐

3. ... und was du selbst von dir hältst.

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... war ich stolz auf mich	☐	☐	☐	☐	☐
2. ... fand ich mich gut	☐	☐	☐	☐	☐
3. ... mochte ich mich selbst leiden	☐	☐	☐	☐	☐
4. ... hatte ich viele gute Ideen	☐	☐	☐	☐	☐

4. In den nächsten Fragen geht es um deine Familie ...

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich mich gut mit meinen Eltern verstanden	☐	☐	☐	☐	☐
2. ... habe ich mich zu Hause wohl gefühlt	☐	☐	☐	☐	☐
3. ... hatten wir schlimmen Streit zu Hause	☐	☐	☐	☐	☐
4. ... haben mir meine Eltern Sachen verboten	☐	☐	☐	☐	☐

5. ... und danach um Freunde.

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich mit Freunden gespielt	☐	☐	☐	☐	☐
2. ... mochten mich die anderen Kinder	☐	☐	☐	☐	☐
3. ... habe ich mich mit meinen Freunden gut verstanden	☐	☐	☐	☐	☐
4. ... hatte ich das Gefühl, dass ich anders bin als die anderen	☐	☐	☐	☐	☐

6. Nun möchten wir noch etwas über die Schule wissen.

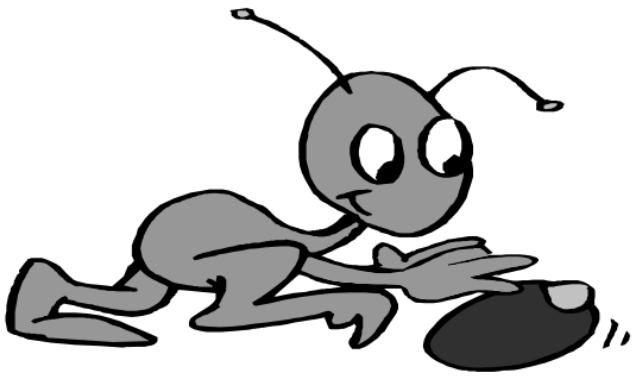
In der letzten Woche, in der ich in der Schule war ...	nie	selten	manch-mal	oft	immer
1. ... habe ich die Schulaufgaben gut geschafft	☐	☐	☐	☐	☐
2. ... hat mir der Unterricht Spaß gemacht	☐	☐	☐	☐	☐
3. ... habe ich mir Sorgen um meine Zukunft gemacht	☐	☐	☐	☐	☐
4. ... habe ich Angst vor schlechten Noten gehabt	☐	☐	☐	☐	☐

VIELEN DANK FÜR DEINE MITARBEIT!

7.2.10.6 Kid-KINDL^{R} additional sub-scale “Disease” for children aged 7-13 (two pages)

Fragebogen für Kinder und Jugendliche

Kid-KINDL ^{R}



Andauernde Erkrankung bzw. längerer Krankenhausaufenthalt

Hallo,

wir möchten gerne wissen, wie es dir zurzeit geht. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Lies bitte jede Frage durch,
- ⇨ überlege, wie es in der letzten Woche war,
- ⇨ kreuze **in jeder Zeile** die Antwort an, die am besten zu dir passt.

Es gibt keine richtigen oder falschen Antworten.
Wichtig ist uns deine Meinung.

Ein Beispiel:	nie	selten	manch-mal	oft	Immer
In der letzten Woche habe ich gerne Musik gehört	☐	☐	☐	☒	☐

Bogen ausgefüllt am:

_____
Tag/Monat/Jahr

Bitte sage uns zunächst etwas zu dir. Kreuze an oder trage ein !

Ich bin ein ☐ Mädchen ☐ Junge

Ich bin _____ Jahre alt

Wieviele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Welche Schule besuchst du? ☐ Grundschule ☐ Hauptschule ☐ Realschule
☐ Gesamtschule ☐ Gymnasium ☐ Sonderschule
☐ privater Unterricht

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hatte ich Angst, meine Erkrankung könnte schlimmer werden	☐	☐	☐	☐	☐
2. ... war ich wegen meiner Erkrankung traurig	☐	☐	☐	☐	☐
3. ... kam ich mit meiner Erkrankung gut zurecht	☐	☐	☐	☐	☐
4. ... behandelten mich meine Eltern wegen der Erkrankung wie ein kleines Kind	☐	☐	☐	☐	☐
5. ... wollte ich, dass keiner etwas von meiner Erkrankung merkt	☐	☐	☐	☐	☐
6. ... habe ich wegen der Erkrankung in der Schule/Ausbildung etwas verpasst	☐	☐	☐	☐	☐

VIELEN DANK FÜR DEINE MITARBEIT!

7.2.10.7 Kid/Kiddo-KINDL^R for parents of children and adolescents aged 7-17 (three pages)

ID: __ __ __ __ __

Fragebogen zur Lebensqualität von Kindern & Jugendlichen

Kid- und Kiddo-KINDL^R
Elternversion

Sehr geehrte Mutter, sehr geehrter Vater,

vielen Dank, dass Sie sich bereit erklärt haben, diesen Bogen zum Wohlbefinden und zur gesundheitsbezogenen Lebensqualität Ihres Kindes auszufüllen.

Bitte beachten Sie beim Beantworten der Fragen folgende Hinweise.

- ⇨ Lesen Sie bitte jede Frage genau durch,
- ⇨ überlegen Sie, wie Ihr Kind sich in der letzten Woche gefühlt hat,
- ⇨ kreuzen Sie **in jeder Zeile** die Antwort an, die für Ihr Kind am besten zutrifft.

Ein Beispiel:

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
... hat mein Kind gut geschlafen.	☐	☐	☐	☒	☐

Mein Kind ist ein: ☐ Mädchen ☐ Junge

Alter des Kindes: _____ Jahre

Sie sind: ☐ Mutter ☐ Vater ☐ Sonstiges: _____

Ausfülldatum: __ / __ / __ (Tag / Monat / Jahr)

1. Körperliches Wohlbefinden

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind sich krank gefühlt	☐	☐	☐	☐	☐
2. ... hatte mein Kind Kopfschmerzen oder Bauchschmerzen	☐	☐	☐	☐	☐
3. ... war mein Kind müde und schlapp	☐	☐	☐	☐	☐
4. ... hatte mein Kind viel Kraft und Ausdauer	☐	☐	☐	☐	☐

2. Seelisches Wohlbefinden

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind viel gelacht und Spaß gehabt	☐	☐	☐	☐	☐
2. ... hatte mein Kind zu nichts Lust	☐	☐	☐	☐	☐
3. ... hat mein Kind sich allein gefühlt	☐	☐	☐	☐	☐
4. ... hat mein Kind sich ängstlich oder unsicher gefühlt	☐	☐	☐	☐	☐

3. Selbstwert

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... war mein Kind stolz auf sich	☐	☐	☐	☐	☐
2. ... fühlte mein Kind sich wohl in seiner Haut	☐	☐	☐	☐	☐
3. ... mochte mein Kind sich selbst leiden	☐	☐	☐	☐	☐
4. ... hatte mein Kind viele gute Ideen	☐	☐	☐	☐	☐

4. Familie

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind sich gut mit uns als Eltern verstanden	☐	☐	☐	☐	☐
2. ... hat mein Kind sich zu Hause wohl gefühlt	☐	☐	☐	☐	☐
3. ... hatten wir schlimmen Streit zu Hause	☐	☐	☐	☐	☐
4. ... fühlte mein Kind sich durch mich bevormundet	☐	☐	☐	☐	☐

5. Freunde

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind etwas mit Freunden zusammen gemacht	☐	☐	☐	☐	☐
2. ... ist mein Kind bei anderen „gut angekommen“	☐	☐	☐	☐	☐
3. ... hat mein Kind sich gut mit seinen Freunden verstanden	☐	☐	☐	☐	☐
4. ... hatte mein Kind das Gefühl, dass es anders ist als die anderen	☐	☐	☐	☐	☐

6. Schule/Ausbildung

In der letzten Woche, in der mein Kind in der Schule/Ausbildung war, ...	nie	selten	manch-mal	oft	immer
1. ... hat mein Kind die Aufgaben in der Schule/Ausbildung gut geschafft	☐	☐	☐	☐	☐
2. ... hat meinem Kind der Unterricht Spaß gemacht	☐	☐	☐	☐	☐
3. ... hat mein Kind sich Sorgen um seine Zukunft gemacht	☐	☐	☐	☐	☐
4. ... hatte mein Kind Angst vor schlechten Noten	☐	☐	☐	☐	☐

Vielen Dank für Ihre Mitarbeit!

7.2.10.8 Kid/Kiddo-KINDL^{R} additional sub-scale “Disease” for parents of children and adolescents aged 7-17 (two pages)

ID: __ __ __ __ __

Fragebogen zur Lebensqualität von Kindern & Jugendlichen

Kid- und Kiddo-KINDL^{R}
Elternversion

Modul: Andauernde Erkrankung bzw. längerer Krankenhausaufenthalt

Sehr geehrte Mutter, sehr geehrter Vater,

vielen Dank, dass Sie sich bereit erklärt haben, diesen Bogen zum Wohlbefinden und zur gesundheitsbezogenen Lebensqualität Ihres Kindes auszufüllen.

Bitte beachten Sie beim Beantworten der Fragen folgende Hinweise.

- ⇨ Lesen Sie bitte jede Frage genau durch,
- ⇨ überlegen Sie, wie Ihr Kind sich in der letzten Woche gefühlt hat,
- ⇨ kreuzen Sie **in jeder Zeile** die Antwort an, die für Ihr Kind am besten zutrifft.

Ein Beispiel:

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
... hat mein Kind gut geschlafen.	☐	☐	☐	☒	☐

Mein Kind ist ein: ☐ Mädchen ☐ Junge

Alter des Kindes: _____ Jahre

Sie sind: ☐ Mutter ☐ Vater ☐ Sonstiges: _____

Ausfülldatum: __ / __ / __ (Tag / Monat / Jahr)

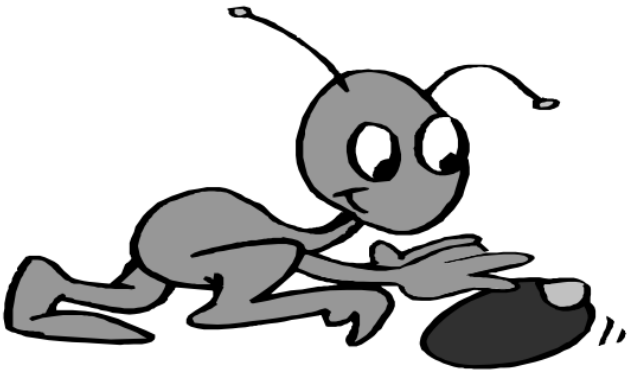
In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hatte mein Kind Angst, die Erkrankung könnte schlimmer werden	☐	☐	☐	☐	☐
2. ... war mein Kind wegen der Erkrankung traurig	☐	☐	☐	☐	☐
3. ... kam mein Kind mit der Erkrankung gut zurecht	☐	☐	☐	☐	☐
4. ... habe ich mein Kind wegen der Erkrankung so behandelt, als ob es ein kleines Kind wäre	☐	☐	☐	☐	☐
5. ... wollte mein Kind, dass keiner etwas von der Erkrankung merkt	☐	☐	☐	☐	☐
6. ... hat mein Kind wegen der Erkrankung in der Schule etwas verpasst	☐	☐	☐	☐	☐

Vielen Dank für Ihre Mitarbeit!

7.2.10.9 Kiddo-KINDL^R for adolescents aged 14-17 (three pages)

Fragebogen für Jugendliche

Kiddo-KINDL ^{R}



Hallo,
wir möchten gerne wissen, wie es dir zur Zeit geht. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Lies bitte jede Frage durch,
- ⇨ überlege, wie es in der letzten Woche war,
- ⇨ kreuze **in jeder Zeile** die Antwort an, die am besten zu dir passt.

Es gibt keine richtigen oder falschen Antworten.
Wichtig ist uns deine Meinung.

Ein Beispiel:	nie	selten	manch-mal	oft	Immer
In der letzten Woche habe ich gerne Musik gehört	☐	☐	☐	☒	☐

Bogen ausgefüllt am:

_____
Tag/Monat/Jahr

Bitte sage uns zunächst etwas zu dir. Kreuze an oder trage ein !

Ich bin ein ☐ Mädchen ☐ Junge

Ich bin _____ Jahre alt

Wie viele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Welche Schule besuchst du? ☐ Grundschule ☐ Hauptschule ☐ Realschule
☐ Gesamtschule ☐ Gymnasium ☐ Sonderschule
☐ privater Unterricht

1. Zuerst möchten wir etwas über deinen Körper wissen, ...

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich mich krank gefühlt	☐	☐	☐	☐	☐
2. ... hatte ich Schmerzen	☐	☐	☐	☐	☐
3. ... war ich müde und erschöpft	☐	☐	☐	☐	☐
4. ... hatte ich viel Kraft und Ausdauer	☐	☐	☐	☐	☐

2. ... dann etwas darüber, wie du dich fühlst ...

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich viel gelacht und Spaß gehabt	☐	☐	☐	☐	☐
2. ... war mir langweilig	☐	☐	☐	☐	☐
3. ... habe ich mich allein gefühlt	☐	☐	☐	☐	☐
4. ... habe ich mich ängstlich oder unsicher gefühlt	☐	☐	☐	☐	☐

3. ... und was du selbst von dir hältst.

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... war ich stolz auf mich	☐	☐	☐	☐	☐
2. ... fühlte ich mich wohl in meiner Haut	☐	☐	☐	☐	☐
3. ... mochte ich mich selbst leiden	☐	☐	☐	☐	☐
4. ... hatte ich viele gute Ideen	☐	☐	☐	☐	☐

4. In den nächsten Fragen geht es um deine Familie ...

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich mich gut mit meinen Eltern verstanden	☐	☐	☐	☐	☐
2. ... habe ich mich zu Hause wohl gefühlt	☐	☐	☐	☐	☐
3. ... hatten wir schlimmen Streit zu Hause	☐	☐	☐	☐	☐
4. ... fühlte ich mich durch meine Eltern eingeschränkt	☐	☐	☐	☐	☐

5. ... und danach um Freunde.

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... habe ich etwas mit Freunden zusammen gemacht	☐	☐	☐	☐	☐
2. ... bin ich bei anderen „gut angekommen“	☐	☐	☐	☐	☐
3. ... habe ich mich mit meinen Freunden gut verstanden	☐	☐	☐	☐	☐
4. ... hatte ich das Gefühl, dass ich anders bin als die anderen	☐	☐	☐	☐	☐

6. Nun möchten wir noch etwas über die Schule/Ausbildung wissen.

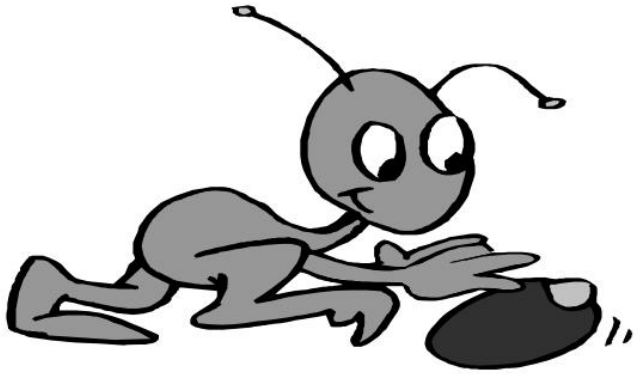
In der letzten Woche, in der ich in der Schule/Ausbildung war, ...	nie	selten	manch-mal	oft	immer
1. ... habe ich die Aufgaben in der Schule/Ausbildung gut geschafft	☐	☐	☐	☐	☐
2. ... hat mich der Unterricht interessiert	☐	☐	☐	☐	☐
3. ... habe ich mir Sorgen um meine Zukunft gemacht	☐	☐	☐	☐	☐
4. ... habe ich Angst vor schlechten Noten gehabt	☐	☐	☐	☐	☐

VIELEN DANK FÜR DEINE MITARBEIT!

7.2.10.10 Kiddo-KINDL^R additional sub-scale “Disease” for adolescents aged 14-17 (two pages)

Fragebogen für Kinder und Jugendliche

Kiddo-KINDL ^{R}



Andauernde Erkrankung bzw. längerer Krankenhausaufenthalt

Hallo,

wir möchten gerne wissen, wie es dir zurzeit geht. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Lies bitte jede Frage durch,
- ⇨ überlege, wie es in der letzten Woche war,
- ⇨ kreuze **in jeder Zeile** die Antwort an, die am besten zu dir passt.

Es gibt keine richtigen oder falschen Antworten.
Wichtig ist uns deine Meinung.

Ein Beispiel:	nie	selten	manch-mal	oft	Immer
In der letzten Woche habe ich gerne Musik gehört	☐	☐	☐	☒	☐

Bogen ausgefüllt am:

_____

Tag/Monat/Jahr

Bitte sage uns zunächst etwas zu dir. Kreuze an oder trage ein !

Ich bin ein ☐ Mädchen ☐ Junge

Ich bin _____ Jahre alt

Wieviele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Welche Schule besuchst du? ☐ Grundschule ☐ Hauptschule ☐ Realschule
☐ Gesamtschule ☐ Gymnasium ☐ Sonderschule
☐ privater Unterricht

In der letzten Woche ...	nie	selten	manch-mal	oft	immer
1. ... hatte ich Angst, meine Erkrankung könnte schlimmer werden	☐	☐	☐	☐	☐
2. ... war ich wegen meiner Erkrankung traurig	☐	☐	☐	☐	☐
3. ... kam ich mit meiner Erkrankung gut zurecht	☐	☐	☐	☐	☐
4. ... behandelten mich meine Eltern wegen der Erkrankung wie ein kleines Kind	☐	☐	☐	☐	☐
5. ... wollte ich, dass keiner etwas von meiner Erkrankung merkt	☐	☐	☐	☐	☐
6. ... habe ich wegen der Erkrankung in der Schule/Ausbildung etwas verpasst	☐	☐	☐	☐	☐

VIELEN DANK FÜR DEINE MITARBEIT!

7.3 Revised study material

7.3.1 Revised Parental Information Form (Revised IFp) (two pages)

JG|U UNIVERSITÄTSmedizin. MAINZ

Augenklinik und Poliklinik

Direktor
Prof. Dr. med. [redacted]

Prof. Dr. [redacted]
Geb. 102
Langenbeckstr. 1
55131 Mainz
Telefon: +49 (0) 6131 17-2119
E-Mail: kinderglaukomregister
@unimedizin-mainz.de

Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Elterninformation

Sehr geehrte Eltern,

wir möchten Sie fragen, ob Sie an der nachfolgend beschriebenen Registerstudie teilnehmen möchten.

Studienhintergrund:
Eine Glaukomerkrankung bei Kindern ist selten. Aufgrund der Seltenheit der Erkrankung gibt es nur wenige Untersuchungen dazu, die meisten wissenschaftlichen Arbeiten berichten über einzelne Fälle und fassen Fälle im Nachhinein zusammen. Gründe für das Auftreten der Erkrankung sind bisher nur wenige bekannt: so wurden beispielsweise verschiedene Gene diskutiert. Die Standardtherapie für die Behandlung eines angeborenen Glaukoms ist die chirurgische Eröffnung der Kammerwinkelstrukturen. Wichtig ist eine Nachuntersuchung. Im Rahmen dieser Pilotstudie sollen Fragebögen für ein deutschlandweites Glaukomregister vorbereitet werden und erste Untersuchungen auf Zusammenhänge von Risikofaktoren in der Schwangerschaft und das Auftreten eines Glaukoms bei Ihrem Kind erfolgen.

Untersuchungen:
Wir werden Sie zur Schwangerschaft mit Ihrem Kind, sowie Ihren Familienerkrankungen befragen. Die Ergebnisse der Untersuchung Ihres Kindes werden bereits im Rahmen der medizinischen Behandlung standardisiert protokolliert und wenn Sie an der Studie teilnehmen im Rahmen der Studie ausgewertet einschließlich der Kontrolluntersuchungen. Die Befragung wird ca.15 Minuten beanspruchen. Bei der nächsten Kontrolluntersuchung beim niedergelassenen Augenarzt (bei Kindern in höherem Alter) wird dem Augenarzt hierfür ein standardisierter Untersuchungsbogen zugesandt. Zudem möchten wir Ihnen als Eltern gerne eine kleine Menge Blut (~~18~~ 2-3 ml) abnehmen, sowie bei Ihrem Kind eine ~~Speichel~~Blutprobe entnehmen. Bei dem Register sollen mit den Proben genetische Untersuchungen bis hin zu genomweiten Analysen des Erbgutes erfolgen. Im Rahmen dieser Pilotstudie möchten wir nur feststellen, ob die so gewonnenen Proben für solche Untersuchungen ausreichend sind. Bei genomweiten Analysen werden alle Abschnitte des Erbguts untersucht, da sich die krankheitsrelevanten Veränderungen im gesamten Erbgut befinden können. Diese Analysen und Vergleiche mit dem Erbgut gesunder Menschen bieten eine einzigartige Möglichkeit, die Rolle und den Beitrag genetische Faktoren zu Gesundheit und Krankheit genauer zu verstehen. Davon erhoffen wir uns ein besseres Verständnis der Vererbungsvorgänge bei dieser seltenen Erkrankung. ~~Von Ihrem Kind wird nur Blut verwendet, welches im Rahmen der üblichen Diagnostik vor der Operation/Narkoseuntersuchung anfällt. Für dieses Register wird also keine zusätzliche Blutentnahme von Ihrem Kind notwendig.~~

 Mainz, 24.04.2017

Genetische Untersuchungen werden nur anonymisiert durchgeführt, das heißt, dass eine Zuordnung zu Ihnen und Ihrem Kind nicht möglich sein wird. Hierbei beabsichtigen wir nach bisher noch nicht bekannten Krankheitsgenen mittels genomweiter Analysen zu suchen, die bisher nicht bekannt sind. Daher werden für Sie keine Zusatzbefunde durch diese genomweiten Untersuchungen entstehen.

Studienteilnahme:
Durch die Teilnahme an dieser Untersuchung entsteht kein unmittelbarer individueller Gesundheitsnutzen für Ihr Kind. Es findet keine Aufwandsentschädigung oder Fahrtkostenerstattung statt. Die erhobenen Daten werden in Papier- und elektronischer Form pseudonymisiert, d.h. codiert ohne Angabe von Name, Adresse oder Ähnlichem erhoben und auf einem gesicherten Server der Universitätsmedizin Mainz gespeichert. Eine Weitergabe von Daten an Dritte, einschließlich Publikation wird nur in anonymisierter Form erfolgen. Erhobene Daten und Biomaterial wird nach Beendigung der Studie, spätestens nach 10 Jahren gelöscht werden, oder zum Zeitpunkt des Widerrufs.

Ein Widerruf der Studienteilnahme ist durch Sie jederzeit mündlich oder schriftlich ohne Angabe von Gründen und ohne jegliche Nachteile möglich, für diesen Fall werden die erhobenen Daten anonymisiert werden. Das entnommene Blut der Eltern ~~und der Speichel~~ wird, sofern noch nicht verbraucht oder anonymisiert, im Falle Ihres Widerrufs vernichtet.

Vorsorglich werden Sie darauf hingewiesen, dass eine Versicherung für nicht schuldhaft verursachte Schäden, die im Zusammenhang mit der Studie auftreten können, nicht abgeschlossen wurde. Ein Versicherungsschutz besteht damit nur, wenn den Arzt oder einen anderen Mitarbeiter der Prüfstelle der Vorwurf eines schuldhaften Fehlverhaltens trifft. Zugunsten des Studienteilnehmers können dabei in bestimmten Fällen Beweiserleichterungen eintreten (Bürgerliches Gesetzbuch, § 630h: zur Beweislast bei Haftung für Aufklärungs- oder Behandlungsfehler). Wegeunfälle sind ebenfalls nicht versichert.

Nachfragen:
Bei Fragen zu dieser Studie wenden Sie sich bitte unter kinderglaukomregister@unimedizin-mainz.de oder 06131-17-2119 an uns.

7.3.2 Revised Patient Information Form under 12 years (Revised IFu12)

UNIVERSITÄTSmedizin. MAINZ

Augenklinik und Poliklinik

Direktor
Prof. Dr. med. [redacted]

Prof. Dr. [redacted]
Geb. 102
Langenbeckstr. 1
55131 Mainz
Telefon: +49 (0) 6131 17-2119
E-Mail: kinderglaukomregister
@unimedizin-mainz.de

Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern"

Patienteninformation für Kinder

Hallo,

wir möchten dich fragen, ob du an der folgenden Studie teilnehmen möchtest.

Warum wir die Studie durchführen:
Um die Glaukomerkrankung, wie du sie hast, noch besser verstehen und behandeln zu können, sollen Daten vieler Patienten in einem Register gesammelt und wissenschaftlich ausgewertet werden.

Untersuchungen:
Wir werden deine Eltern einige Fragen bezogen auf die Krankheit kurz befragen. Die Befragung wird ca. 15 Minuten beanspruchen. Später sollen auch andere Ärzte, die den Verlauf der Krankheit jedes Jahr untersuchen, jeweils zu deiner Gesundheit befragt werden. Zudem möchten wir bei dir eine ~~Speichel~~Blutprobe entnehmen, um genetische Untersuchungen durchzuführen. Wir werden von dir nur Blut verwendet, welches dir für deine Behandlung bereits entnommen wurde.

Studienteilnahme:
Wenn du an dieser Studie teilnehmen möchtest, wirst du genauso behandelt wie wenn du nicht teilnimmst. Die erhobenen Daten werden auf Papier und elektronisch gespeichert, ohne dass dein Namen oder Ähnliches hierbei vermerkt wird. Alle Daten und Proben bei dieser Studie werden spätestens nach 10 Jahren gelöscht.
Solltest du an dieser Studie später nicht mehr teilnehmen mögen, kannst du jederzeit durch einen Anruf oder schriftlich (Brief oder Email) die Studie für dich beenden.

Nachfragen:
Bei Fragen zu dieser Studie wende dich bitte unter **kinderglaukomregister@unimedizin-mainz.de** oder unter 06131-17-2119 an uns.

7.3.3 Revised Patient Information Form over 12 years (Revised IFo12)

UNIVERSITÄTSmedizin. MAINZ

Augenklinik und Poliklinik

Direktor
Prof. Dr. med. [redacted]

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Langenbeckstr. 1
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E-Mail: kinderglaukomregister
@unimedizin-mainz.de

Mainz, 24.04.2017

„Pilotstudie zur Etablierung eines Registers für Glaukome bei Kindern“

Patienteninformation für Jugendliche ab 12 Jahre

Hallo,

wir möchten dich fragen, ob du an der folgenden Studie teilnehmen möchtest.

Warum wir die Studie durchführen:
Eine Glaukomerkrankung, wie du eine hast, ist bei Kindern und Jugendlichen selten. Deshalb gibt es nur wenige Untersuchungen dazu. Gründe für das Auftreten der Erkrankung sind bisher nur wenige bekannt: so werden zum Beispiel verschiedene Gene diskutiert. Die Standardtherapie für die Behandlung eines angeborenen Glaukoms ist eine Operation. Wichtig ist auch eine regelmäßige Nachuntersuchung. Im Rahmen dieser Studie sollen Fragebögen für ein deutschlandweites Glaukomregister vorbereitet werden und erste Untersuchungen auf Zusammenhänge von Risikofaktoren für das Auftreten eines Glaukoms erfolgen.

Untersuchungen:
Wir werden deine Eltern zur Schwangerschaft mit dir, sowie zu Familienerkrankungen befragen. Die Befragung wird ca.15 Minuten beanspruchen. Bei der nächsten Kontrolluntersuchung beim niedergelassenen Augenarzt wird dem Augenarzt hierfür ein standardisierter Untersuchungsbogen zugesandt. Zudem möchten wir bei dir eine ~~Speichel~~Blutprobe entnehmen, um genetische Untersuchungen durchzuführen. Mittels dieser Untersuchungen wird dein Erbgut (DNA) daraufhin untersucht, ob es dort einen Grund für das Auftreten deiner Krankheit gibt. Davon erhoffen wir uns ein besseres Verständnis der Vererbungsvorgänge bei dieser seltenen Erkrankung. Da wir diese Untersuchungen nur anonymisiert durchführen, wird eine Zuordnung zu dir selbst nicht möglich sein. Daher werden sich hierfür für dich keine Zusatzbefunde ergeben.

Studienteilnahme:
Durch die Teilnahme an dieser Untersuchung entsteht kein unmittelbarer Nutzen für dich: wenn du an dieser Studie teilnehmen möchtest, wirst du genauso behandelt wie wenn du nicht teilnimmst. Die erhobenen Daten werden auf Papier und elektronisch gespeichert, ohne dass dein Name oder Ähnliches hierbei vermerkt wird. Eine Weitergabe von Daten an Dritte wird nur so erfolgen. Alle Daten und Proben werden spätestens nach 10 Jahren gelöscht. Du kannst aber auch vorher es uns mitteilen, wenn du die Teilnahme an der Studie nicht mehr willst, dann werden die Daten und Proben gelöscht.

Nachfragen:
Bei Fragen zu dieser Studie wende dich bitte unter **kinderglaukomregister@unimedizin-mainz.de** oder unter 06131-17 2119 an uns.

7.3.4 Control Medical History Questionnaire (cMQ)

ReKiG-Stationsbogen v1.0, 14.06.2016

14.06.2016

Anamnese: Datum: __ __ . __ __ . __ __ __ __ (TT/MM/Jahr) **Bogen-ID:** _____

Klinik: _____ ***Augenerkrankung***: _____

Geburtsdatum: __ __ . __ __ . __ __ __ __ (Tag / Monat / Jahr)

Geschlecht: O männlich O weiblich

Herkunftsland: O Deutschland O Ausland: _____ (Land)

Postleitzahl des Wohnortes in Deutschland: __ __ __ __ __

Datum der Verdachtsdiagnose: __ __ . __ __ . __ __ __ __ (Tag / Monat / Jahr)

Von O Augenarzt O Kinderarzt O Klinik: _____

Datum Erstvorstellung Augenarzt: __ __ . __ __ . __ __ __ __ (Tag / Monat / Jahr)

Augenseite mit der Diagnose (Elternangabe): O rechtes Auge O linkes Auge

Therapie seit Erstdiagnose: O mit Augentropfen O keine O Operation (inkl. Laser)

O andere:_____

Falls Augentropfen: Wirkstoffart und Häufigkeit: _____

Augenseite mit Therapie: O rechtes Auge O linkes Auge

Falls Operation: wo, wann und welche wurde durchgeführt:

_____

_____

_____

Andere Erkrankungen des Kindes (nicht nur am Auge): O nein O ja

Falls ja, welche: _____

_____

Einnahme von Medikamenten (außer Augentropfen): O nein O ja

Falls ja, welche: _____

7.3.5 Revised Gestational and Family History Questionnaire (Revised GFQ) and one version of the Verification Document (VD)

ReKiG-Auskunftsbogen v3.0, 24.04.2017

Wer beantwortet den Bogen? O Mutter O Vater des Kindes Bogen-ID: _____

Geburtsdatum Mutter: __ __ __ __ (Jahr), Geburtsdatum Vater: __ __ __ __ (Jahr)

Sind Sie miteinander verwandt? O Ja O Nein

Falls ja, waren Sie: O Cousin/Cousine O Groß-Cousin/-Cousine O _____

Haben Sie andere leibliche Kinder mit dem Vater des Kindes O Ja O Nein

Falls ja, wie viele Kinder? _____ Jungen _____ Mädchen

Hat in Ihrer Familie (Sie, Ihr Partner, Ihre Eltern, Ihre anderen Kinder)
jemand ein Glaukom im Kindesalter (< 18 Jahre) bekommen? O Ja O Nein
Ist jemand im jungen Alter (< 18 Jahre) erblindet? O Ja O Nein

Zur Geburt:
War Ihr Kind ein O Frühgeborenes, O Normalgeborenes, oder O Übertragenes Kind?

In welcher Schwangerschaftswoche ist Ihr Kind geboren? _____

Geburtsgewicht Ihres Kindes: _____ (Gramm), Geburtsgröße Ihres Kindes: _____ (cm)

Zur Schwangerschaft:
Ist die Schwangerschaft auf
O natürlichem Weg oder O durch künstliche Befruchtung erfolgt?

Hat die Mutter Ihres Kindes in der Schwangerschaft geraucht? O Ja O Nein
Falls ja, wie viele Zigaretten hat sie durchschnittlich pro Tag geraucht?

_____ Zigaretten/Tag

Hat die Mutter Ihres Kindes in der Schwangerschaft Alkohol getrunken? O Ja O Nein

Falls ja, wie viel Alkohol hat sie durchschnittlich pro Woche getrunken?

_____ Flaschen Bier/Woche, _____ Flaschen Wein/Woche
O Genuss höherprozentiger alkoholhaltiger Getränke

Hat die Mutter Ihres Kindes in der Schwangerschaft Drogen konsumiert? O Ja O Nein

Hat die Mutter Ihres Kindes in der Schwangerschaft Medikamente eingenommen?
O Ja O Nein

Falls ja, welche Medikamente und in welcher Schwangerschaftswoche?

_____

Hat die Mutter Ihres Kindes vor bzw. während der Schwangerschaft eine Folsäure-Prophylaxe durchgeführt? O Ja O Nein

7.3.6 Parent Examination Form (PEF)

Untersuchung der Eltern an der Spaltlampe Pat.-ID: _____

a) Mutter: *Datum:* _ _. _ _. _ _ _ _

>Vorderer Augenabschnitt: Auffälligkeiten? O nein O ja, folgende:

>Fundus: Auffälligkeiten? O nein O ja, folgende:

>Augeninnendruck [mmHg]: **OD:** _____ **OS:** _____

>Gonioskopie: Auffälligkeiten? O nein O ja, folgende:

b) Vater: *Datum:* _ _. _ _. _ _ _ _

>Vorderer Augenabschnitt: Auffälligkeiten? O nein O ja, folgende:

>Fundus: Auffälligkeiten? O nein O ja, folgende:

>Augeninnendruck [mmHg]: **OD:** _____ **OS:** _____

>Gonioskopie: Auffälligkeiten? O nein O ja, folgende:

Arzt-Unterschrift (und lesbarer Name):

8 Acknowledgements

Foremost, I am thankful to my doctoral supervisor, **Prof** [redacted], for granting me the opportunity to engage in this exceptional project and pursue my doctorate within its framework.

Special thanks go to my mentor, **MD** [redacted], who tirelessly addressed my questions and concerns during the pilot study. [redacted] was my go-to person whenever uncertainties arose, consistently offering guidance. Even after leaving the project team, he continued to provide mental support and showed genuine interest in my progress.

When challenges arose beyond [redacted]'s and [redacted]'s expertise, **Prof** [redacted] was there with the answers. I am grateful to him for always being approachable regarding questions about the project's structure and implementation. [redacted]'s consistent competence, objective support, and willingness to address my queries were valuable.

My gratitude goes to **MD** [redacted] who provided generous support, motivation, and validation by correcting substantial portions of the thesis. Your help was greatly appreciated.

Special personal thanks are owed to **MD** [redacted] during her time working at the AIDAH ward. Her presence greatly facilitated the project work, despite not being a project team member. She also took on most medical tasks that I, as a student, was not allowed to perform. Thank you very much for your interest and mental support, [redacted].

I want to express my heartfelt gratitude to my fiancé, **Mr.** [redacted]. Despite not being an expert in the medical field, he has consistently provided me with valuable suggestions based on his personal experience in academic writing and project work. [redacted] always lent a sympathetic ear to my concerns, offering unwavering support during moments of uncertainty, and lifting me up when I needed it most. He was my greatest source of mental support.

I am grateful to my parents, **Mrs.** [redacted], and **Mr.** [redacted], for their keen interest in my doctorate and support, allowing me the time to complete my thesis after medical school. I am especially proud of my father's proficient English skills and appreciate his help with linguistic corrections.

My thanks go to my school friend, **Ms.** [redacted], for the many hours we spent working on our doctoral theses. You were a source of motivation, inspiring me to keep writing diligently.

I appreciate the constant interest, sincere mental support, and encouraging motivation from my close friend, **Mr.** [redacted], throughout my doctoral thesis.

Last but not least, I would like to express my gratitude to **all participating patients and parents** for their involvement in the pilot study. Without them, this project would not have been possible. I genuinely hope that each participant found something positive in this experience.

9 Curriculum vitae

Heidi Diel

Date and place of birth

17th January 1996 in Camperdown,
New South Wales, Australia

Education

12/2018 – today

Doctorate in Medicine

Johannes Gutenberg University (JGU) Mainz, Germany

- Topic: Results of a pilot study at the Department of Ophthalmology at Mainz University Medical Center to establish a nationwide registry for childhood glaucoma in Germany
- Department: Ophthalmology at University Medical Center Mainz

04/2015 – 06/2022

Medical school

Johannes Gutenberg University (JGU) Mainz, Germany

- Final grade: "good" (2.16)
- Elective tertial in the Practical Year (PJ): Ophthalmology at University Medical Center Mainz
- Further tertials of the PJ: Surgery at University Medical Center Mainz, Internal medicine at Heidelberg University Hospital

08/2002 – 03/2014

School education

Ganztagsgymnasium Theresianum, Mainz
Final grade: „very good" (1.2)

Theodor-Heuss-Grundschule, Mainz

Language skills

Native languages:

1. German
2. English [TOEFL iBT 08/2022, Total score: 104 out of 120]
3. Mandarin (Chinese) [03-05/2023 language studies at **National Taiwan Normal University** in Taipei, Taiwan]

Advanced qualification in Latin [Ger.: Großes Latinum]

Work experience

10/2017 – 09/2020

Mainz University Medical Center

Student medical assistant in the Eye and Ear, Nose and Throat Emergency Unit

01/2024 – today

Mainz University Medical Center

Research assistant at the Paediatric Oncology Centre

Publications

First authorship:

- **Diel H**, Ding C, Grehn F. *et al.* First observation of secondary childhood glaucoma in Coffin-Siris syndrome: a case report and literature review. BMC ophthalmology. 2021

Co-authorship:

- Aghayeva FA, Schuster AK, **Diel H** *et al.* Childhood glaucoma registry in Germany: initial database, clinical care and research (pilot study). BMC research notes. 2022
- Stingl JV, Diederich S, **Diel H** *et al.* First Results from the Prospective German Registry for Childhood Glaucoma: Phenotype-Genotype Association. Journal of clinical medicine. 2021

Congresses

- Short presentation at the 34th Congress of the German-speaking Society for Intraocular Lens Implantation, Interventional and Refractive Surgery (34. Kongress der Deutschsprachigen Gesellschaft für Intraokularlinsen-Implantation, interventionelle und refraktive Chirurgie DGII), Mainz 2020

Mainz, 22nd March 2024