PROTOCOL TITLE:

1 WEEK CROSSOVER DISPENSING STUDY: [redacted] VERSUS [redacted] [redacted] SOFT CONTACT LENSES

Sponsor Study Code:	[redacted]
Site Study Code: (if applicable)	N/A
Version Number:	1.0
Date:	[redacted]
Sponsor Company:	COOPERVISION, INC.
Clinical Site:	[redacted]
Study Stage:	[redacted]

Protocol Author:	[redacted]
Sponsor Management:	
Data Management/Statisticia	
CVI Operations Lead:	

Document Change History

Version	Originator	Description of Change(s)	Date
1.0	[redacted]	Original Protocol	[redacted]

Protocol Signature Page – Principal Investigator

Protocol: [redacted]

Study Title: 1 Week Crossover Dispensing Study: [redacted] versus [redacted] Soft Contact Lenses

Protocol Version: v1.0, Date: [redacted]

I have received and read this protocol and agree to adhere to the requirements. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or informed consent form must first be approved by CVIL, Inc. and the Institutional Review Board, except those changes necessary to eliminate apparent immediate hazards to subjects. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding their role in the study. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements, and with the reviewing Institutional Review Board (IRB) requirements. I agree to commence this study only after documented IRB approval is obtained.

[redacted]

Study Personnel

Name:
Title:
Address:

Telephone:
Email:

Principal Investigator:

Name:
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Address:

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Statistician:

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CVI Operations Lead:

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Title:
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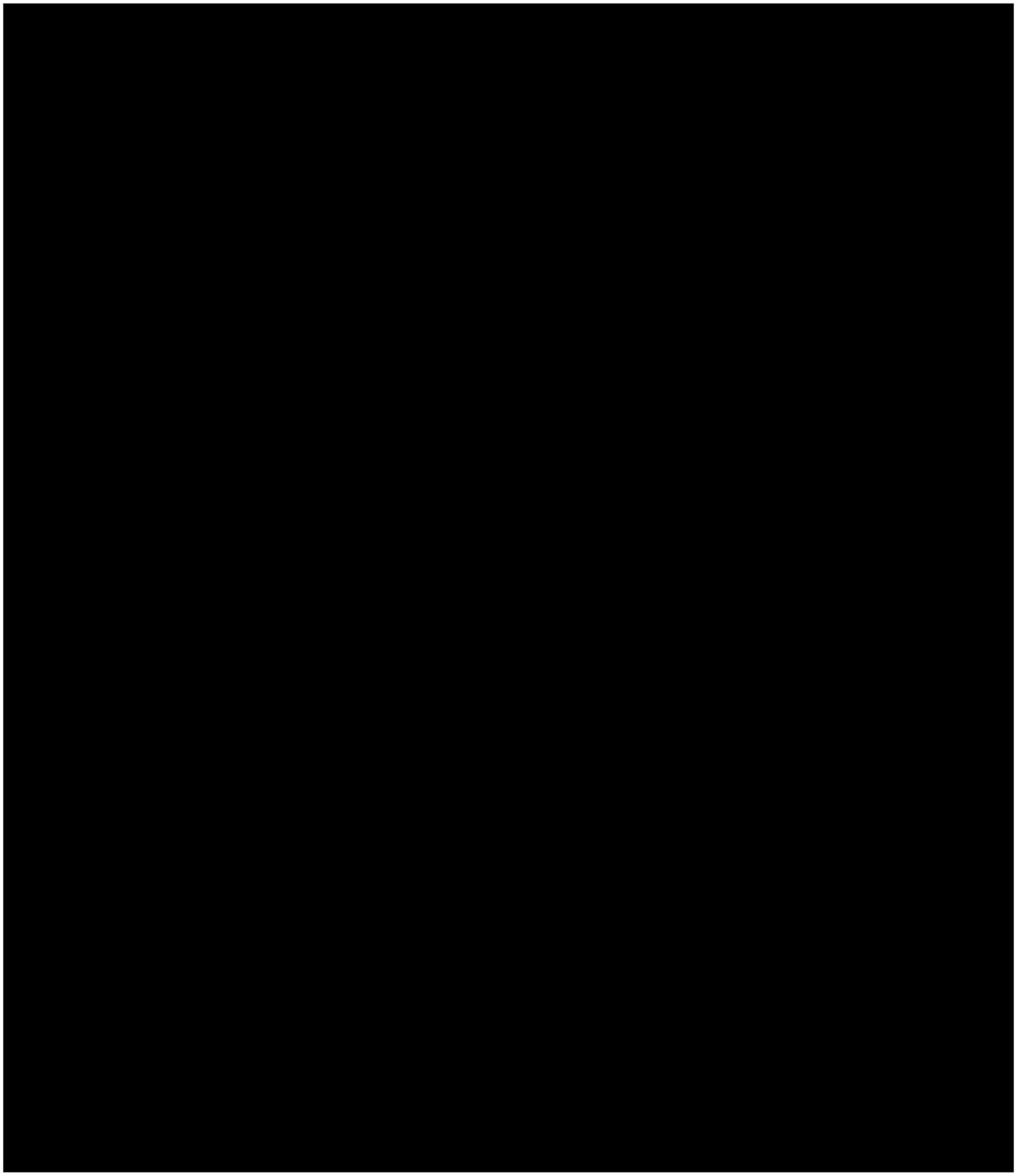
Email:

Overall Synopsis of the Clinical Investigation Plan (Protocol)



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1 Study Objective

The objective of this Design Validation clinical investigation is to compare the visual clinical performance of the [redacted] investigational contact lens to [redacted] contact lenses. CooperVision, Inc. (CVI) is aiming to compare visual acuity and subjective vision ratings of vision quality between two CooperVision lenses: [redacted] versus [redacted] in habitual soft lens wearers. The [redacted] lens is a daily disposable investigational lens in this study (as this lens has not been yet approved or commercially available in the US), the [redacted] is commercially available in the US for myopia control.

[redacted] lens is a silicone hydrogel daily disposable (DD) lens with a similar design to [redacted] hydrogel DD lenses. CooperVision, Inc. is interested in comparing visual acuity and subjective vision ratings between these two lenses of different materials to gain insight into the differences between these lenses from this aspect.

The primary outcome variable for this study is:

- High contrast, binocular, distance visual acuity (logMAR) at 1-week visit.

The secondary outcome variable is:

- Subjective vision quality (0-100 scale) at 1-week visit

[redacted]

2 Study Design

This will be a prospective, multiple day, double (investigator and subject) masked, randomized, bilateral crossover study comparing a Test lens against an appropriate Control lens. Each subject will wear the Test lens or the Control lens in a bilateral fashion for 7 days (+ 3 days) followed by the alternate lens for 7 days (+ 3 days). The order of lenses will be randomized.

There will be a total of 3 visits in the study as described in Section 7.5 below.

3 Study Devices and Comparator Products

3.1 Contact Lenses

A summary description of the Test and Control lenses to be used in the clinical study are shown in Table 1. The Test lens is an investigational silicone hydrogel lens with a slight modification to an approved contact lens design [redacted] The Control lens is a currently marketed contact lens.

Further details regarding the investigational lens are described in the Investigator Brochure.

Table 1: Study lenses

[redacted]

3.1.1 Intended Use

In this clinical investigation, the study lenses are intended to be used as a single use. Single use lenses will be used for a maximum of one day of lens wear recommended by the Sponsor.

3.1.2 Storage of Lenses and Lens Care Solutions

The study materials must be stored in a secured area. All lenses and lens care solutions should be stored at controlled room temperature (59-86°F).

3.2 Adjunct Products

3.2.1 Contact Lens Care Products

No contact lens care is required for this study as lenses are to be worn for a single day only. No contact lens wetting drops will be used during this study.

3.2.2 Other

No other medical devices will be used in this study.

4 Justification for the Study Design

Nonclinical testing methods are not adequate to provide the information needed to advance the development of the [redacted] Contact Lens. A biocompatibility assessment has been completed and the benefit/risk assessment (see Section 5 below) supports the use of the device in this feasibility study. A synopsis of the biocompatibility assessment and prior clinical testing can be found in the Investigator Brochure.

A crossover design has been chosen since it minimizes the impact of potential sympathetic effects between the two eyes (e.g. an uncomfortable lens in one eye may impact the subjective rating of the fellow eye). The study contact lenses do not alter the physiology and hence there is no carryover effect requiring a washout period. The order effect will be tested.

The choice of comparator product was made in order to assess the clinical performance against a currently marketed product representative of generally accepted state of the art.

5 Benefits/Risks of Study Device(s) and Study Procedures

5.1 Anticipated Clinical Benefits

There might not be direct benefits to the subjects in this study, however participation in a new study may contribute to scientific research information that may be used in the development of new contact lens products. In addition, subjects will receive an examination of the front of their eyes and may have the opportunity to try a different type of soft contact lens and/or different lens care products at no cost to them.

5.2 Anticipated Adverse Device Effects

Ocular complications that may occur during the wearing of contact lenses include discomfort, dryness, aching or itching eyes, burning, grittiness, excessive tearing, discharge, hyperemia and variable or blurred vision. More serious risks may include photophobia, iritis, corneal edema or eye infection. Although contact lens-related infections are very infrequent, the possibility does exist. The incidence of infection due to daily-wear soft lenses is 0.035%.[1] Almost always an infection will occur only in one eye. This risk is assumed by 35-million Americans who currently wear contact lenses.

Subjects will need to meet the vision requirements for driving if they are old enough and plan to drive while participating in this study.

5.3 Risks Associated with Participation in the Clinical Investigation

This is considered a non-significant risk study based on United State Food and Drug administration (FDA) guidelines due to the daily wear nature of the study. The risks associated with the investigational contact lenses have been estimated in accordance with ISO 14971. A synopsis of pre-clinical and prior clinical testing results are included in the Investigator's Brochure. Risk controls to reduce the risk as far as possible have been implemented and any residual risks will be further mitigated through close evaluation by the investigators under this clinical protocol and communicated via informed consent.

5.4 Risks of Clinical Procedures to be Utilized in the Study

Routine, non-invasive procedures will be conducted in this study. Routine clinical procedures include auto-refraction, auto-keratometry, visual acuity, anterior ocular health assessment, and

contact lens fitting will be used. In addition, standard research procedures such as high magnification imaging of the lens fit may be made using 35 mm or digital cameras, in vivo confocal microscopy, and/or specular microscopy.

5.5 Possible Interactions with Concomitant Medical Treatments

The use of contact lenses can interact with concomitant topical, ocular and/or systemic medical treatments, therefore only healthy subjects who are not currently taking concomitant medical treatments will be included in this study assure in exclusion. Artificial tears, re-wetting drops, and lubricating agents are not considered medical treatments. Only those products approved for the use with contact lenses can be used according to their indication under this protocol.

5.6 Steps That will be Taken to Control or Mitigate the Risks

The following Information for Safety for contact lens wear during the clinical study will be reviewed with each subject:

Hands should be washed and dried prior to touching the lenses for insertion or removal. If inserting the lenses yourself, they should be checked for tears and/or whether they are inside out prior to insertion. Eye rubbing should be avoided. Contact lenses should never be worn while swimming or in any other hazardous environment. The contact lenses are not to be slept in during the study or worn overnight and are to be replaced with a new pair according to the study lens wear schedule.

5.7 Rationale for Benefit-Risk Ratio

The knowledge gained from this feasibility study may lead to important conclusions regarding the ocular response and performance of new contact lens materials and designs. The potential risks for participating in this study are minimal, therefore the benefit-risk ratio is acceptable.

6 Ethics Review / Statement of Compliance

6.1 Relevant Standards / Guidelines

This study was developed in accordance with 21 CFR Part 812 Investigational Device Exemptions and the good clinical practice (GCP) principles and ethical considerations of ISO 14155 Clinical Investigation of Medical Devices for Human Subjects and Declaration of Helsinki. The detailed

descriptions of ocular Adverse Events details and the biomicroscopy grading scales are adapted from ISO 11980 Ophthalmic Optics – Contact lenses and lens care products – Guidelines for clinical investigations.

6.2 Institutional Review Board

This study will be conducted in accordance with Institutional Review Board regulations (U.S. 21CFR Part 56.103) or applicable IEC regulations. Copies of all IRB/IEC correspondence with the investigator/Sponsor will be kept on file.

This study will adhere to a protocol and informed consent document approved by the [redacted]. Each study subpart/implementation will be submitted to Sterling for approval prior to commencing the study.

6.3 Informed Consent

Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is carried out.

6.4 Clinical Trial Registration

This study will be registered, and a description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

7 Design of the Clinical Investigation

7.1 Study Endpoints

The primary study endpoint:

- High contrast, binocular, distance visual acuity (logMAR) at 1-week visit.

The secondary study endpoint is:

- Subjective vision quality (0-100 scale) at 1-week visit

7.2 Clinical Site

The clinical site was selected based on the availability of representative population of subjects and Investigator's clinical research experience.

The Investigators will be required to fulfill the following criteria:

- Trained and experienced in the conduct of clinical research
- Willingness to follow the study protocol
- Trained in Good Clinical Practice (GCP) and the study protocol prior to commencing the study.

7.3 Subjects

A maximum of up to 40 subjects will be enrolled in this study, in order for a minimum of 10 subjects and a maximum of up to 30 subjects, to complete the study. Each subject will be given a unique ID

number. ID numbers will not be re-used. All subjects must meet the study inclusion and exclusion criteria listed below.

7.3.1 Inclusion criteria

A person is eligible for inclusion in the study if they have:

- Are 8 to 18 years of age (inclusive)
- Have read, signed and dated:
    - Age 18 - The Participant Informed Consent Form (participant only)
    - Age 12-17 – The Parental Permission Form (participant and parent)
    - Age 8-11 - The Parental Permission Form (parent) and Assent form (participant)
- Are willing and able to follow instructions and maintain the appointment schedule.
- Are habitual daily wearers of spherical single vision soft contact lenses to correct for distance vision in each eye, including myopia control soft contact lenses as below
- Currently wears spherical soft contact lenses or myopia control soft contact lenses.
- Have a pair of wearable back-up spectacles.
- Are willing and able to wear contact lenses for at least 10 hours a day, 6 days a week while in the study.
- Are myopic with subjective refraction: -0.75D to -7.00D spherical, with an astigmatism ≤ -0.75D in each eye with maximum spherical equivalent anisometropia of 1.00D
- Are correctable to a visual acuity of +0.10 logMAR or better (in each eye) with sphero-cylindrical subjective refraction.
- Have clear corneas with no corneal scars or any active ocular disease.
- Can be fit with the study contact lenses with a power between -0.75 and -7.00 DS; this translates to best corrected vision sphere refraction that vertexes to a CL power between -0.75 and -7.00 (inclusive) at screening visit.
- Demonstrate an acceptable fit with the study contact lenses.
- Demonstrate that they can safely and independently insert and remove contact lenses at the screening/fitting visit.

7.3.2 Exclusion Criteria

A person will be excluded from the study if they have:

- Have taken part in another clinical research study within the last 14 days.
- Are currently habitual wearers of toric contact lenses.
- Have worn any rigid contact lenses or ortho-keratology contact lenses in the past 30 days.
- Are an extended contact lens wearer (i.e., sleeping with their contact lenses)
- Are on ongoing atropine treatment for myopia control.
- Have a difference of > 1.0 D in best vision sphere subjective refraction between eyes.
- Have amblyopia and/or strabismus/binocular vision problem.
- Have any known active* ocular disease, allergies and/or infection.
- Have a systemic condition that in the opinion of the investigator may affect a study outcome variable;*
- Are using any systemic or topical medications that in the opinion of the investigator may affect a study outcome variable;*
- Have a known sensitivity to the diagnostic pharmaceuticals to be used in the study.
- Have undergone refractive error surgery or intraocular surgery.
- Are a member of [redacted] directly involved in the study.

* For the purposes of this study, active ocular disease is defined as infection or inflammation which requires therapeutic treatment. Mild (i.e. not considered clinically relevant) lid abnormalities (blepharitis, meibomian gland dysfunction, papillae), corneal and conjunctival staining and dry eye are not considered active ocular disease. Neovascularization and corneal scars are the result of previous hypoxia, infection or inflammation and are therefore not active.

* Any potential exclusion will be reviewed with the Principal Investigator or Sub-Investigator prior to final decision making.

7.4 Procedures to Minimize Bias

7.4.1 Labelling and Masking

The Test will be labelled with an investigational label, according to local regulations where the clinical study is being conducted. The investigational label will also include study contact lens coding in order to facilitate investigator masking.

Although approved for use in the country where the clinical study is taking place, the Control contact lenses will be labelled with an investigational label to facilitate masking.

Decoding/Masking Procedures:

The Principal Investigator will be provided, prior to commencing the study, with the masking codes in a sealed envelope and decoding/demasking procedures for use in a medical emergency or where Serious Adverse Events are considered to be related to the Investigative or Control devices.

7.4.2 Randomization procedures

In this crossover study design, each subject will wear the Test contact lens or the Control contact lens first in a bilateral fashion followed by the alternate contact lens. The order of contact lenses will be determined by a predetermined randomization schedule.

7.5 Visit Procedures

Study visits and study visit flow will be per Table 2 and Figure 1 below.

Table 2: Study Visits

Visit number	Visits
1-A	Screening / Baseline Visit
1-B	Pair 1 Dispense
2-A	7 (+3 days) Follow-up Assessment of Pair 1
2-B	Pair 2 Dispense
3-A	7 (+3 days) Follow-up Assessment of Pair 2 and Study Exit

7.5.1 Visit 1A: Baseline Visit

A documented informed consent process will be conducted with all participants prior to their enrollment in the study and prior to any data collection or measurements.

All participants who signed the informed consent/assent letter will be assigned a study ID number. The investigator will determine participant eligibility using the inclusion and exclusion criteria.

Ineligible participants will be discontinued from the study. The procedures to be performed are outlined below.

Visit procedures:

1. The participant is expected to attend the screening visit with their habitual glasses NOT having worn their habitual contact lenses and/or used any rewetting/tear drops from at least one day prior to the study day.
2. The parent (for participants ages 8 to 17) and participant will be required to read and sign a Parental Permission and Assent Form respectively prior to enrollment. This is not applicable to participants aged 18, who will be instead required to read and sign an Informed consent form prior to enrollment. When the parent (for those aged 17 and younger) and participant have signed the necessary forms as stated below, the participant will be considered enrolled in the study.
    - Age 18 - The Participant Informed Consent Form (participant only)
    - Age 12-17 – The Parental Permission Form (participant and parent)
    - Age 8-11 - The Parental Permission Form (parent) and Assent form (participant)
3. Participant demographics and medical history (age, sex, medical conditions, medications, allergies).
4. Contact lens history (habitual contact lens information and wearing habits).
5. [redacted]

[redacted]

14. Slit lamp biomicroscopy will be assessed using Efron grading scale as specified in Appendix 2.
15. The investigator will confirm that the participant meets the eligibility specifications set out in the inclusion criteria and exclusion criteria and is eligible to continue in the study.

7.5.2 Visit V1-B: Pair 1 Dispensing

The Screening Visit (V1-A) will be immediately followed by Pair 1 Dispensing Visit (V1-B) on the same day.

Visit procedures:

16. Contact lens Pair #1 will be provided to participants in a manner that does not unmask the participant or investigator as per the randomization schedule in Appendix 3.
17. Participant to open blister packs and apply the Contact lens pair 1 OU – powers matched to vertexed best sphere refraction OU. Allow to settle for 15 minutes.
18. Monocular over-refraction (photopic screen luminance with dim room illumination), change in power (allow 15 min settling time if CL power is changed) if VA is improved by 3 letters.
19. LogMAR visual acuity measurements (with Room light illuminance and screen luminance conditions as specified in Appendix 4):

    Mesopic vision (mesopic screen luminance with dim room illumination, after 10 minutes of dark adaptation):

    Distance (6m) Low illumination (LI) HC VA; OU (logMAR)

    Photopic vision (photopic screen luminance with dim room illumination):

    Distance (6m) LIHC VA; OD & OS & OU (logMAR)

    Distance (6m) Low room Illumination Low contrast (LILC) VA; OU (logMAR)

    High contrast near VA (near chart with high room illumination):

    Near (40 cm) HIHC VA; OU (logMAR)

[redacted]

[redacted]

22. Review contact lens usage instruction and required wearing time (10 hours per day and 6 days per week) with participants and also with parents/guardians where subjects are 17 years and younger.
23. Dispense Pair 1 lenses. Unmasked staff to apply masked over-labels to sufficient R & L Contact lenses to last until next visit (include at least 2 spare pairs)
24. Schedule for 1-week follow up visit (7 + 3 days from Visit 1)

7.5.3 Visit V2-A: 7 (+3 days) Follow-up Assessment of Pair 1

Visit procedures:

25. The participant will attend the visit having worn study Contact lenses at least 2hrs prior to visit.
26. Review wearing time, problems with CL wear, adverse events, protocol deviations.
27. Unworn Pair 1 (OU) contact lenses will be collected from the subject by the Investigator.

[redacted]

30. LogMAR visual acuity measurements (with Room light illuminance and screen luminance conditions as specified in Appendix 4):

    Mesopic vision (mesopic screen luminance with dim room illumination, after 10 minutes of dark adaptation):

    Distance (6m) Low illumination (LI) HC VA; OU (logMAR)

    Photopic vision (photopic screen luminance dim room illumination):

Distance (6m) LIHC VA; OD & OS & OU (logMAR)

Distance (6m) Low room Illumination Low contrast (LILC) VA; OU (logMAR)

High contrast near VA (near chart with high room illumination):

Near (40 cm) HIHC VA; OU (logMAR)

31. Over-refraction (best sphere monocular) distance and monocular photopic screen luminance dim room illumination VA (if any over-refraction)

35. The subject will remove the Pair 1 (OU) study contact lenses worn on the day of Visit 2A, which will be retained and stored in saline solution for return to the Sponsor.
36. Slit lamp biomicroscopy will be assessed using Efron grading scale as specified in Appendix 2.
37. Subjects will undergo washout with saline solution.

7.5.4 Visit V2-B: Pair 2 Dispensing

The Pair 1 follow-up visit (Visit V2-A) will be immediately followed by Pair 2 Dispensing visit (Visit V2-B) on the same day.

Visit procedures:

38. Contact Lens Pair #2 will be provided to participants in a manner that does not unmask the participant or investigator as per the randomization schedule (Appendix 3).
39. Participant to open blister packs and apply the Contact Lens pair 2 OU – powers matched to vertexed best sphere refraction OU. Allow to settle for 15 minutes.
40. Monocular over-refraction (photopic screen luminance with dim room illumination), change in power if VA is improved by 3 letters.

41. LogMAR visual acuity measurements (with room light illumination and screen luminance conditions as specified in Appendix 4):

    Mesopic vision (mesopic screen luminance with dim room illumination, after 10 minutes of dark adaptation):

    Distance (6m) Low illumination (LI) HC VA; OU (logMAR)

    Photopic vision (photopic screen luminance with dim room illumination):

    Distance (6m) LIHC VA; OD & OS & OU (logMAR)

    Distance (6m) Low room Illumination Low contrast (LILC) VA; OU (logMAR)

    High contrast near VA (near chart with high room illumination):

    Near (40 cm) HIHC VA; OU (logMAR)

44. Review contact lens usage instruction and required wearing time (10 hours per day and 6 days per week) with participants and also with parents/guardians where subjects are 17 years and younger.
45. Dispense Pair 2 contact lenses. Unmasked staff to apply masked over-labels to sufficient R & L Contact lenses to last until next visit (include at least 2 spare pairs).
46. Schedule for 1-week follow up visit (7 + 3 days from Visit 2A)

7.5.5 Visit V3-A: 7 (+3 days) Follow-up Assessment of Pair 2 and Study Exit

47. The participant will attend the visit having worn study Contact lenses for at least 2hrs prior to visit.
48. Review wearing time, problems with CL wear, adverse events, protocol deviations.
49. Unworn Pair 2 (OU) contact lenses will be collected from the subject by the Investigator.

[redacted]

52. LogMAR visual acuity measurements (with Room light illuminance and screen luminance conditions as specified in Appendix 4):

    Mesopic vision (mesopic screen luminance with dim room illumination, after 10 minutes of dark adaptation):

    Distance (6m) Low illumination (LI) HC VA; OU (logMAR)

    Photopic vision (photopic screen luminance dim room illumination):

    Distance (6m) LIHC VA; OD & OS & OU (logMAR)

    Distance (6m) Low room Illumination Low contrast (LILC) VA; OU (logMAR)

    High contrast near VA (near chart with high room illumination):

    Near (40 cm) HIHC VA; OU (logMAR)

53. Over-refraction (best sphere monocular) distance and monocular photopic screen luminance dim room illumination VA (if any over-refraction)

[redacted]

[redacted]

57. The subject will remove the Pair 2 (OU) study contact lenses worn on the day of Visit 3A, which will be retained and stored in saline solution for return to the Sponsor.

58. [redacted]

59. Slit lamp biomicroscopy will be assessed using [redacted]

60. Subjects will undergo washout with saline solution.

7.5.6 Study Exit

Exit visual acuity (LIHC) will be recorded with subjective spherocylindrical refraction result from V1-A refraction (OD & OS & OU (logMAR)). An exit biomicroscopy assessment will be conducted including FI staining, if participant was fitted with study contact lenses at the screen visit or if biomicroscopy was not completed at a concurrent visit after the screening.

After the exit assessments have been completed, the participant and investigator will complete the study exit and remuneration forms. At this time, the participant will be considered as having exited the study.

When a participant exits the study, the study exit form will be completed. Therefore, this form will be completed either at completion of the study, or if the participant is discontinued from the study at another time. A study exit form must be completed for all participants who have taken a study ID number. If in the opinion of the investigator post-follow-up visits are required, the exit form will be completed after the last follow-up visit.

7.5.7 Summary of Visits and Procedures

Table 3 summarizes the visits and procedures for the study.

Table 3: Summary of Visits and Procedures

Procedures / Data	Visit 1-A	Visit 1-B & 2-B (Dispense)	Visit 2-A & 3-A (Follow Up)	Exit Visit	Unscheduled/ Adverse Events
Visit window	N/A		7 + 3 days	-	N/A
Informed assent/ consent	✓	-	-	-	-
Meet inclusion / exclusion criteria	✓	-	-	-	-
Demographics	✓	-	-	-	-
Presenting VA	✓	-	✓	-	✓
History at baseline	✓	-	-	-	-
History since last visit, including updated medical problems / previous events / treatment	✓	✓	✓	-	✓
[redacted]					
Spherical Over-refraction + logMAR VA	✓	✓	✓	-	-
LogMAR VA with CLs	-	✓	✓	-	-
[redacted]					
Wear time	-	-	✓	-	*
CL dispense & review wear instructions	-	✓	-	-	*
Compliance assessment / Contact lens and solution returns	-	-	✓	-	*
Slit lamp biomicroscopy: CL assessment worn at visit and ocular assessment	✓	-	✓	✓	✓
[redacted]					
Photos / video	*	*	*	-	*
Adverse event assessment	✓	✓	✓	✓	✓
Visit summary	✓	✓	✓	-	✓
* Investigator discretion					
** Related to habitual CLs					

8 Adverse Events

8.1 Adverse Event Definitions

An 'adverse event' refers to any undesirable clinical occurrence in a participant, whether it is considered to be device-related or not. Adverse events (AE) may be classified as 'unanticipated adverse device effects,' 'serious adverse events,' 'significant adverse events,' or 'non-significant adverse events,' as defined below.

Classification	Definition
Serious Adverse Event	Those events that are life-threatening, or result in permanent impairment of a body function, or permanent damage to a body structure or necessitate medical (therapeutic) or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.
Significant Adverse Event	Those non-serious adverse events that occur with contact lens usage that are not sight-threatening but are usually symptomatic and may warrant therapeutic management and /or temporary or permanent discontinuation of contact lens wear.
Non-Significant Adverse Events	Those less severe non-serious adverse events that occur with contact lens usage that are not sight-threatening, may or may not be symptomatic and may warrant palliative management, such as ocular lubricants or temporary interruption of contact lens wear.
Unanticipated Adverse Device Effect	Adverse events in a clinical trial that were not previously identified in the protocol in terms of nature, severity, or degree of incidence. An Unanticipated Serious Adverse Device Effect is an unanticipated adverse event that is serious in nature and caused by or associated with the device and is considered reportable.

AE classification, coding (for reporting to the Sponsor) and examples are provided in the following table of Contact Lens Adverse Event Classification and Reporting table:

Code	Condition	Reporting
Serious Adverse Events		
01	Presumed infectious keratitis or infectious corneal ulcer	Notify Sponsor as soon as possible, **within 24 hours;** IRB reporting as per requirements
02	Permanent loss of ≥ 2 lines of best spectacle corrected visual acuity (BSCVA)	
03	Corneal injury that results in permanent opacification within central cornea (6mm)	
04	Uveitis or Iritis (e.g. presence of anterior segment inflammation as described in ISO 11980, Annex B)	
05	Endophthalmitis	
06	Hyphema	
07	Hypopyon	
08	Neovascularization within the central 6mm of cornea	
00	Other serious event	
Significant Adverse Events		

11	Peripheral (outside central 6mm), non-progressive, non-infectious ulcer	Notify Sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
12	Symptomatic corneal infiltrative event	
13	Superior epithelial arcuate lesions (SEALs) involving epithelial split	
14	Corneal staining ≥ dense coalescent staining up to 2mm in diameter (e.g. moderate, ISO 11980 grade 3)	
15	Corneal neovascularization ≥ 1.0mm vessel penetration (e.g. ≥ ISO 11980 Grade 2), if 2 grade change from baseline	
16	Any temporary loss of ≥ 2 lines BSCVA for ≥ 2wks	
17	Any sign and/or symptom for which subject is administered therapeutic treatment or which necessitates discontinuation of lens wear for ≥ 2 weeks	
10	Other significant event	
Non-significant Adverse Events		
21	Conjunctivitis (bacterial, viral or allergic)	Notify Sponsor as soon as possible, **within 5 working days**; IRB reporting as per requirements
22	Papillary conjunctivitis if ≥ mild scattered papillae/follicles approximately 1mm in diameter (e.g. ISO 11980 Grade 2), if 2 grade change from baseline	
23	Asymptomatic corneal infiltrative events	
24	Any sign and/or symptom for which temporary lens discontinuation for > 1 day is recommended (if not already classified)	
20	Other sign and/or symptom warranting classification as a non-significant adverse event	

Normal or adaptive symptoms

Transient symptoms such as end-of-day dryness, contact lens awareness, itching or burning or other discomfort may occur with contact lens wear and may occasionally reduce wearing time. ***These are not reported as adverse events unless in the investigator's opinion they are unexpected in nature, severe or have a high rate of occurrence.***

This clinical study will also ascertain satisfaction or preference with subjective attributes such as comfort, vision, or contact lens handling. Responses to these subjective questionnaires will not be considered as Adverse Events.

8.2 Adverse Events Management

Treatment of an adverse event will depend on its nature and severity. Based on the clinical judgment of the investigator the subject may be referred to an ophthalmologist for treatment.

Expenses incurred for medical treatment as part of study participation will be paid by the Sponsor (bills and prescription receipts kept). The subject must be followed until resolution and an Adverse Event Outcome Form (Appendix 10) completed indicating the course of treatment and resolution of the condition.

8.3 Reporting Adverse Events

An Adverse Event Notification Form (Appendix 10) will be completed for each adverse event. Whenever possible, the adverse event will be photo documented.

All potential Serious and Unanticipated Adverse Device Effects that are related or possibly related to subject participation will be reported to the Principal Investigator and the Sponsor within 24 hours of the investigator becoming aware of the event. The Principal Investigator will report the event to the IRB as soon as possible (by fax, mail/delivery, phone, or email). All fatal or life-threatening events will be reported immediately to the IRB.

Significant and Non-Significant Adverse Events will be reported to the Sponsor as soon as possible, but no later than 5 days after the occurrence.

Sponsor contact details **for adverse events** are:

Contact: Clinical Operations, CooperVision

[redacted]

8.4 Discontinuation from the Study

A subject's study participation may be discontinued at any time if, in the opinion of the Sponsor or the investigator, it is in the best interest of the subject. All discontinuations will be fully documented on the appropriate study forms and a discontinuation/exit form will be completed.

9 Device Deficiency Reporting

9.1 Product Defect Reporting (Investigator Responsibility)

Product Defect is the terminology typically used in contact lens products for an *unexpected* observation related to the identity, quality, durability, reliability, or usability of the product under investigation.

NOTE: Observations on study products that are anticipated as a part of the device development process are not considered to be Product Defects or Device Deficiencies.

If the Product Defect is associated with an adverse event, the investigator shall report the Product defect via the Adverse Event Notification Form (Appendix 10).

If the Product Defect is not associated with an adverse event, the investigator shall report the Product Defect via the Clinical Product Defect Notification Case Report Form (Appendix 11).

If the investigator judges that the Product Defect could have led to a Serious Adverse Event if no preventative action was taken, the Product Defect should be reported to the Sponsor via the Product Defect Notification Case Report Form within 24 hours of becoming aware of the defect. The investigator should report to the IRB/EC per their reporting requirements.

All other Product Defects should be reported to CVI as soon as possible, but no later than 5 working days after occurrence.

Sponsor contact details **for Product Defect Notifications** are:

Contact: Clinical Operations, CooperVision

[redacted]

9.2 Device Deficiency Reporting (Sponsor Responsibility)

Device Deficiency is defined as the inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

The Sponsor will review the Product Defect Notification Case Report Form, gather additional information if needed from the Investigator/CRO and determine whether the notification represents a Device Deficiency. Device Deficiencies will be reported as per Internal CVI procedures.

A summary of Device Deficiencies will be documented in the clinical study report. If no Device Deficiencies are observed in a study, then a statement stating as such will be included in the clinical study report.

10 Statistical Design and Analysis

10.1 Statistical Hypothesis

The primary hypothesis to be tested in this study will be that the binocular high contrast distance visual acuity achieved with [redacted] Test contact lenses is non-inferior to that achieved with [redacted] Control soft contact lenses.

10.2 Sample Size Calculations

The target sample size for this study is 30 participants to be randomized and to wear both contact lens types. This target was determined based on the sample size calculation below:

to demonstrate non-inferiority in high contrast binocular distance logMAR visual acuity for the Test contact lens compared with the Control contact lens, the sample size estimation is based upon a one-sided paired t-test with α =0.025, ß = 0.200 and a non-inferiority margin of 0.050 logMAR when postulating a true difference of 0.00 logMAR with a standard deviation of 0.07 logMAR a total of 26 participants is required. The target for this study will be for 30 participants to complete the study without a significant protocol deviation.

Therefore, in this study, a maximum of 40 participants may be randomized to achieve a maximum of 30 completed.

10.3 Statistical Analysis

Statistical analysis will be undertaken by the study biostatistician. The critical measure for statistical significance is set at alpha = 5% level with a P-value ≤ 0.05. All subjects who have completed the study will be included in the analysis.

Lens performance will be compared per study design. Descriptive statistics (e.g., mean, standard deviation) and/ or frequency of counts for categorical data may be produced for primary and/or second interests. Paired t-test may be used to compare slit lamp biomicroscopy, contact lens fit and subjective scores between study contact lens types. Where applicable, Repeated Measures Analysis of Variance (ANOVA) or paired analysis may be used to compare the variables between study visits. Binomial tests may be used to analyze the results for the frequencies of subjective and objective preferences.

10.4 Interim Data Analysis

Interim data analysis may be performed to take business decisions. The Sponsor may stop enrollment for this study if needed after any interim read.

10.5 Data Management

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the clinical site Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

The clinical data for this study may be entered by designated study site personnel onto paper or electronic case report forms (CRFs). Case history and symptoms questionnaires may be given to subjects to complete in paper or electronic form.

Unless otherwise documented, the CRFs will be considered the source document.

The Sponsor or Sponsor's representatives will be authorized to gain access to the source documentation for the purposes of monitoring and auditing the study.

If study information is collected using an automated piece of equipment, the information may be recorded directly from the instrument display, captured electronically as output, or printed and entered into the CRF. The CRF will become the source document if there is no printout.

10.6 Data Quality Assurance

The CRFs will be completed at the time of the visit. All clinical data generated in the study will be submitted to the Sponsor for quality assurance review and analysis. All forms will be reviewed for completeness and evident recording errors will be rectified by contacting the appropriate clinical site. Computerized editing routines will be used to identify missing, invalid, inconsistent, or questionable data entries for verification prior to data analysis. These data issues will be resolved by contacting the relevant clinical site.

11 General Study Management

11.1 Monitoring Plan

The Sponsor will ensure site qualification of the investigative site has been completed prior to conducting the clinical study in order to ensure that the site facility is adequate, personnel are qualified and resources are satisfactory.

The protocol will be reviewed by the investigators prior to enrollment of the first subject. This will involve an overview of the protocol, which includes information on study objectives, inclusion and exclusion criteria, study visits and adverse event reporting. Data collection forms will also be reviewed and this will provide an opportunity to discuss any questions.

During the course of the study, a site visit may be conducted to verify that written informed consent was obtained using the IRB approved ICF prior to each subject's participation in the study.

Findings of non-compliance shall be reviewed with the Investigator and disclosed in a written monitoring report. The Monitor report will docuemnt any non-compliance with signed agreements, conditions imposed by the IRB/EC and the requirements of the study protocol. The Sponsor shall then either secure compliance or discontinue shipments of the lenses to the study contact lenses to the Investigator and may terminate the Investigator's participation in the investigation, if required.

Prior to final data freeze, a close-out visit/discussion may be warranted to check for accuracy and completeness of records. The Sponsor will be authorized to gain access to the source documentation for the purposes of monitoring and auditing the study.

11.2 Amendments

Amendments to this Protocol that may affect the rights, safety, or well-being of subjects will require review and approval from IRB before the changes are implemented in the study. Investigators at the site will be provided with the revised protocol version, the site trained and the Protocol Signature Page of the amended protocol completed prior to enacting the amendments.

11.3 Protocol Deviations

A Protocol Deviation is an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol. Investigators will not deviate from the protocol except to protect the

rights, safety and well-being of human subjects. Under emergency circumstances deviations may proceed without prior approval of the Sponsor and the IRB. Deviations shall be reported to the Sponsor, IRB and the regulatory bodies, as required.

Significant deviations which require changes to the research protocol or informed consent process/document or other corrective actions to protect the safety, welfare, or rights of patients or others must be reported to the IRB/EC within ten business days of the deviation occurring (or its discovery). All deviations shall be reported to the Sponsor within two working days.

All deviations occurring during the study will be documented on a protocol deviation form and documented in the final Clinical Study Report (CSR).

Sponsor contact details **for Protocol Deviations** are:

Contact: Clinical Operations, CooperVision

[redacted]

11.4 Suspension or Premature Termination of the Clinical Investigation

The study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the Investigator, the Sponsor and the Institutional Review Board (IRB), as appropriate. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reasons for the termination or suspension. In terminating the clinical investigation, CooperVision and the Principal investigator will assure that adequate consideration is given to the protection of the subject's interests.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The blinding/masking code may be broken and communicated to the Principal Investigator only in the case of an emergency, such as an Adverse Event that requires knowledge of the identity of the investigational product in order to manage the subjects' condition.

The study may resume once concerns about safety, protocol compliance or data quality are addressed and satisfy the Sponsor and IRB/EC.

Subjects will continue to receive follow-up care until they are able to be exited from the study (in the case of study termination) or are able to resume participation in the study (in the case of temporary study suspension), whereupon they will also be followed to exit.

11.5 Record Retention

Following study completion, data will be available in electronic and/or paper format for audit, Sponsor use, or subsequent analysis.

Documents will be retained in a manner which allows for timely retrieval. Where documents are maintained in an electronic system, the system will be required to be maintained for the life of the document or the documents migrated to a system allowing for the continued retrieval of the document until the retention period has been completed.

Access to the Network, eQMS or other electronic storage is secured to minimize potential loss or unauthorized changes. Documents will be stored in a manner to prevent loss and damage.

Applicable hard copy documents will be secured as appropriate and maintained in a manner to prevent loss or damage.

If hard copy records are retained in an archive store, a log of the content of each pallet and box in the archive should be kept in order to enable swift record retrieval. This log should contain the pallet and box owning department, record type and date range covered.

The content of archives should be reviewed periodically. The storage of the records in the archive must be appropriate and in good condition to ensure that records inside are not damaged.

Certain Quality/Regulatory Documented Information is noted as having permanent retention periods due to complex regulatory requirements. Permanent records should be held securely. A fireproof room or safe may be used.

Permanent records may be considered for destruction. Consideration will be based on a documented request forwarded to the site Quality Assurance leader, or a member of the Global Quality Systems team. The request must be reviewed and approved prior to any destruction.

The request and approval will include:

- the requestors name and title,
- date of the request,
- approvers name and title,
- date of approval,
- list of the Documented Information to be destroyed.

Since this Protocol document is indicated for Design Validation purposes, as indicated on the title page, all original raw data forms and completed CRF's will be forwarded to the Sponsor at completion of the final report.

11.6 Confidentiality and Privacy

This study is confidential in nature. [redacted] any information disclosed to the other party under that Agreement and identified verbally or in writing as confidential.

All records will be handled in accordance with HIPAA (1996) standards. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. Documentation containing personal and/or confidential identifying information for clinical trial subjects participating in studies will be maintained in a secured locked location. The principal investigator or investigation site shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections.

12 Device Accountability

12.1 Clinical Supply Inventory

The investigator must keep an accurate accounting of the study product during the study. A detailed inventory must be completed for study supplies. The study supplies are to be used in accordance with the study protocol by subjects who are under the direct supervision of an investigator.

12.2 Disposal of Consumables

This study dispenses consumables (contact lenses) to participants for use during the study. Study contact lenses worn by participants at the Follow-up visits (Visits 2A & 3A) will be collected at the visit, and any unworn contact lenses for each lens pair at the Follow-up visit (Visits 2A & 3A).

12.3 Ordering and Accountability of Study Materials

The Test and Control contact lenses will be provided by the Sponsor. The investigator must complete an accurate accounting of the study product at the completion of the study. All unused and used materials will be returned to the Sponsor at the end of the study unless the investigator is otherwise directed by the study Sponsor.

13 Study Costs

The Sponsor will compensate the clinical site and the subjects for their time and participation in this voluntary study.

Expenses incurred for medical treatment as part of study participation will be paid by the Sponsor (bills and prescription receipts kept). The participant must be followed until resolution and a written report completed indicating the subsequent treatment and resolution of the condition.

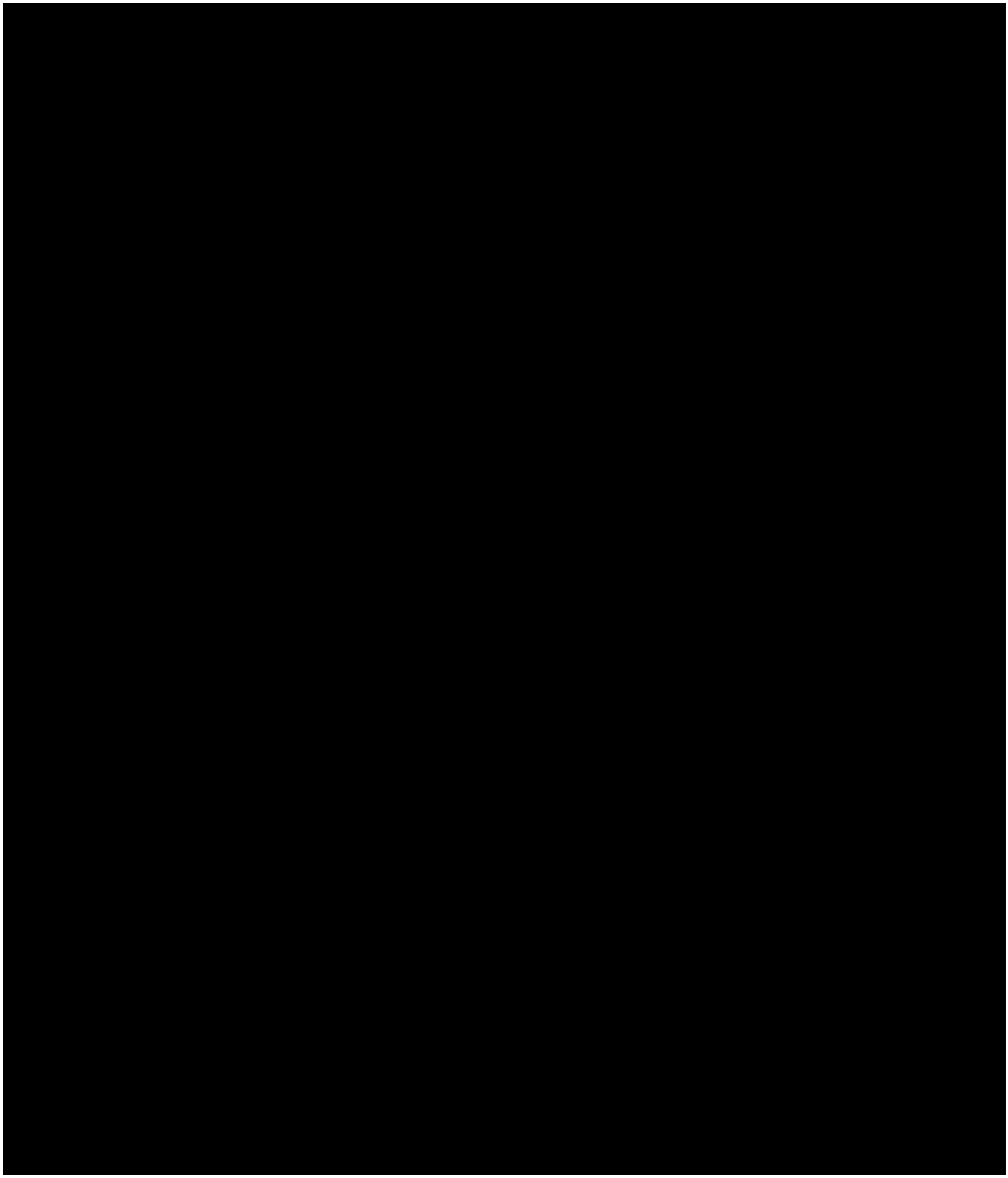
14 Publication Policy

[redacted] may publish the results of this study, subject to the conditions laid out in the [redacted]

15 References

[1] Cheng K, Leung S, Hoekman H, Beekhuis W, Mulder P, Geerards A, Kijlstra A. Incidence of contact-lens-associated microbial keratitisand its related morbidity. The Lancet 1999; 354:181-185.

17 Appendix 1 – Subjects Habitual CL wear Questionnaire (Visit 1)



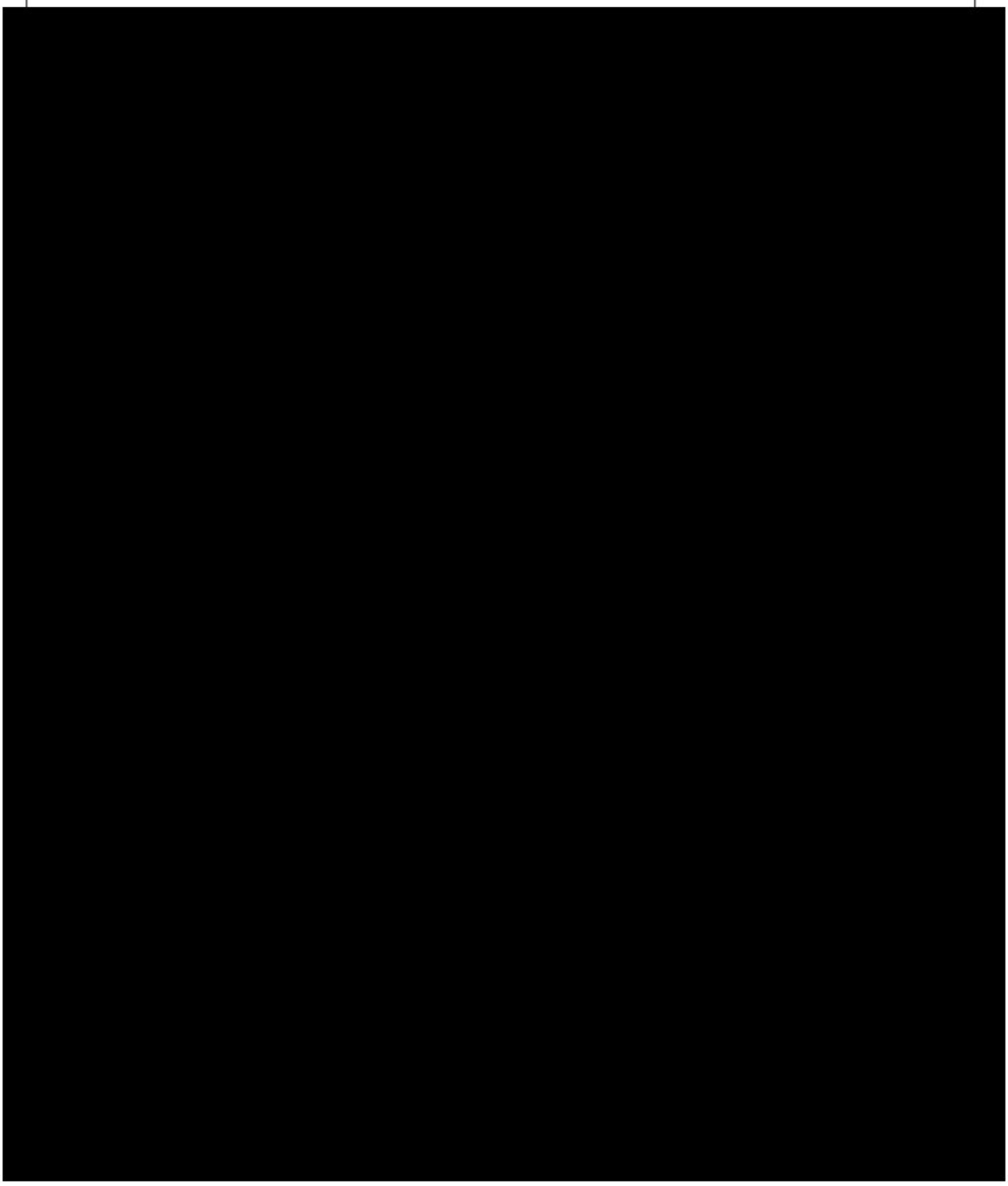
HABITUAL CONTACT LENS QUESTIONNAIRE

[redacted]

HABITUAL CONTACT LENS QUESTIONNAIRE

[redacted]

HABITUAL CONTACT LENS QUESTIONNAIRE



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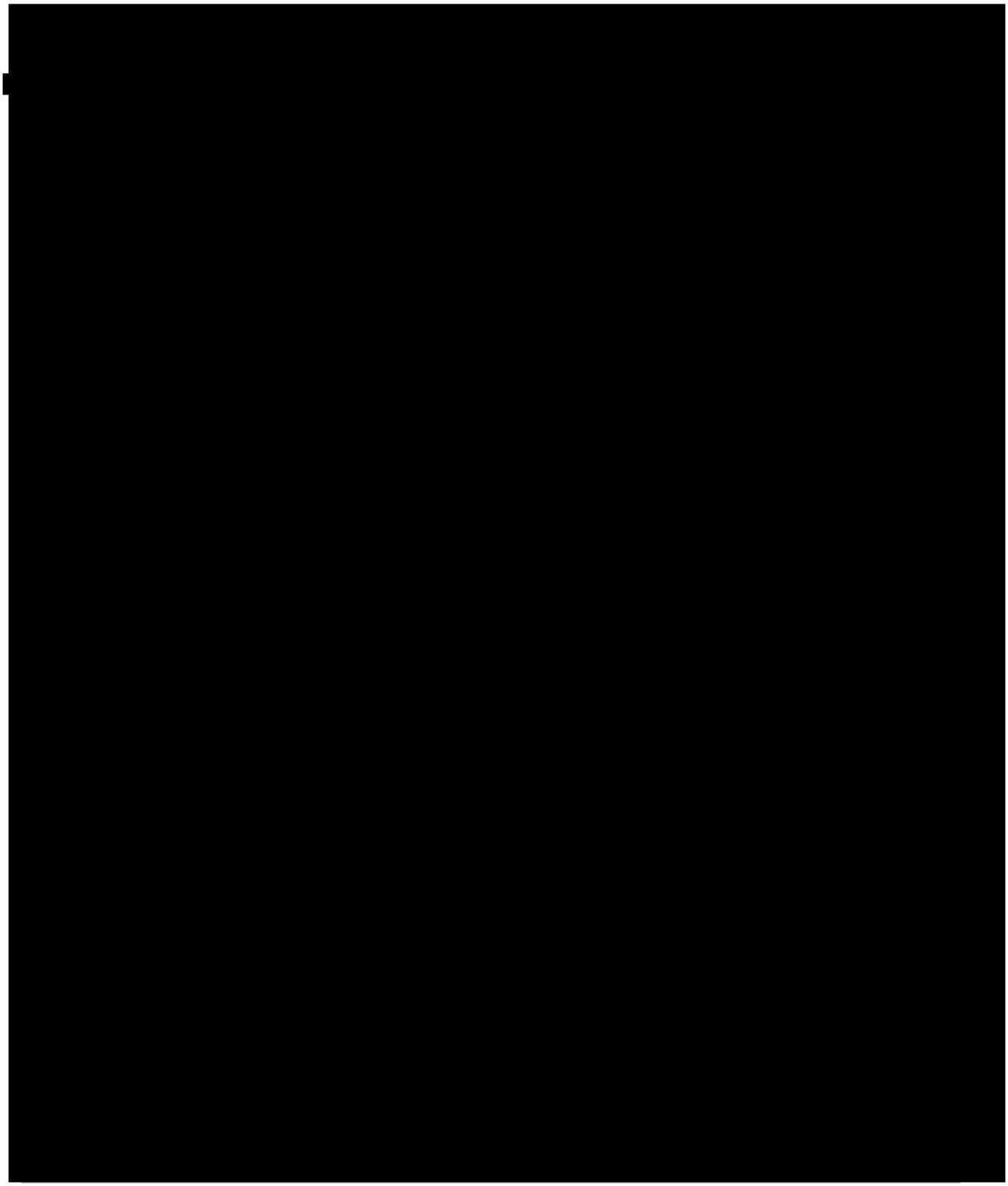
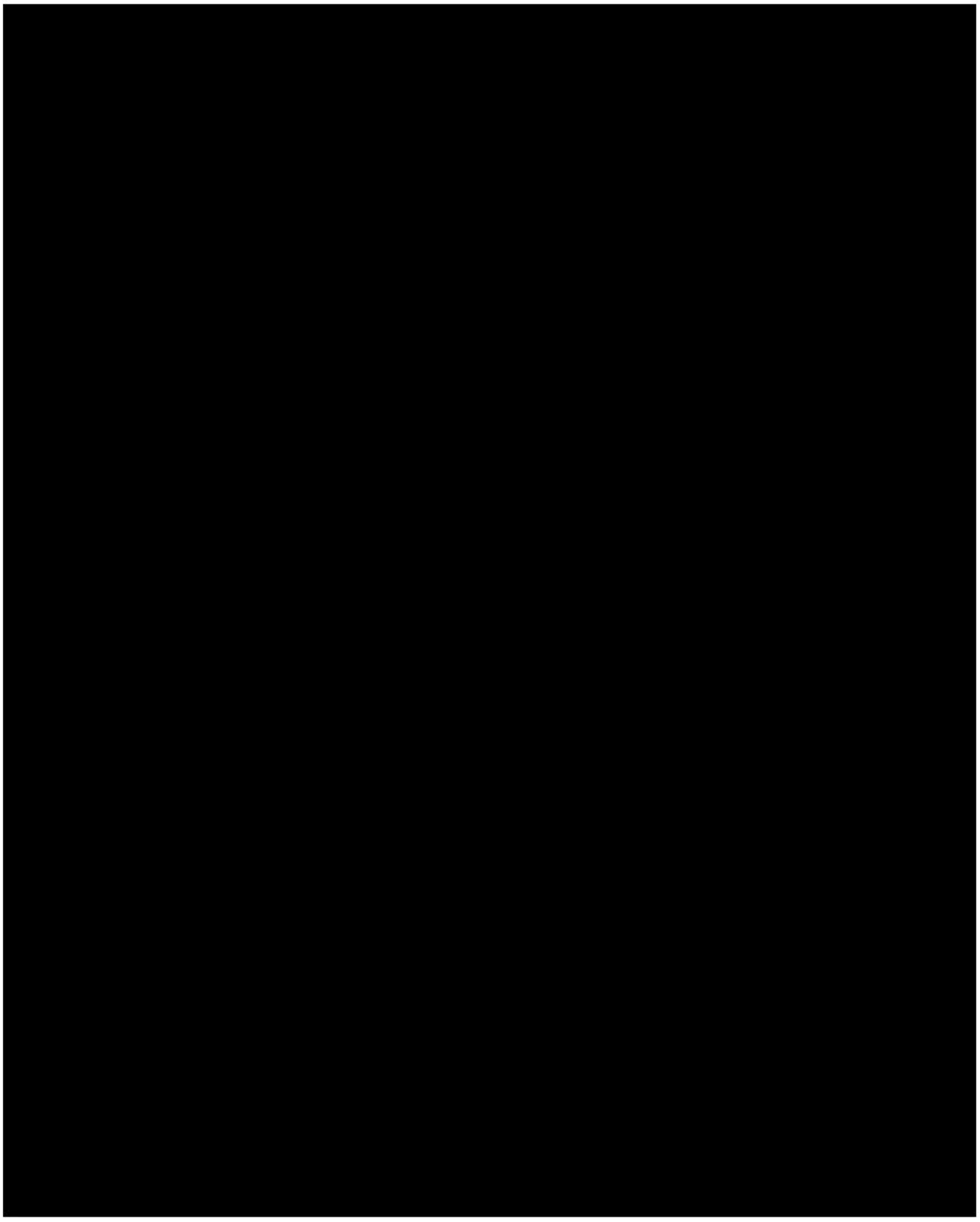
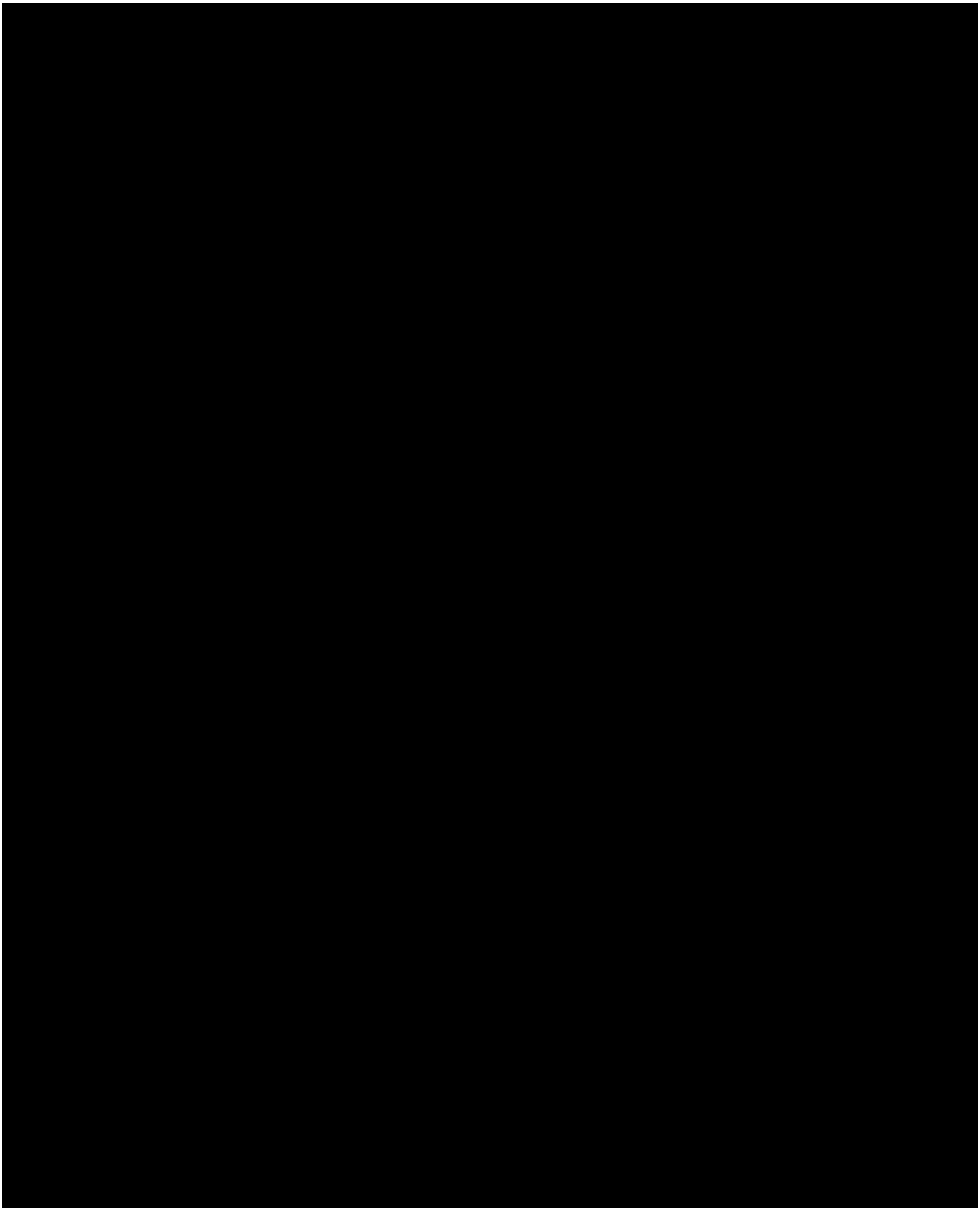
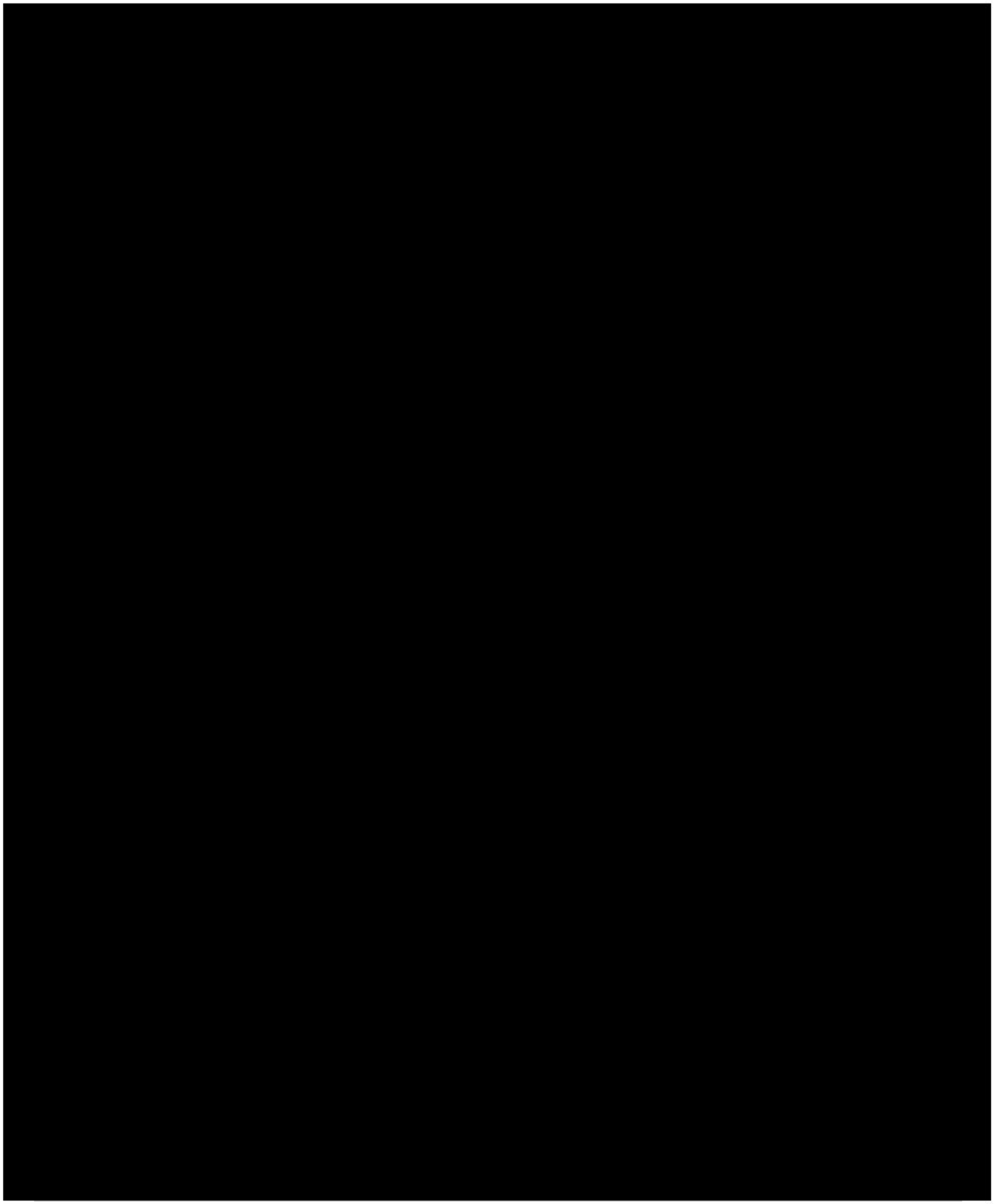
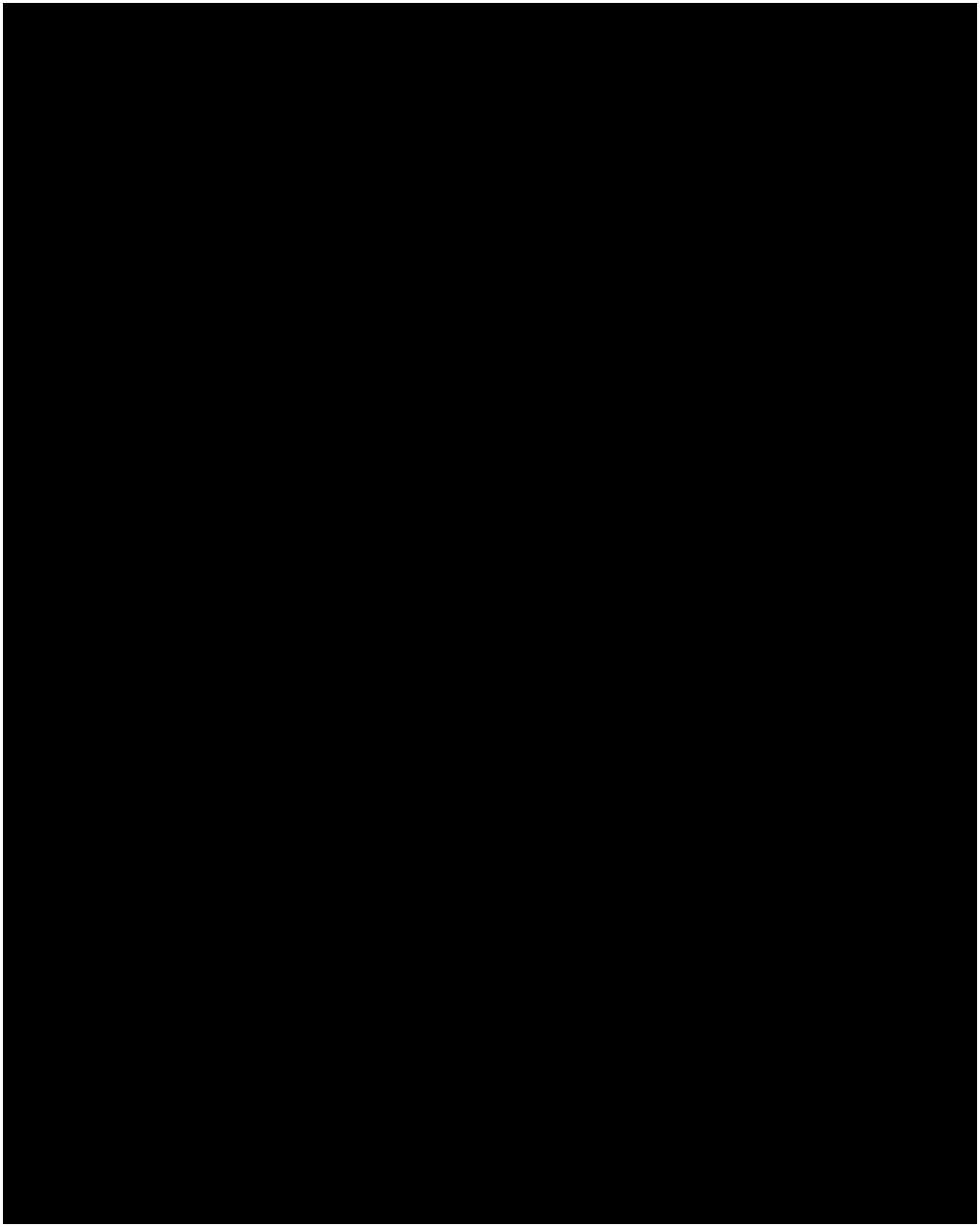


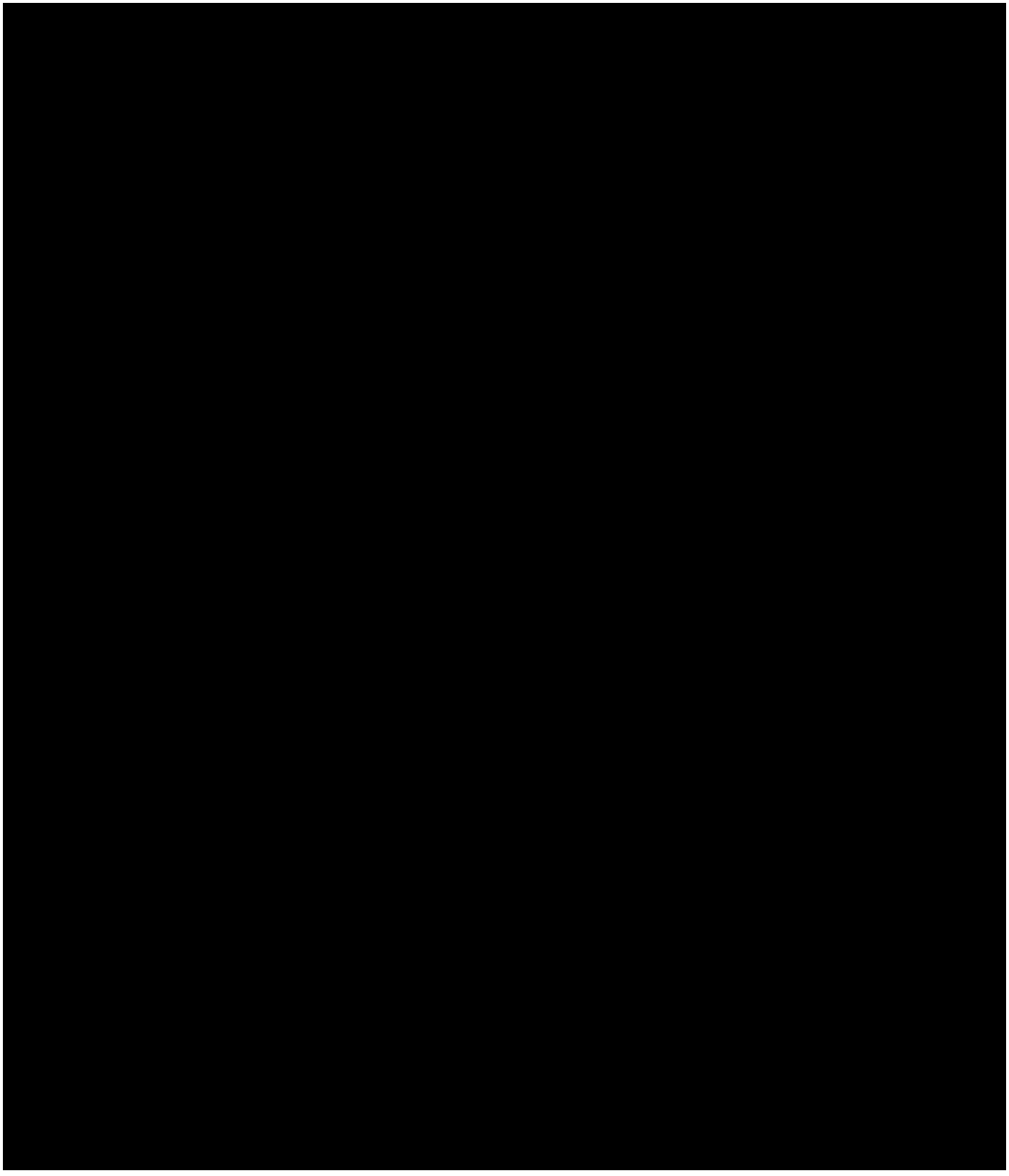




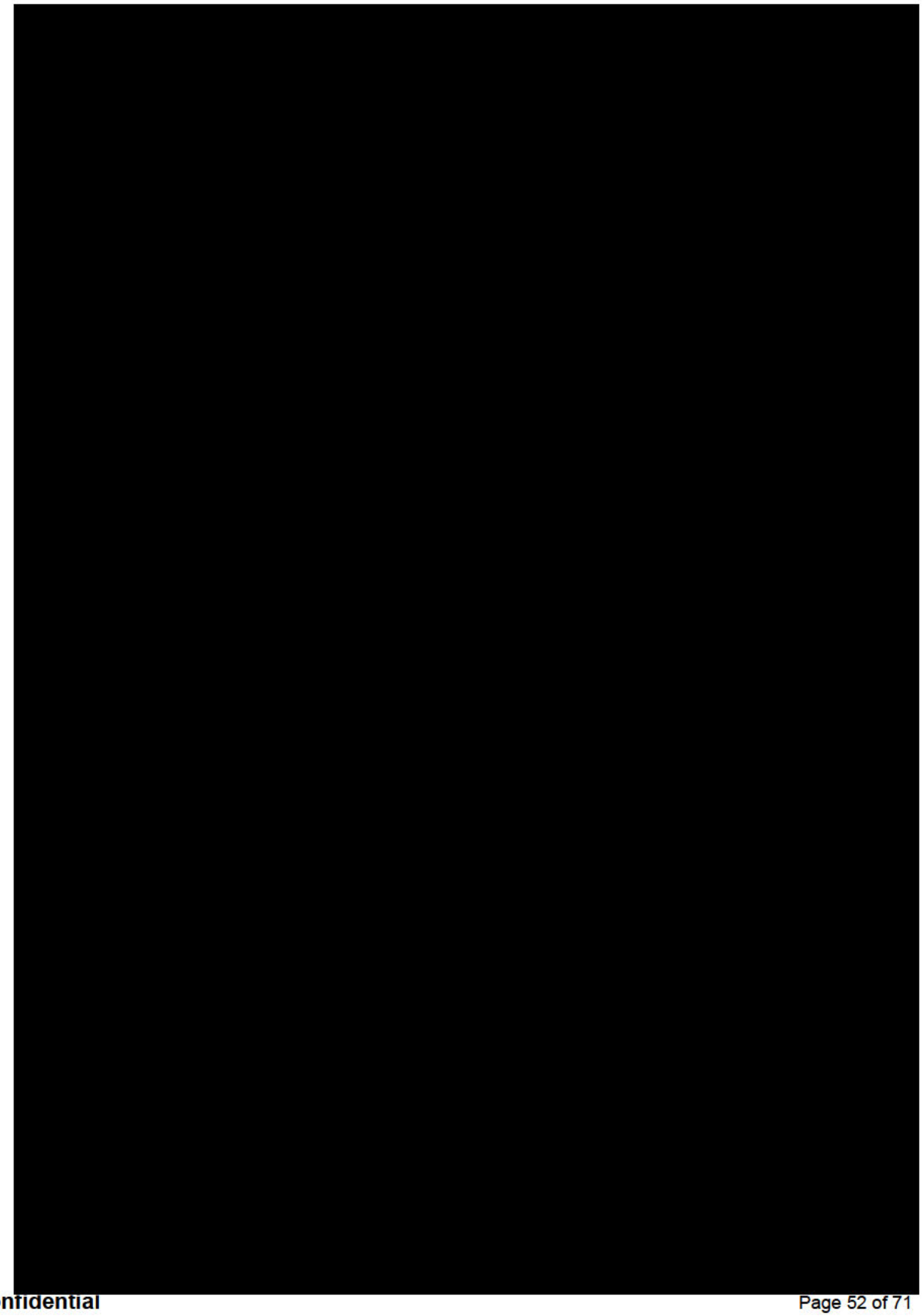




18 Appendix 2 – Slit Lamp Biomicroscopy Grading Scales



19 Appendix 3 – Randomization



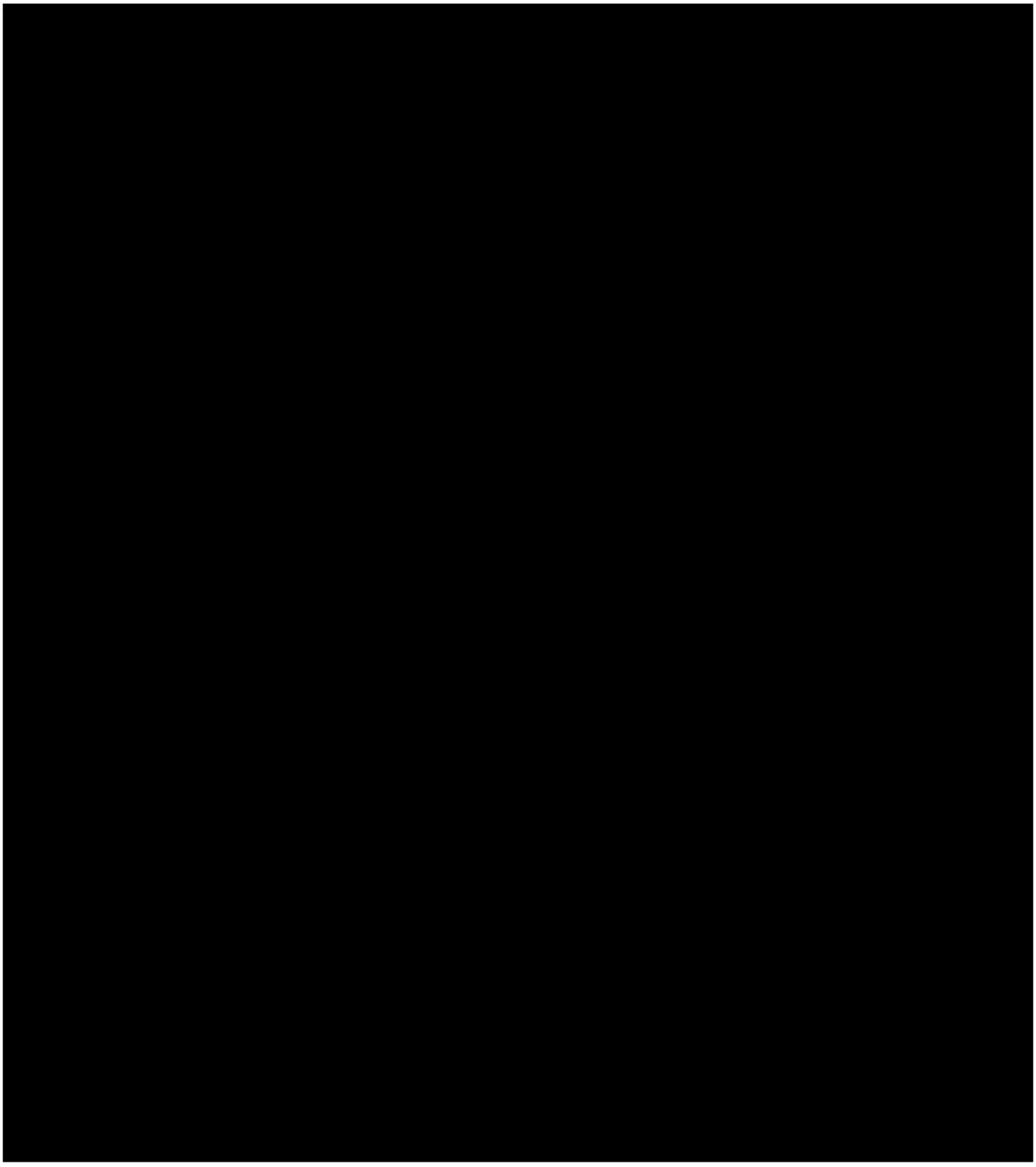
20 Appendix 4 – Room Illumination and Screen Luminance

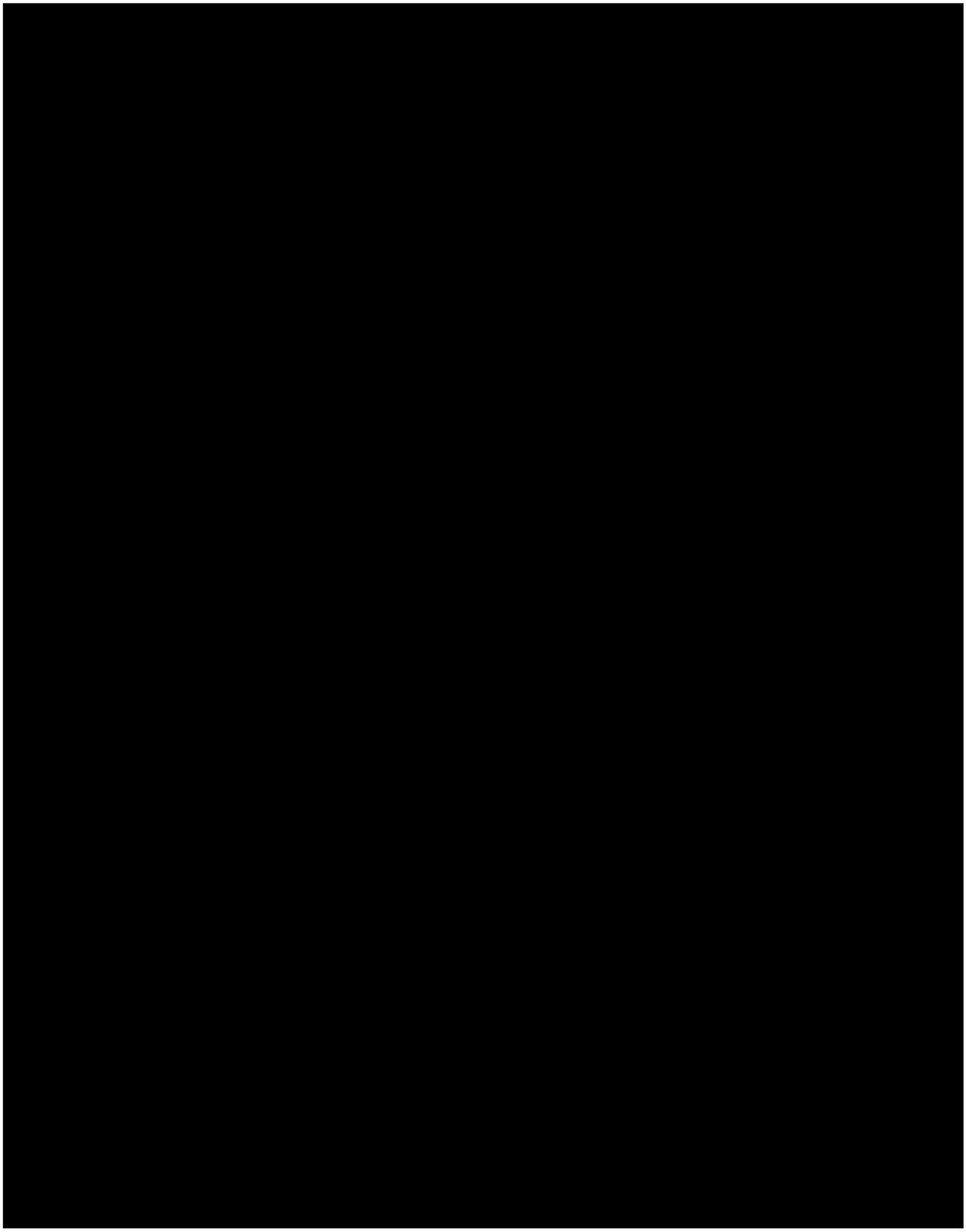
21 Appendix 5 – Objective Lens Assessments (Pairs 1&2)

Lens Surface Assessments

Lens Fit

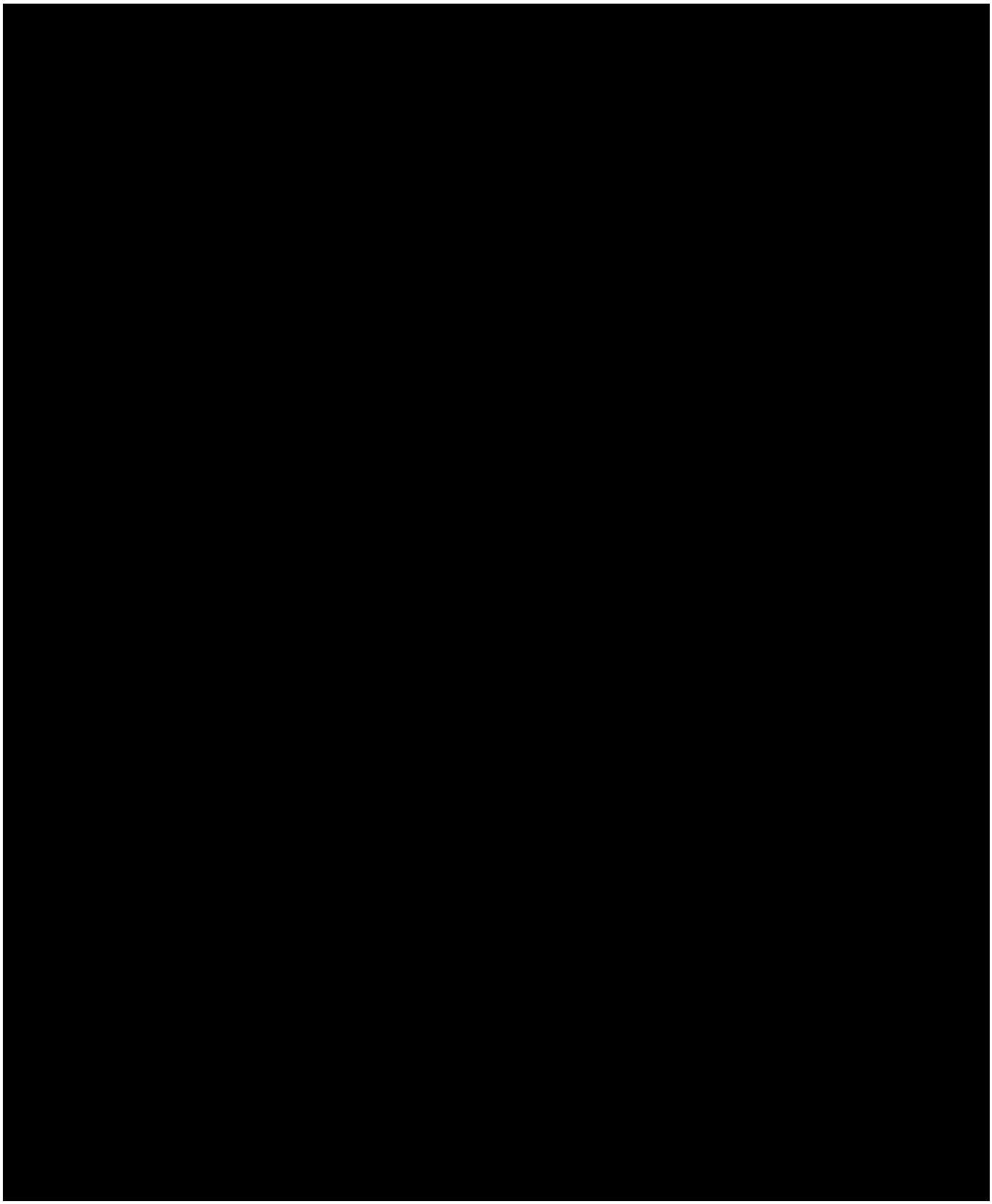
22 Appendix 6 – Vision and Comfort Questionnaire (Follow Up Visits 2A & 3A)





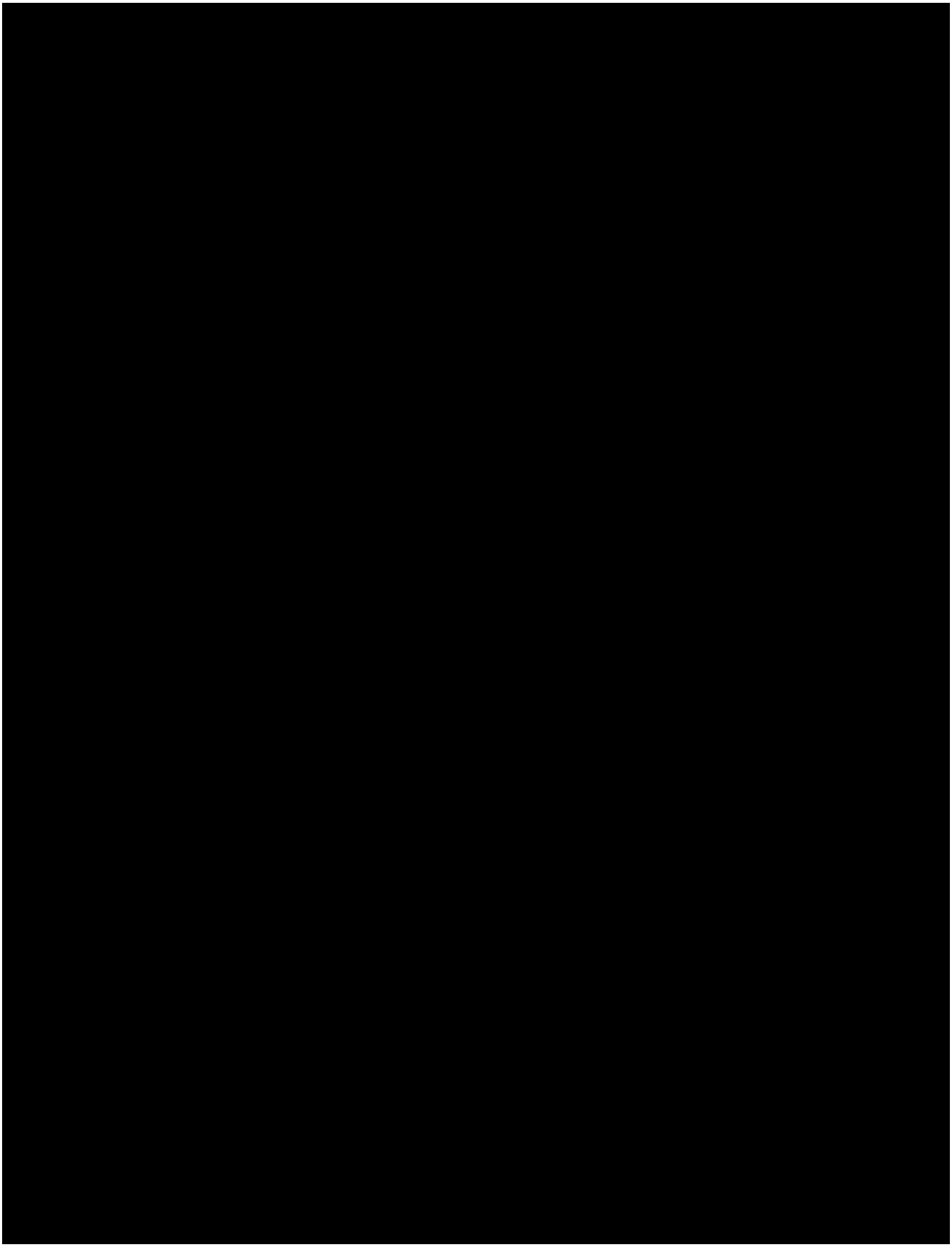
23 Appendix 7 – [redacted]

[redacted]



24 Appendix 8 – [redacted]

[redacted]



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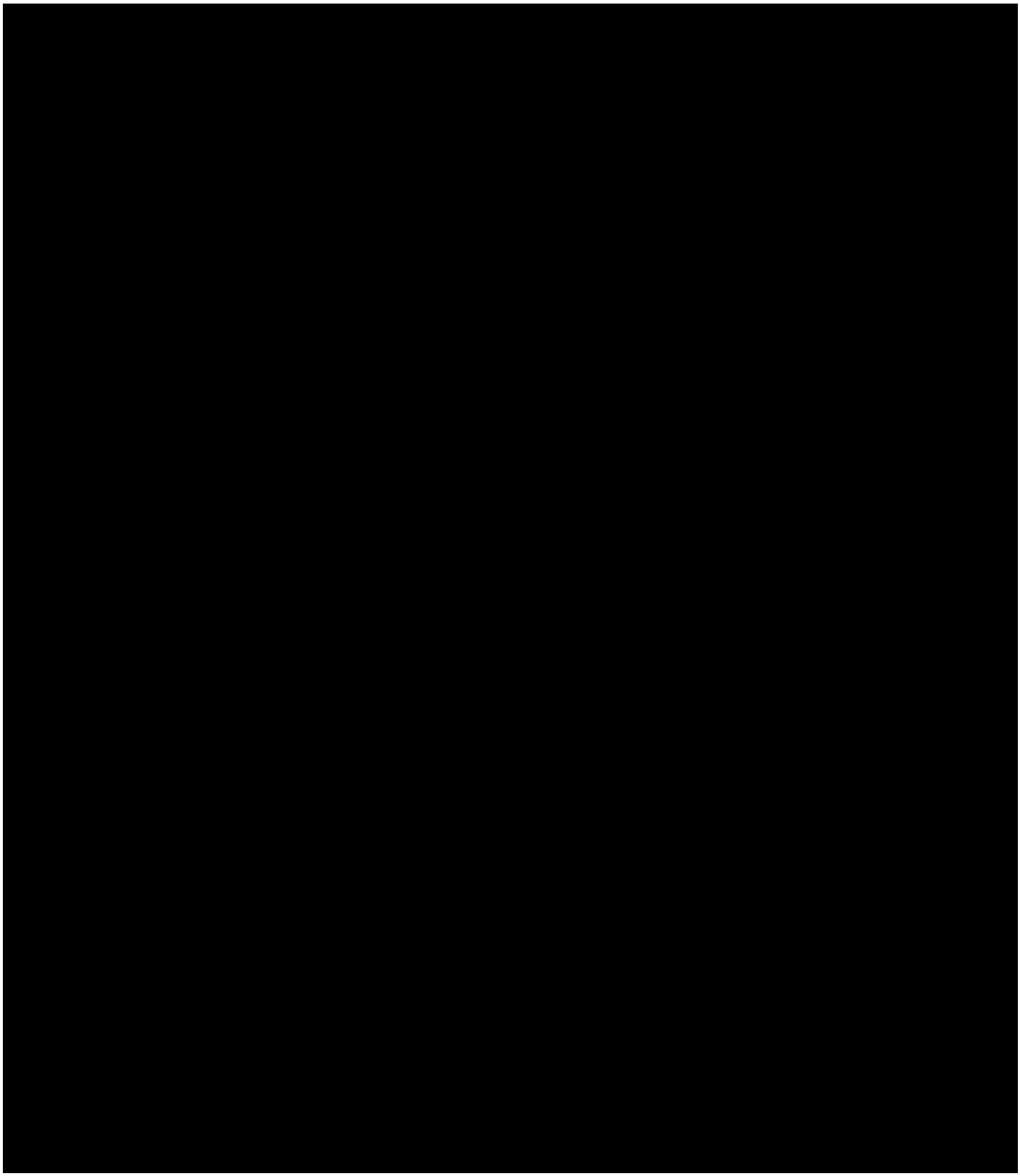

25 Appendix 9 – [redacted]

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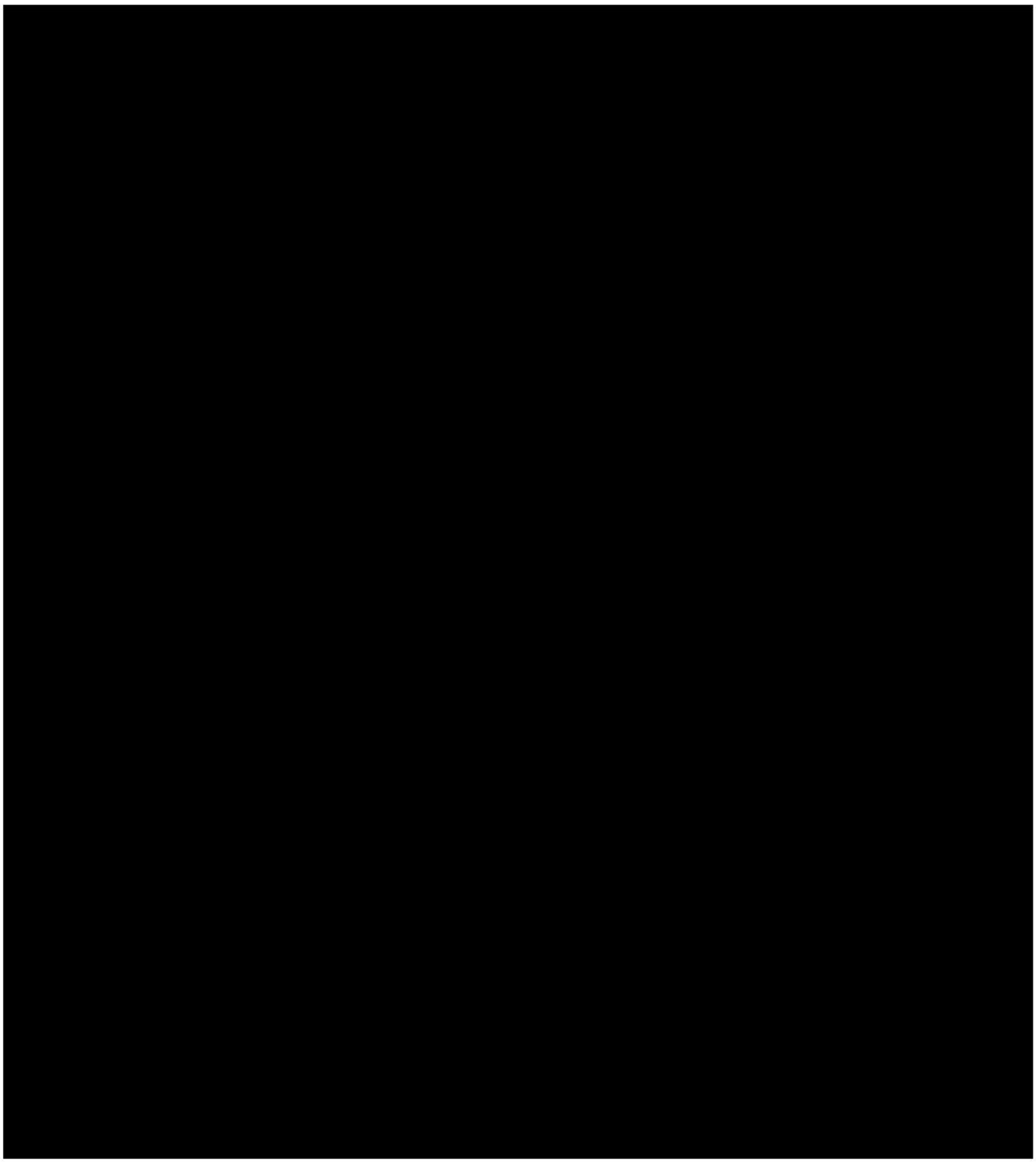
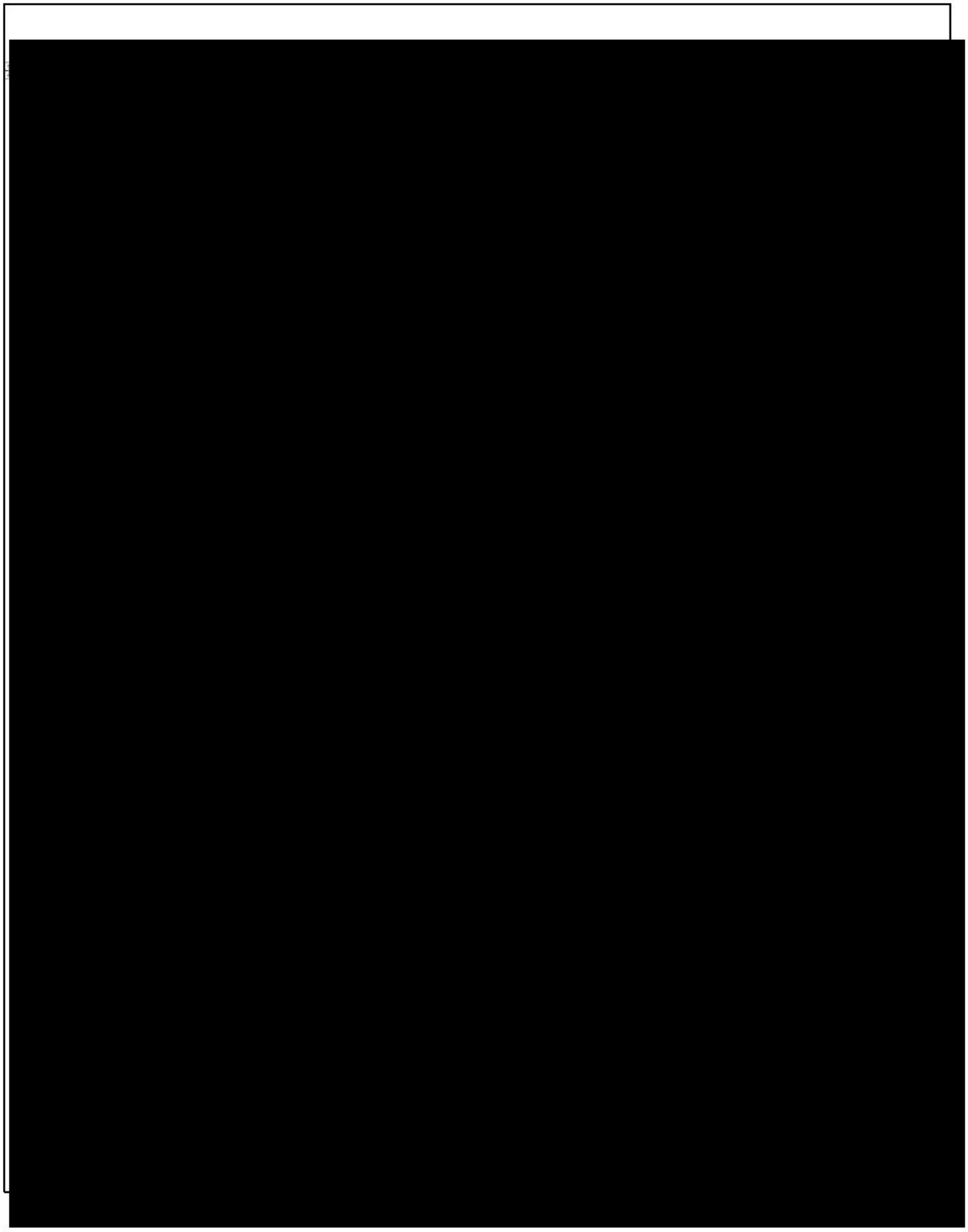


Responses reviewed by:

Investigator Signature_____ Date:_____

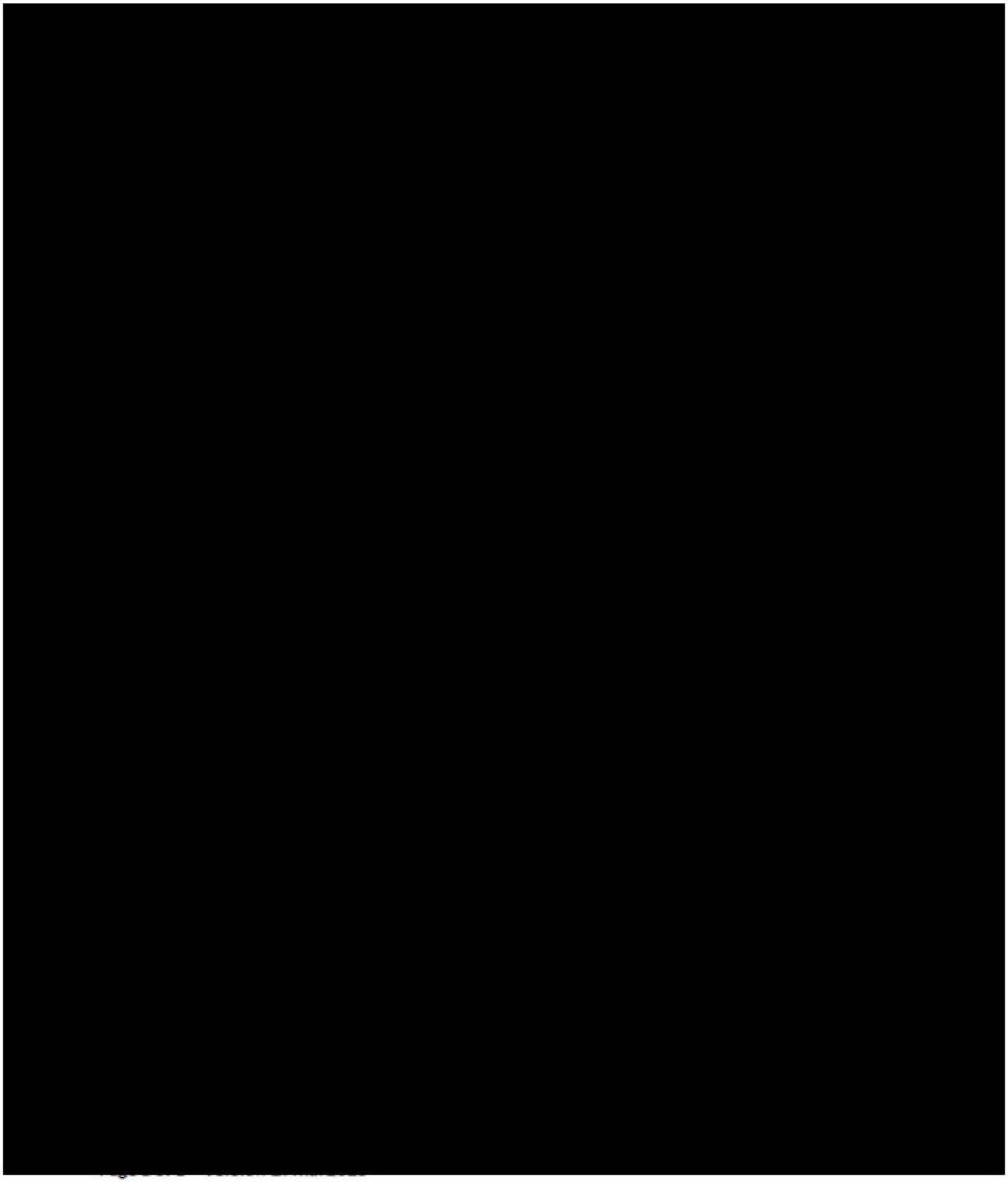
26 Appendix 10 – Adverse Event Case Report Forms



CVI ADVERSE EVENT NOTIFICATION FORM

[redacted]

CVI ADVERSE EVENT OUTCOME FORM



27 Appendix 11 – Clinical Trial Product Defect Notification Form