STATISTICAL ANALYSIS PLAN

Protocol Number:	1920201
Title:	A Phase 2, Multicenter, Open-Label Study to Evaluate the Efficacy and Safety of DaxibotulinumtoxinA for Injection (DAXI for Injection) for the Combined Treatment of Upper Facial Lines (Glabellar Lines, Dynamic Forehead Lines and Lateral Canthal Lines)
Study Phase:	2
Sponsor:	Revance Therapeutics, Inc. 7555 Gateway Blvd. Newark, CA 94560
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAP Date:	16 Jul 2020
SAP Version Number:	Version 1.0
Protocol Version:	25 October 2019

[redacted]

TABLE OF CONTENTS

LIST OF TABLES

[redacted]

[redacted]

LIST OF FIGURES

[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
[redacted]	[redacted]
AE	Adverse event
CI	Confidence interval
DAXI	DaxibotulinumtoxinA
FASE	Facial Age Self Evaluation
FHL	Forehead lines
GAIS	Global Aesthetic Improvement Scale
GL	Glabellar lines
ICF	Informed consent form
IGA-FWS	Investigator Global Assessment Frown Wrinkle Severity
IGA-FHWS	Investigator Global Assessment Forehead Wrinkle Severity
IGA-LCWS	Investigator Global Assessment Lateral Canthal Wrinkle Severity
IM	Intramuscular
IP	Investigational product
kDa	Kilodalton
LCL	Lateral canthal lines
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
PFWS	Patient Frown Wrinkle Severity
PFHWS	Patient Forehead Wrinkle Severity
PLCWS	Patient Lateral Canthal Wrinkle Severity
PNA	Patient Naturalness Assessment
PT	Prothrombin time
SAE	Serious adverse event
SAP	Statistical analysis plan
TEAE	Treatment-emergent adverse event
UPT	Urine pregnancy test
WOCBP	Women of childbearing potential

1. INTRODUCTION

[redacted]

This study will complement the available data from the dose-ranging GL, FHL, and LCL studies to provide a better understanding of the safety and efficacy of DAXI for injection in the treatment of the upper facial lines reflective of real-world applications onabotulinumtoxinA (De Boulle, 2018).

This statistical analysis plan (SAP) describes the objectives of the study and the safety and efficacy assessments that are collected. The safety endpoints and the efficacy endpoints are defined, and the

statistical methods used to analyze them are presented. Table shells for the planned end-of-text tables, figures, and listings are included in a separate document, but the titles are specified following the text of the SAP.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary study objective is to evaluate the efficacy and safety of DAXI for injection in the combined treatment of GL, FHL, and LCL.

2.2 Trial Endpoints

[redacted]

[redacted]

2.2.3 Safety Endpoints

Safety will be evaluated using the following assessments:

- Vital signs
- Physical examination
- Injection site evaluation
- Concomitant therapies/medications
- Clinical laboratory tests (hematology, serum chemistry, prothrombin time [PT], urinalysis)
- [redacted]
- Adverse events (AEs), including the incidence, severity, and relationship to study drug of TEAEs and serious adverse events (SAEs) during the overall study duration.

3. OVERALL STUDY DESIGN AND PLAN

3.1 Study Design

This is a phase 2, multicenter, open-label, dose-escalation study to evaluate the safety and efficacy of DAXI for injection for the treatment of subjects with moderate to severe GL, FHL and LCL. This study will be conducted at 8 sites in the United States and Canada.

Approximately 48 subjects (18 years of age and above) with moderate to severe GL, FHL and LCL (all assessed at maximum contraction) will be screened for eligibility and enrolled to receive DAXI for injection after providing informed consent. [redacted]

[redacted]

The total study duration will be up to 38 weeks, including up to 2 weeks for screening. After treatment on Day 1, subjects will be followed for a minimum of 24 weeks and up to 36 weeks. Subjects will complete the study at Week 36 or earlier (on or after Week 24), if the severity scores for GL, FHL, and LCL return to baseline (Day 1 pretreatment) or worse based on both the investigator and subject evaluations. Subjects who return to baseline or worse in GL, FHL, and LCL severity scores prior to Week 36 will complete a Final Evaluation Visit upon the site confirming their status as an early completer, by referring to baseline evaluations.

[redacted]

3.1.1 Determination of Sample Size

A sample size of 48 is selected. [redacted]

3.1.2 Treatments Administered

This is an open-label, non-randomized study. All subjects will receive DAXI for injection as IM injections. A subject will receive 40 U of DAXI for injection in a standard 5-point injection paradigm in the GL-complex (procerus and corrugator muscles), 32 U of DAXI for injection in a 4-point injection paradigm in the frontalis muscle, and 48 U of DAXI for injection in a 3-point injection paradigm per side in the lateral canthal areas.

3.2 Efficacy and Safety Assessments

The efficacy assessments will include investigator assessment of GL, FHL, and LCL severity and improvement on the IGA-FWS, IGA-FHWS, and IGA-LCWS respectively, as well as subject assessment of severity and improvement of GL, FHL, and LCL on the PFWS, PFHWS, and PLCWS respectively.

3.2.1 Frown, Forehead, and Lateral Canthal Wrinkle Severity

Frown, Forehead, and Lateral canthal wrinkle severity is assessed by both the subject and the investigator using the same 4-point rating scale, where scores range from 0 = none to 3 = severe.

3.2.2 Subject Global Satisfaction with Treatment

At each clinic visit after treatment, the subject will be asked to complete the Subject Global Satisfaction with Treatment Questionnaire to rate their satisfaction with the treatment results using a 7-point scale. The scale ranges from 0 = Very Dissatisfied to 6 = Very Satisfied, with a rating of 3 = Neither Satisfied nor Dissatisfied.

3.2.3 Global Aesthetic Improvement Scale (GAIS)

The Investigator and subject will assess the visual appearance (at maximum contraction) of the improvement from the baseline condition in GL, FHL, and LCL (individually) using the 7-point severity GAIS. The scale ranges from -3 = Very much worse to 3 = Very much improved, with a rating of 0 = No change. Subjects will use the baseline assessment photograph for comparison when reviewing the visual appearance for GL, FHL, and LCL to assess improvement following treatment.

3.2.4 Facial Age Self Evaluation (FASE)

The subject will be asked to rate their perceived age on a FASE questionnaire (see Appendix 6 of the protocol). The subject will rate their perception of how old they think they look following the treatment.

3.2.5 FACE-Q™

The subject will be asked to complete the FACE-Q™ Appraisal of Lines: Overall, FACE-Q™ Appraisal of Lines: Forehead, FACE-Q™ Appraisal of Lines: Between Eyebrows, FACE-Q™ Appraisal of Lines: Crow's Feet Lines, FACE-Q™ Satisfaction with Forehead and Eyebrows, FACE-Q™ Satisfaction with Outcome and FACE-Q™ Psychological Function. Refer to Appendix 8 of the protocol.

The questionnaires ask subjects to rate how bothered they are by the lines on their entire face, as well as by their FHL, GL and LCL using questions about general appearance with a rating scale of 1 to 4 with 1 = Not Bothered and 4 = Extremely Bothered. They also ask about satisfaction with eyebrow

and forehead appearance with a rating scale of 1 to 4 with 1 = Very Dissatisfied to 4 = Very Satisfied. Additionally, the subject is asked to rate 6 statements about the outcome and 10 statements related to positive feelings about themselves keeping their facial appearance in mind using a rating scale of 1 to 4, with 1 = Definitely disagree to 4 = definitely agree.

3.2.6 Patient Naturalness Assessment

The subject will be asked to rate how strongly they agree or disagree with the statement "the results of my treatment look natural" using a 7-point scale. The scale ranges from -3 = Strongly Disagree to 3 = Strongly Agree, with a rating of 0 = Neutral.

[redacted]

3.3 Safety Assessments

3.3.1 Adverse Events

All AEs will be recorded and classified on the basis of the Medical Dictionary for Regulatory Activities (MedDRA) terminology. AE severity will be graded as mild, moderate, or severe as defined in Section 7.4.1.7 of the protocol. Relationship of an AE will be graded as definite, probable, possible, or unrelated. AEs with an onset on or after the date and time of trial treatment, or events which were present before treatment and which worsened after treatment, will be considered as treatment-emergent.

AEs with missing severity will be considered as "severe". AEs with missing relationship will be considered as "related". If the start of an AE relative to the administration of trial treatment cannot be definitively determined, it will be considered to have occurred after treatment and the event considered as treatment-emergent.

3.3.2 Injection Site Evaluation

Injection sites will be evaluated at screening to assess for skin inflammation or active skin disease and at later time points to determine if there is an immediate reaction to the investigational product. The assessment will be done as a global evaluation of the 5 GL injection sites, the 4 FHL injection sites, and each of the 3 injection sites for LCL on each side of the face.

3.3.3 Clinical Laboratory Data

Table 3.2 outlines the clinical laboratory tests that will be conducted during this study. Blood and urine specimens will be collected using applicable safety precautions and will be processed according to the central clinical laboratory's instructions. Urinalysis will be evaluated at the study center using supplies provided by Revance or designee.

Table 3.2: Clinical Laboratory Tests

Serum Chemistry	Hematology	Urinalysis	Additional Tests
Glucose	Hemoglobin	Specific gravity	Prothrombin time (PT) (screening only)
Total bilirubin	Hematocrit	pH	
Alanine aminotransferase	Leukocyte Count (total)	Glucose	UPT (WOCBP only)*
Aspartate aminotransferase	Leukocyte Count (differential)	Protein	
Alkaline phosphatase	Red Blood Cell Count	Blood	
Blood urea nitrogen	Platelet Count	Bilirubin	
		Ketones	

WOCBP = Women of child-bearing potential
*If positive at timepoints after study treatment, confirm by serum pregnancy test

[redacted]

3.3.5 Vital Signs

Vital signs (i.e., body temperature, respiration rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures) will be obtained. New abnormal findings or worsening from baseline (Day 1 prior to treatment) at subsequent assessments, if judged clinically significant, should be recorded as an AE.

If a subject reports signs or symptoms of distant spread of toxin at a given visit, vital signs (body temperature, respiratory rate, sitting radial pulse, and sitting systolic and diastolic blood pressure) will be measured and recorded.

3.3.6 Physical Examination

A targeted physical examination, including neurologic examination of the face, will be conducted. Significant physical examination findings that are present prior to investigational product administration will be reported as Medical History.

Significant physical examination findings after investigational product administration which meet the definition of an AE will be recorded as an AE.

[redacted]

3.4 Interim Analyses and Data Monitoring

3.4.1 Interim Analysis

A formal interim analysis of the data will be performed when all subjects finish 8 weeks after receiving the GL/FHL/LCL treatment or have withdrawn from the study earlier. This interim analysis will be a high level analysis of study conduct, efficacy and safety. The analysis will be performed by the study team in a restricted access folder. Efficacy will focus on the primary and secondary endpoints.

Individual tables, listings, and figures to be included in the interim analyses are denoted in Section 9 below with an asterisk.

4. ANALYSIS POPULATIONS AND SUMMARY GROUPS

Three analysis populations will be specified: Enrolled, Evaluable, and Safety. Analyses performed on the Enrolled and Evaluable populations will utilize the planned treatment assignment(s). Analyses performed on the Safety populations will utilize the actual treatment(s) received.

4.1 Enrolled Population

All subjects who signed ICF, confirmed eligible and received treatment.

4.2 Evaluable Population

All enrolled subjects who receive treatment and have any post treatment assessment of IGA-FWS at maximum frown.

A Modified Evaluable population may be created for the subset of subjects who have Week 4 assessment data for the IGA-FWS, IGA-FHWS and IGA-LCWS.

4.3 Safety Population

All enrolled subjects who receive at least 1 treatment (injection).

5. CONVENTIONS AND DERIVATIONS

5.1 Definition of Baseline

The baseline value will be the last available non-missing value prior to treatment on Day 1. Assessments taken on the same day as treatment will be assumed to be prior to treatment unless indicated to be obtained post-treatment.

5.2 Definition of Day 1

Day 1 of treatment is defined as the day of DAXI doses for GL, FHL, and LCL treatment. All time-to-event analyses for assessments of GL, FHL, and LCL will utilize the date of treatment as the start date.

5.3 Demographic and Disposition

Age in years at time of enrollment will be derived relative to the date of informed consent as (consent date – date of birth + 1)/365.25 and truncated to 0 decimal points. Age will also be categorized into two groups: <65 years and ≥65 years.

[redacted]

5.4 Prior and Concomitant Medications

Prior therapies and medications are those which began and were stopped before receipt of study medication. Concomitant therapies and medications are those which were ongoing at the receipt of study medication and those which were taken during the study (i.e., between the date of first dose and the last study visit).

[redacted]

[redacted]

5.6 Global Aesthetic Improvement Scale (GAIS)

Indicators of response for each assessment will be derived based on the following criteria:

- Achieving a score of ≥1 on the GAIS for each of the following separately: at maximum frown for GL, at maximum eyebrow elevation for FHL and at maximum smile for LCL.
- Achieving a score of ≥2 on the GAIS for each of the following separately: at maximum frown for GL, at maximum eyebrow elevation for FHL, and at maximum smile for LCL.
- Achieving a score of ≥3 on the GAIS for each of the following separately: at maximum frown for GL, at maximum eyebrow elevation for FHL, and at maximum smile for LCL.

5.7 FACE-Q

The FACE-Q assessments will be scored and converted to a transformed score which ranges from 0 to 100 according to scoring rules for the assessment: Section 8.1 for scoring of the FACE-Q Appraisal of Lines Overall; Section 8.2 for scoring of the FACE-Q Appraisal of Lines: Forehead; Section 8.3 for scoring of the FACE-Q™ Satisfaction Appraisal of Lines: Crow's Feet Lines; Section 8.4 for the scoring of the FACE-Q Appraisal of Lines: Between Eyebrows; Section 8.5 for scoring of the FACE-Q Satisfaction with Forehead and Eyebrows; Section 8.6 for scoring of the FACE-Q Satisfaction with Outcome; and, Section 8.7 for scoring of the FACE-Q Psychological Function.

5.8 Adverse Events

Treatment-emergent AEs are those AEs with an onset on or after the date and time of trial treatment or events which were present before treatment and which worsened after treatment.

AEs with missing severity will be summarized as "severe". AEs with missing relationship will be summarized as "related".

6. STATISTICAL METHODS

All statistical programming will be performed using Statistical Analysis System (SAS) version 9.4 or higher.

In general, descriptive summaries will include means, standard deviations, median, first and third quartiles, as well as the minimum and maximum values for continuous variables; and counts and proportions for categorical measures. Unless otherwise stated, a 95% exact confidence interval (CI) will be provided for proportions.

6.1 Subject Disposition

The number and percentage of subjects who have signed informed consent, enrolled, received each treatment (GL, FHL, and LCL), and completed visits will be tabulated and included in a listing. Reasons for not completing the study will also be tabulated using numbers and percentages; this data will also be included in a listing. For those subjects who are considered to have failed screening, the reason(s) for failure will be provided in a listing.

The number and percentage of subjects included and excluded from the analysis populations will be tabulated. Reason(s) for exclusion from each population will be summarized and listed.

A summary of the duration of the subject participation in the study will be produced, including the n, mean, standard deviation (SD), median, first and third quartiles, minimum, and maximum duration in weeks, as well as the number and percentage of subjects in the duration categories.

Major protocol deviations will be listed and summarized.

6.2 Demographic and Baseline Characteristics

Descriptive statistics will be used to summarize demographic and baseline characteristics.

Demographic data include age, age category, sex, ethnicity, and race. Baseline characteristics include prior Botulinum toxin Type A in GL, FHL and LCL, time since last prior Botulinum toxin Type A injection in the GL FHL, and LCL, and Fitzpatrick skin type, as well as the baseline values of the efficacy assessments, PFWS, PHFWS, PLCWS, IGA-FWS, IGA-FHWS, and IGA-LCWS. Summaries will be produced for the Enrolled population. If the Safety population differs from the Enrolled population, then the summaries will be produced for each.

6.3 Medical History

Medical history will be classified on the basis of MedDRA terminology, using the latest terminology at the time of database finalization. Medical history will be summarized for the Safety population by system organ class, and by preferred term; and, will be listed.

6.4 Prior and Concomitant Medications

Prior therapies/medications and concomitant therapies/medications will be coded using the World Health Organization (WHO) drug dictionary and summarized by Anatomical Therapeutic Chemical (ATC) second level term and Preferred Name for the Safety population. Prior and concomitant medications will be summarized separately.

6.5 Efficacy Analyses

Descriptive statistics will be provided for all efficacy variables at all visits. A 95% exact CI will be provided for proportions. All analyses displaying proportions will use population counts as denominators at all visits regardless of the number of actual observations recorded. As this is an open-label study with no placebo comparator arm, no formal hypothesis tests are planned.

[redacted]

[redacted]

6.6 Safety Analyses

Safety summaries and analyses will be performed on the Safety population and will be presented overall. Descriptive statistics will be presented to summarize the safety data. By visit safety summaries will use denominators based on the number of subjects with valid observations at that visit unless otherwise specified.

6.6.1 Extent of Exposure

All subjects are planned to receive three treatments of investigational product (GL, FHL and LCL treatments). The dosage of investigational product injected and the dose of investigational product injected at each of the injection sites will be summarized overall for each administration using descriptive statistics (number of non-missing observations, mean, median, first and third quartiles, minimum, maximum, and standard deviation).

6.6.2 Injection Site Evaluations

The injection site evaluations for GL, FHL, and LCL will be summarized separately using number and percentage of subjects with a reaction at any post-treatment visit. In addition, the number and percentage of subjects experiencing an AE of special interest related to GL, FHL, and LCL injection site reactions will be summarized by system organ class and preferred term.

6.6.3 Adverse Events

All AEs will be recorded and classified on the basis of MedDRA terminology. All treatment-emergent AEs will be summarized by system organ class, preferred term, severity, and seriousness. When summarizing events by causality and severity by subject, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest relationship and highest severity within each classification. Additionally, some summaries will present the number of AEs as well as incidence.

An overall summary of treatment-emergent AEs (TEAEs) will be provided. The number and percentage of subjects experiencing an AE, an SAE, a related AE, a related SAE, an AE of special interest, an AE leading to study discontinuation, and an AE resulting in death will be summarized.

Individual summaries will be presented as follows:

- TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- TEAEs by system organ class, preferred term, and severity
- Serious TEAEs by system organ class, preferred term, and severity
- Related TEAEs by system organ class and preferred term
- Serious Related TEAEs by system organ class and preferred term
- TEAEs of special interest (distant spread of toxin) by system organ class and preferred term
- TEAEs leading to study discontinuation by system organ class and preferred term
- TEAEs resulting in death by system organ class and preferred term
- Serious AEs occurring during the screening period by system organ class and preferred term
- Non-Serious TEAEs by system organ class and preferred term occurring in >5% of subjects (for clinicaltrials.gov posting)

All information pertaining to AEs noted during the trial will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding trial drug, corrective treatment, outcome, and drug relatedness. The event onset relative (in number of days) to the date of treatment, as well as to the date of last treatment administration prior to the event, will be provided. In addition, a list of adverse events that lead to the subject's premature discontinuation of the trial will be provided. Serious adverse events (SAEs) will be listed by subject.

6.6.4 Laboratory Tests

6.6.4.1 Clinical Safety Laboratory Parameters

Laboratory test results will be summarized with descriptive statistics by visit. Change from baseline to post-baseline visits will be summarized for continuous test results. A summary of abnormal urinalysis incidence will be presented displaying normal, abnormal (not clinically significant), and abnormal (clinically significant) results.

Shift tables will be presented to summarize laboratory test results at Baseline and Final Evaluation Visit. Normal ranges established by the central laboratory will be used to determine shifts. A listing of all out-of-range laboratory test results at any evaluation will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by the investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

6.6.4.2 Pregnancy Tests

Urine pregnancy tests will be presented in data listings for all treated subjects in the category of woman of child-bearing potential.

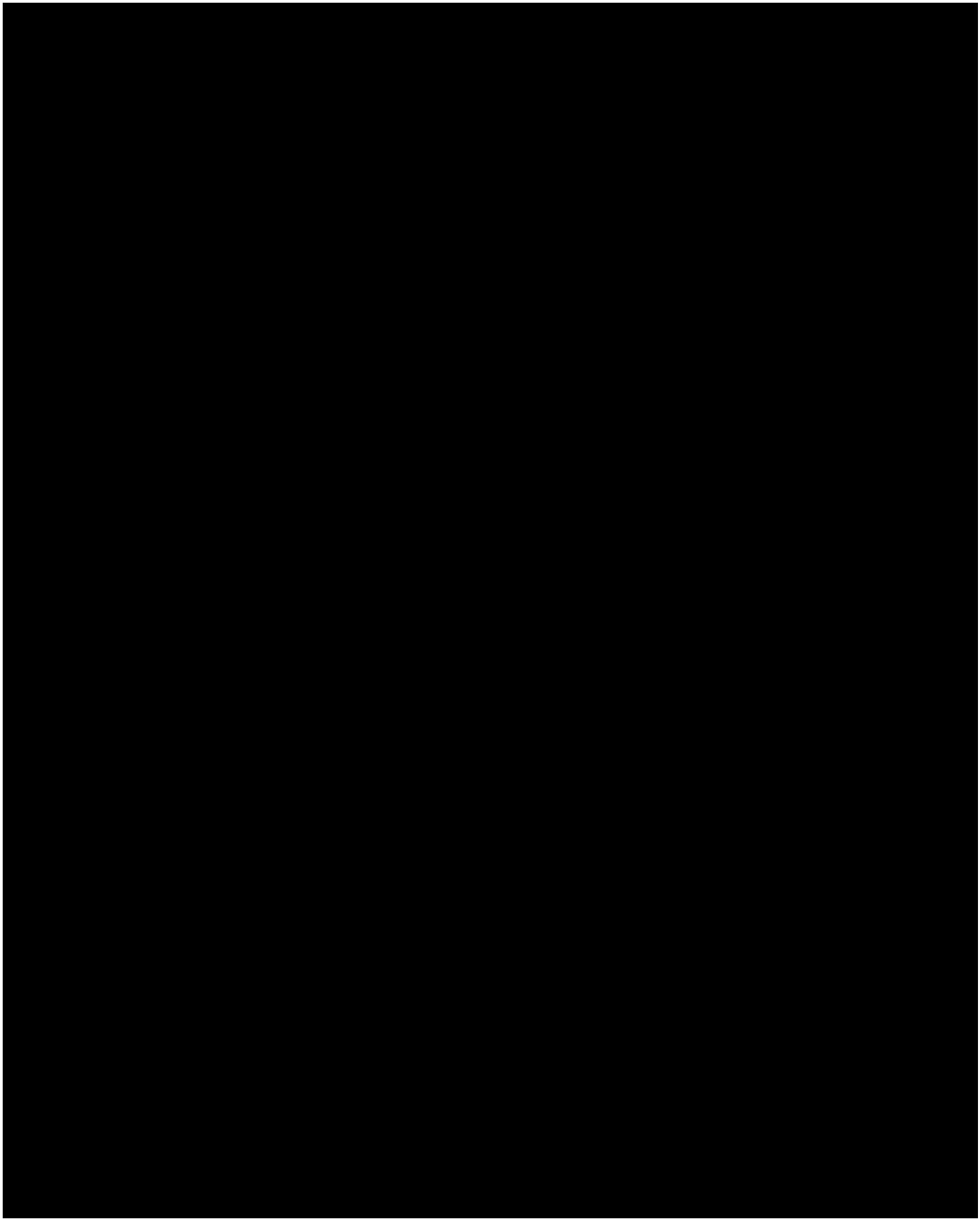
[redacted]

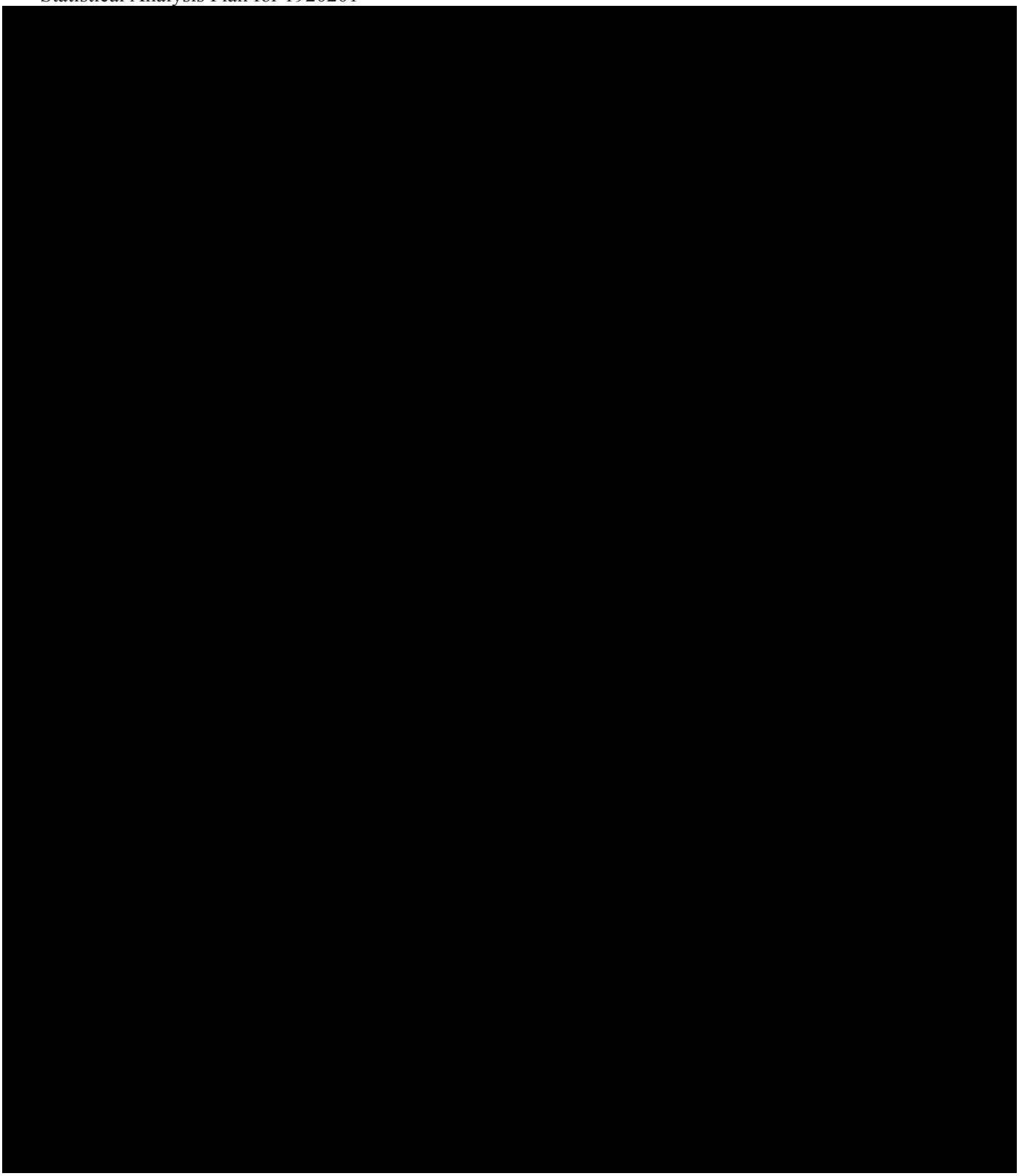
6.6.6 Vital Signs and Physical Examination

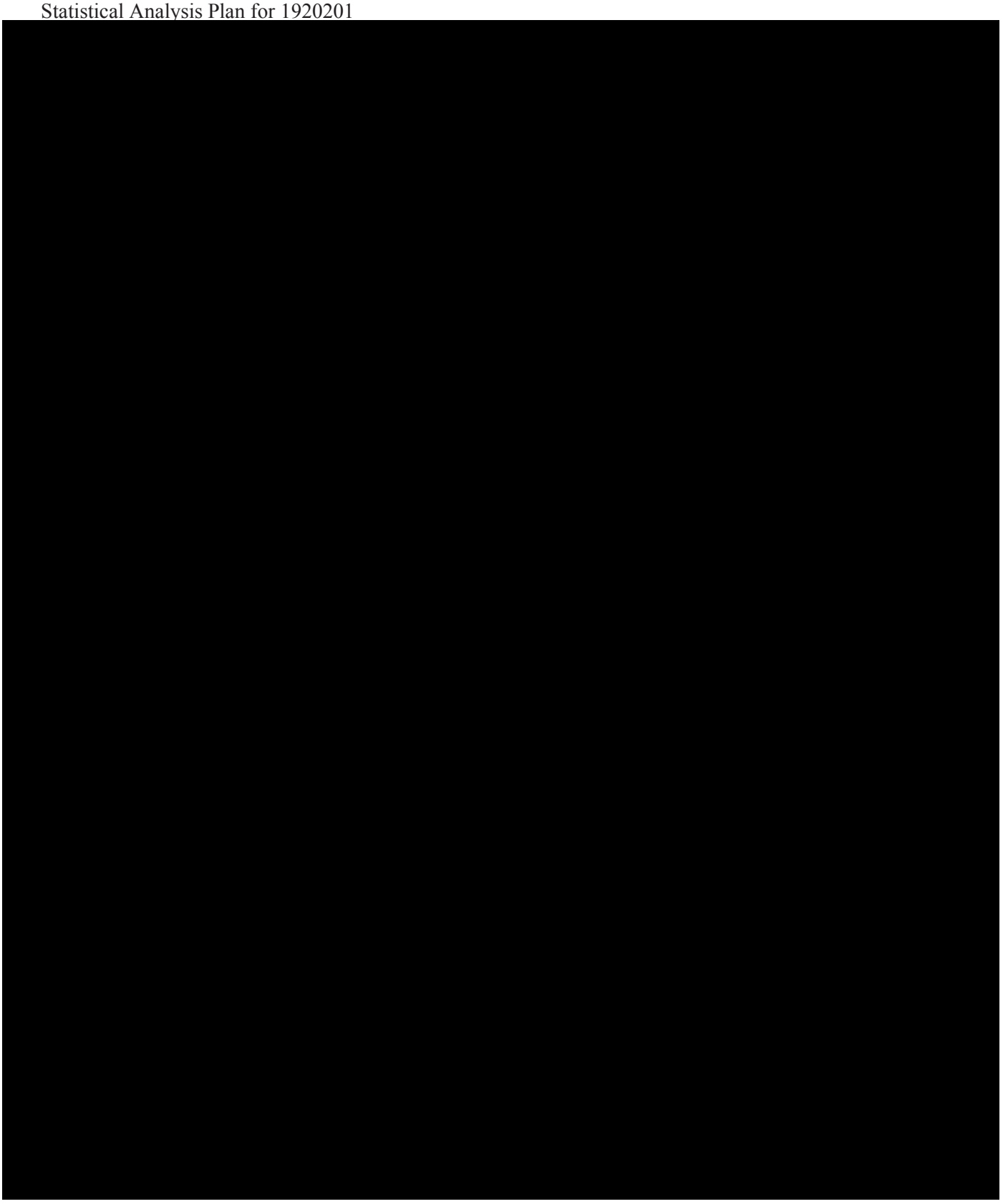
Vital signs will be summarized with descriptive statistics by visit. Vital signs will summarize the actual value as well as the change from baseline for each visit for continuous parameters.

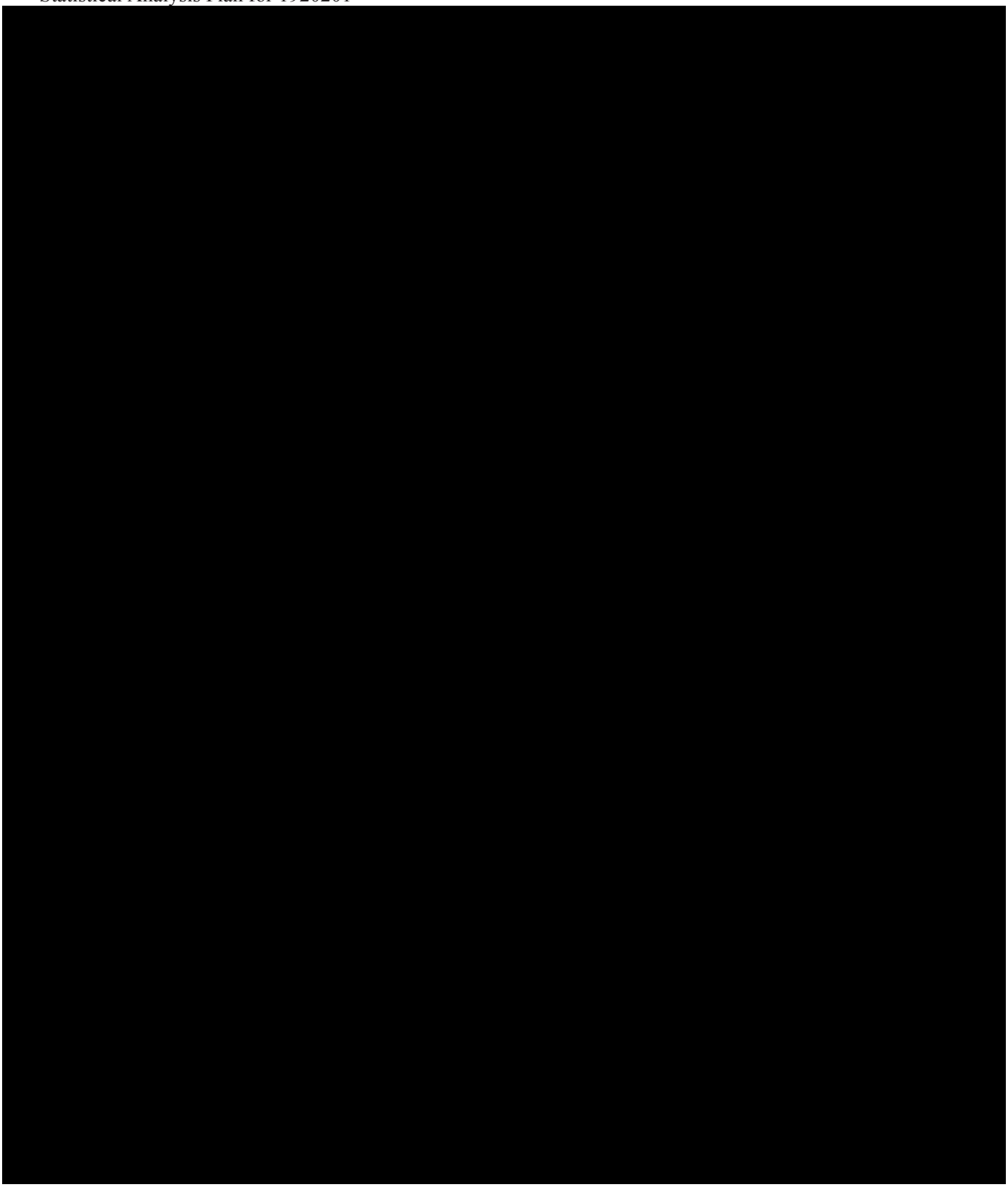
Abnormal findings from the physical examination will be summarized by body system using number and percentage of subjects with a normal, abnormal and clinically significant, or abnormal and not clinically significant result.

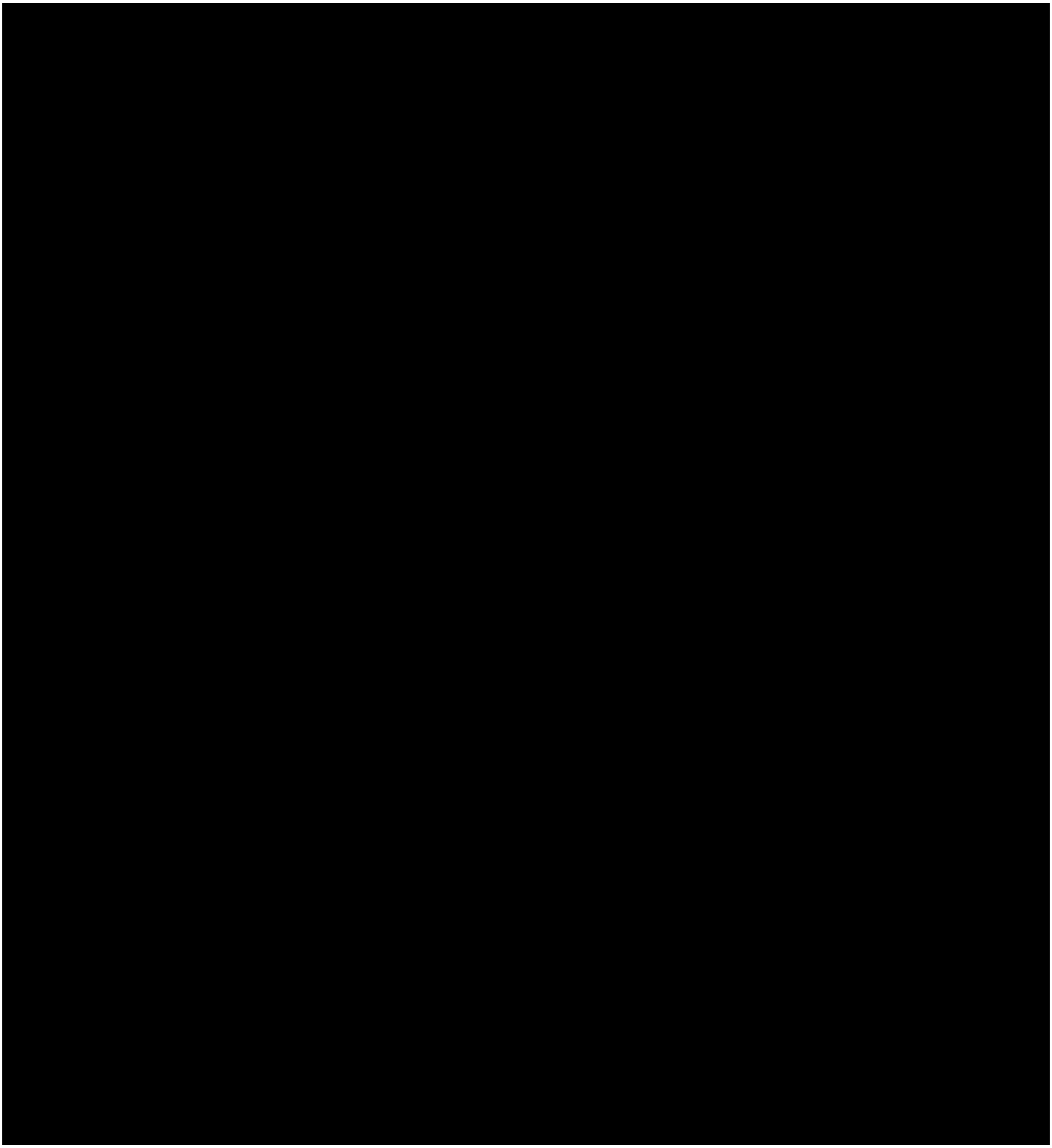
[redacted]

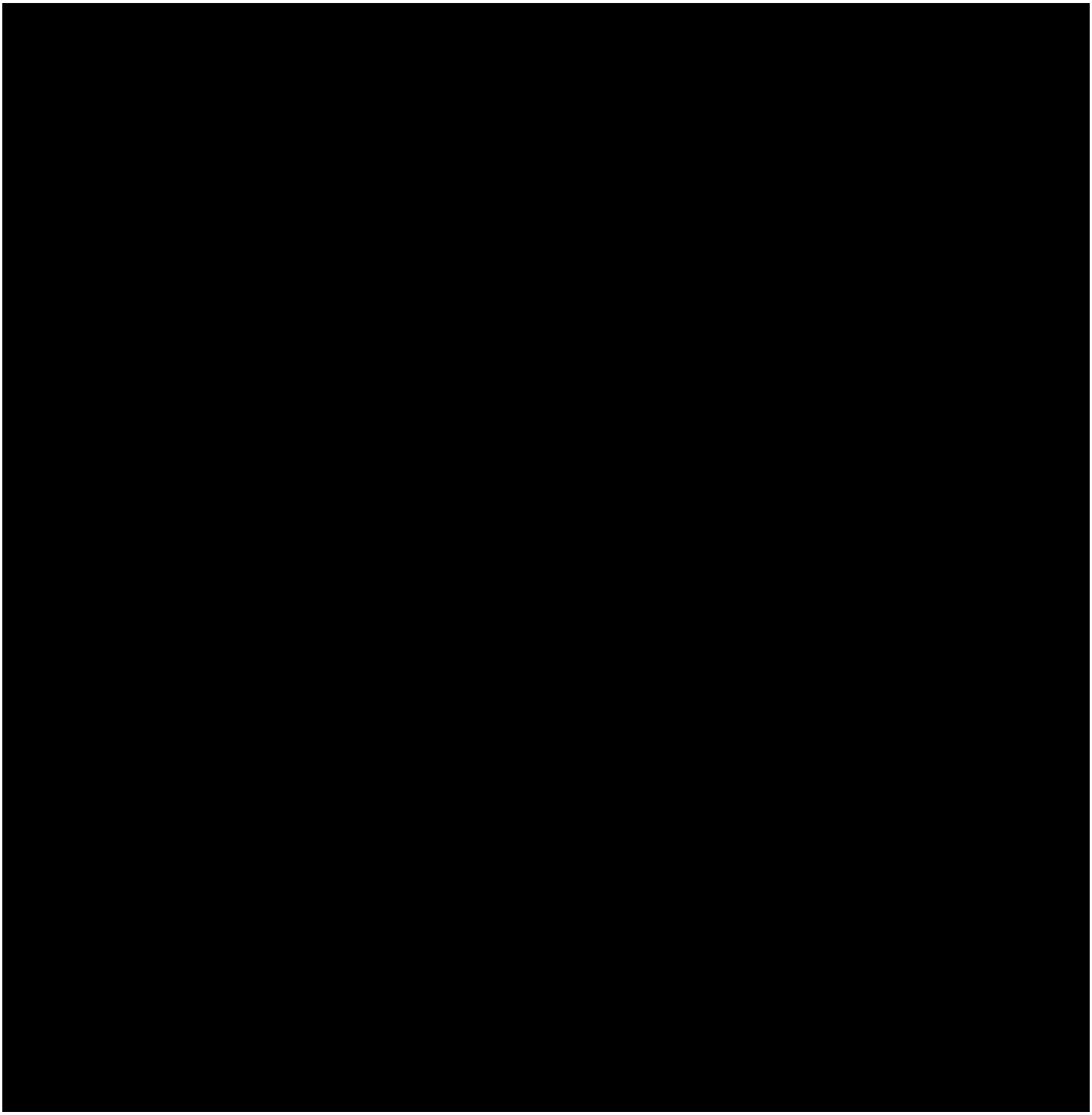




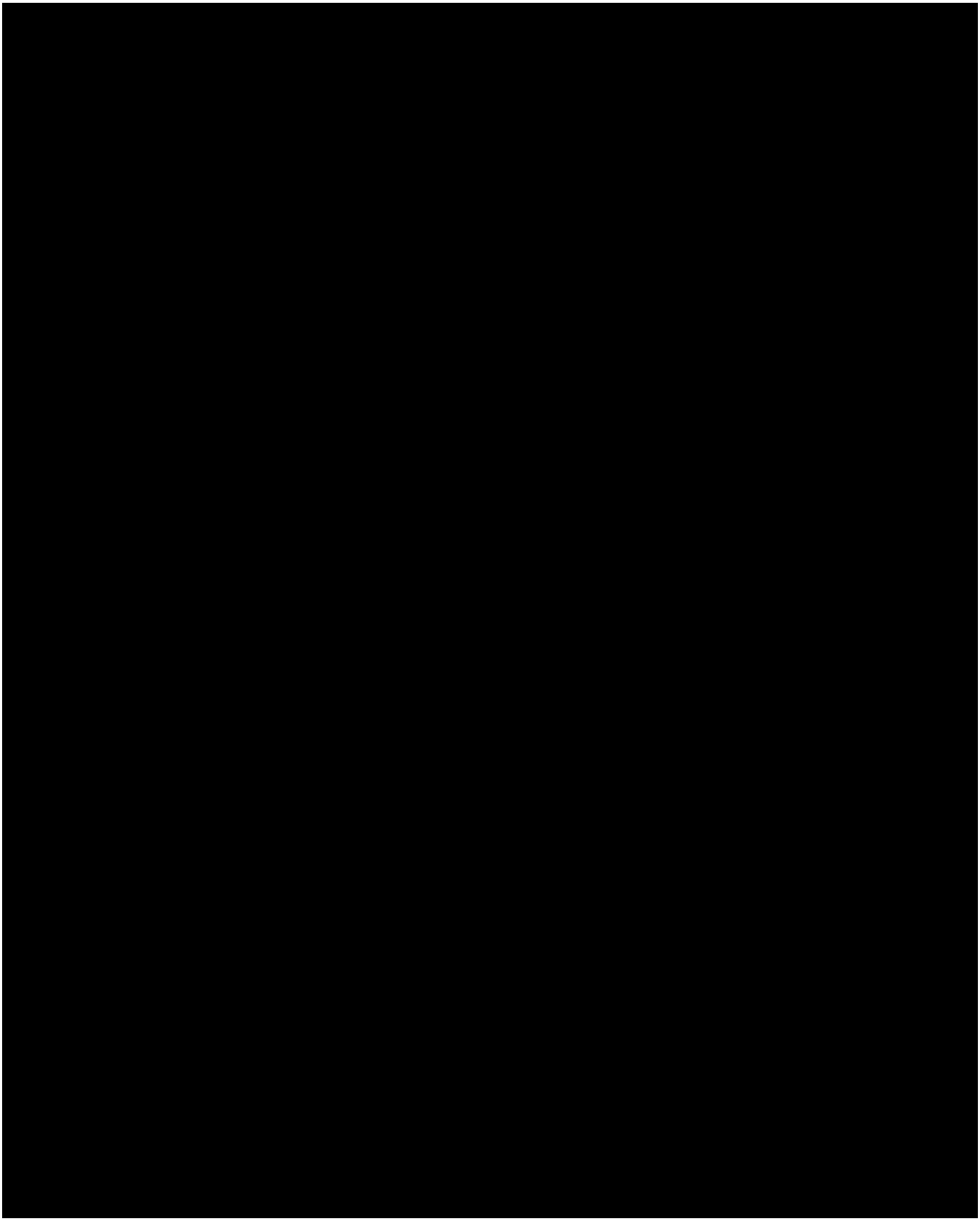




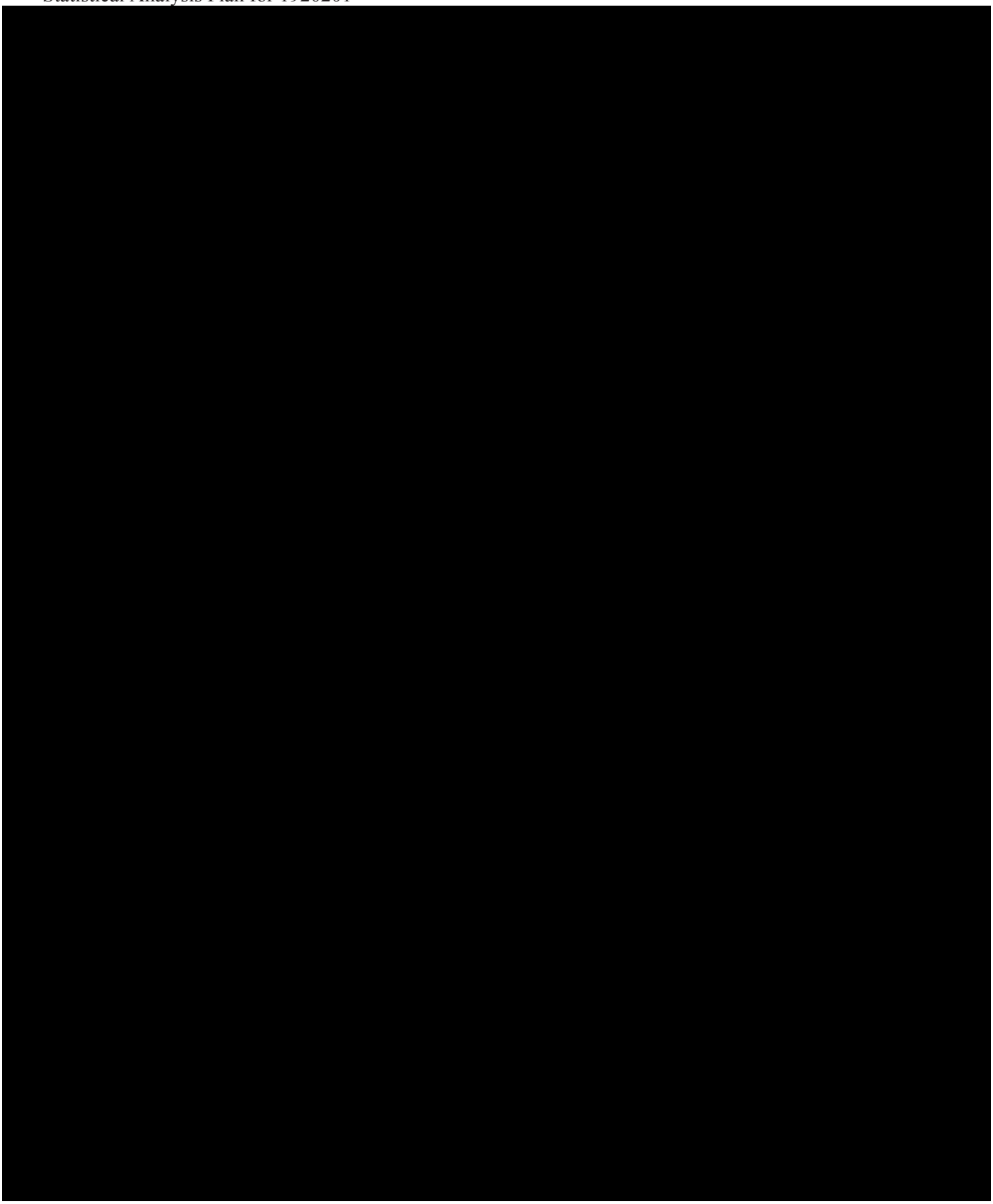




[redacted]

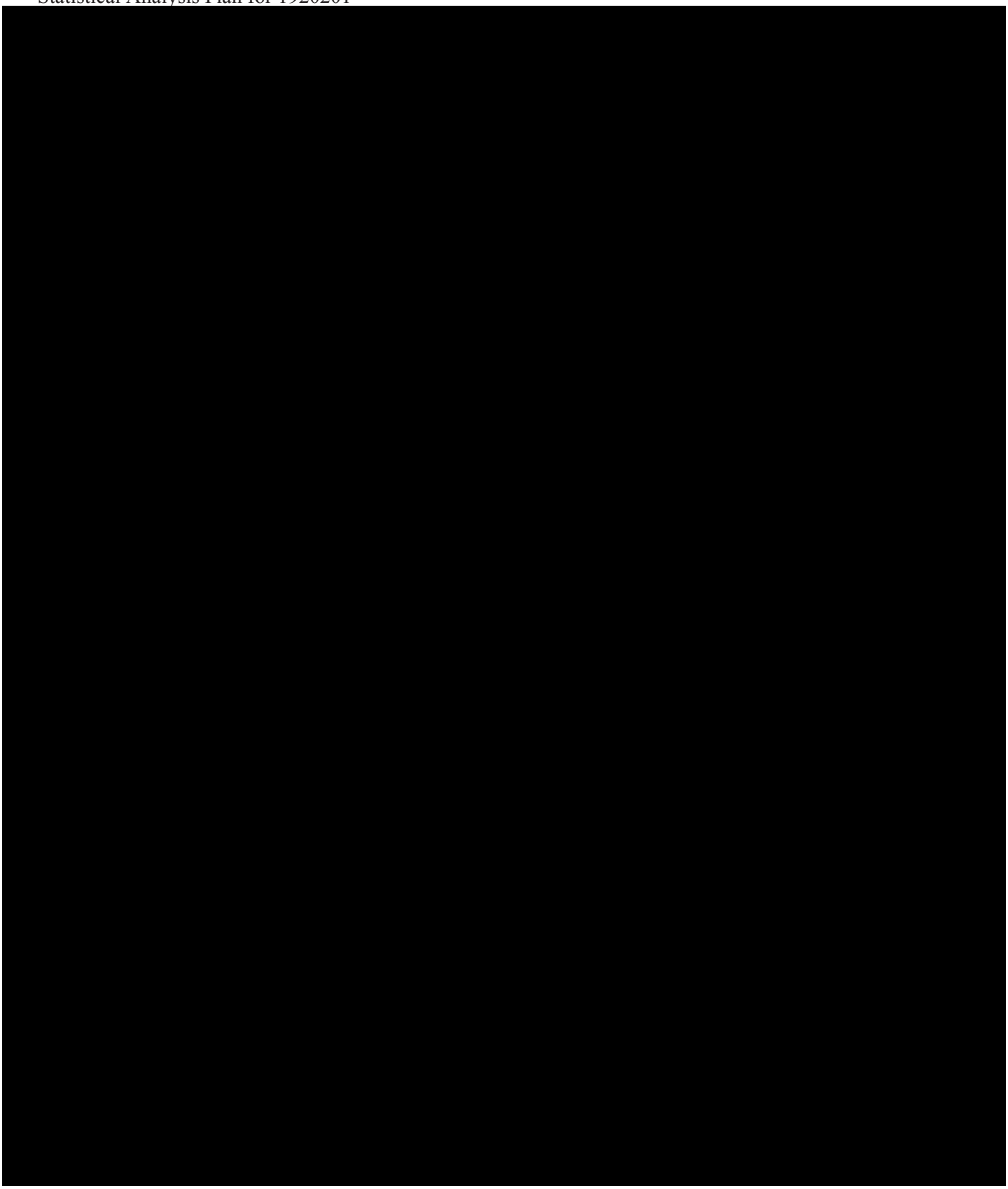


[redacted]



[redacted]

[redacted]



[redacted]