CLINICAL PROTOCOL

Title of Study: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis

Protocol Number: **RT002-CL008**

Version: **Amendment 3**

Date: **13 January 2017**

Sponsor: Revance Therapeutics, Inc.
7555 Gateway Blvd.
Newark, CA 94560
Phone: 1-510-742-3400

Study Center: Wake Forest School of Medicine
Medical Center Blvd.
Winston-Salem, NC 27006
Phone: 1-336-716-2878

Study Monitor: [redacted]

Lead Clinical Investigator: L. Andrew Koman, MD
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The study will be conducted in compliance with the obligations as detailed in this protocol, and all applicable regulations and guidelines (e.g., International Conference on Harmonisation Good Clinical Practices guidelines).

INVESTIGATOR'S AGREEMENT

I have carefully read the protocol entitled: "*A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis*" and,

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, in compliance with all applicable laws and regulations, and in accordance with the ethical principles stipulated in the Declaration of Helsinki.

_____
Investigator (Signature)

_____ _____
Printed Name Date

_____
Institution Name

_____
Address

_____ _____
City, State Zip Code Phone Number

Study Synopsis

Title of Study:	A Prospective, Randomized, Double-Blinded, Placebo-Controlled Trial of DaxibotulinumtoxinA for Injection for the Management of Plantar Fasciitis
Study Type:	Phase 2
Study Center(s):	Up to 2
Study Design:	Prospective, double-blinded, randomized, placebo-controlled clinical trial
[redacted]	[redacted]
Objective:	The specific aim of the study is to compare the safety and efficacy of a single administration of DaxibotulinumtoxinA for Injection versus placebo for managing plantar fasciitis
Study Population:	Male and female adult subjects who have plantar fasciitis that has not responded to conservative treatment modalities
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Number of Subjects:	Sixty subjects (60) will be randomly assigned to one of two study groups: - Group 1 subjects (n=30) will receive active daxibotulinumtoxinA injections - Group 2 subjects (n=30) will receive placebo vehicle-only injections.
Duration of Study:	Total length of time required to complete study: 6–12 months.

Total length of subject follow-up: 4 months.

Inclusion criteria:

1. Written informed consent, including authorization to release health information
2. Skeletally mature, male or female patients 18 to 65 years of age with diagnosis of unilateral plantar fasciitis by physical examination and/or ultrasonography
3. Unilateral plantar fasciitis as defined as no symptoms or signs in the contralateral foot with no sought medical attention in the contralateral foot
4. Persistent heel pain for more than three months

[redacted]

Exclusion criteria:

1. No previous injections of botulinum toxins
2. Entrapment of the posterior tibial, lateral plantar, or medial plantar nerve (local nerve entrapment)
3. Fixed hindfoot varus
4. Posterior tibial tendon dysfunction
5. Severe pes planus
6. Midfoot collapse
7. Significant talar or navicular callus
8. Tarsal coalition or rigid flatfoot
9. Systemic disease associated with foot pain
10. Sciatica
11. Severe osteoarthritis of the forefoot, midfoot, or ankle
12. Aminoglycoside therapy
13. Peripheral vascular disease
14. Rheumatoid arthritis
15. Poorly controlled diabetes mellitus (hemoglobin A1C greater than 8%)
16. Previous surgery on the midfoot or hindfoot
17. Spasticity
18. Neuromuscular disease
19. Systemic muscle weakness
20. Fibromyalgia
21. Allergy or sensitivity to any components of the study treatments
22. Comorbidities that confound the evaluation of the feet

[redacted]

[redacted]

Conduct of Study: Prospective, randomized, placebo-controlled, double-blinded study.
[redacted]

Criteria for Evaluation:

Primary Safety Endpoint

- Adverse events associated with the two study treatments

Primary Outcome Endpoint

- Improvement in the American Orthopaedic Foot and Ankle Score (AOFAS)

[redacted]

Statistical Methods: Study data will be analyzed according to each subject's randomization assignment. All evaluable data will be included in the analysis following the intent-to-treat principle. The primary analysis will focus on the improvement in the AOFAS.

[redacted]

Sample Size: Based upon the design of similar proof of concept trials, a total of 60 subjects will be enrolled in the clinical trial. [redacted]

PROTOCOL

Background

Ten percent of the general population experiences heel pain or plantar fasciitis during their lifetime (Babcock, 2005). Heel pain is the most common chief complaint of patients who present to podiatrists and orthopaedic foot and ankle surgeons. Plantar fasciitis, the most common etiology of heel pain, causes significant discomfort and negatively impacts the health-related quality of life of affected individuals.

Plantar fasciitis is a self-limiting condition for many patients (Monteagudo, 2013). However, 10% of patients continue to experience symptoms for six to nine months or more. The cause of plantar fasciitis is multifactorial and incompletely elucidated (League, 2008; Monteagudo, 2013). Age, high body mass index, abnormal foot posture, use of poor foot wear, and repetitive trauma have all been suggested as risk factors (League, 2008). Treatment options include: leg/foot stretching exercises, manual therapy, taping, night splints, electrotherapy, phonophoresis, ultrasound, shoe inserts, heel pads, steroid injections, botulinum toxin injections, extracorporeal shock wave therapy, platelet rich plasma injections, and surgery (Martin, 2014).

The principal investigator theorized over a decade ago the potential efficacy of using botulinum toxin in the management of plantar fasciitis (Seyler, 2008). Our experience and the results of five clinical trials (Babcock, 2005;Diaz-Llopis, 2012;Diaz-Llopis, 2013;Elizondo-Rodriguez, 2013;Huang, 2010) have documented the potential efficacy of botulinum toxin in managing the symptoms of plantar fasciitis.

[redacted]

Pathophysiology/Biomechanics

Although the etiology of plantar fasciitis is understood incompletely, foot pain occurs with weight bearing and is accompanied by: 1) functional shortening of the short plantar muscles and plantar fascia; 2) tenderness at the insertion of the plantar fascia on the calcaneus (with or without a spur); and 3) shortening/tightening of the gastrocnemius/soleus (equinus). In addition, the plantar nerves may become entrapped or inflamed.

Diagnosis

Symptoms

- Foot pain with weight bearing (classically more pain is experienced in the morning than in the afternoon)
- Tenderness associated with pressure on the plantar arch

Signs

- Tenderness of the plantar fascia
- Tenderness at the calcaneus
- Relative equinus contracture of the ankle (with the hind foot stabilized)
- Reproduction of pain with palpation of the proximal insertion of the plantar fascia
- Positive Tinel's sign for the posterior tibial, medial plantar, and/or lateral plantar nerves (exclusion finding)

Overview of Treatment Options

Stretching Therapy: Stretching of the plantar fascia and gastrocnemius/soleus complex is a home program that can be performed by patients after instructions are provided by their physician or under supervision by a physical therapist (Martin, 2014). The optimal frequency and duration of stretching exercises has not been established, and there are no well controlled studies documenting its efficacy (League, 2008).

Shoe Inserts/Orthoses*:* Shoe inserts and orthoses are used frequently to decrease the biomechanical forces on plantar structures during loading of the foot during gait (Neufeld, 2008). These devices modify the shape of the heel pad, reduce the load on the plantar fascia, and decrease excessive pronation (Neufeld, 2008). In a randomized, controlled trial evaluating subjects experiencing symptoms of plantar fasciitis for less than six months, treatment with four types of prefabricated shoe inserts were compared with custom orthotics (Pfeffer, 1999). All subjects also participated in a stretching program. The study concluded that the use of a "…prefabricated shoe insert is more likely to result in reduced symptoms as part of the initial treatment of proximal plantar fasciitis than a custom polypropylene orthotic device." Current recommendations include the use of orthoses for support of the medial longitudinal arch in order to provide cushioning for the heel and reduce pain (Martin, 2014). However, orthoses should be cautiously prescribed for patients who stand for long periods.

Steroid Injections: Steroid injections are used frequently in the management of plantar fasciitis. Results are variable, and side-effects including subcutaneous fat pad atrophy, plantar fascia rupture, peripheral nerve injury, muscle damage, transient hyperglycemia (in diabetic patients), and injection site pain have been reported (Landorf, 2008; Uden, 2011). Because of the limited evidence to support the use of corticosteroid injections and due to the negative effects of the injections, steroid injections are not considered to be a first tier intervention (Martin, 2014). However, steroid injections are used with great frequency by foot/ankle physicians.

Extracorporal Therapy: The effectiveness of low energy extracorporeal shock wave therapy in reducing night pain, resting pain, and pressure pain is supported in case studies (Park, 2014) and randomized placebo-controlled trials (Vahdatpour, 2012). The procedure is painful, requires sedation or anesthesia, and is expensive. The evidence supporting the use of extracorporal shockwave therapy is conflicting due to inconsistencies in clinical trial methodology (League, 2008). Recent guidelines noted that stretching and therapeutic ultrasound is more effective in reducing pain than extracorporal shockwave therapy (Martin, 2014).

Botulinum Toxin: Botulinum toxins have been used as injectable agents in the management of refractory plantar fasciitis without complication and with demonstrable clinical efficacy. In two randomized trials, plantar foot toxin injections were compared to placebo in 27 subjects (Babcock, 2005) and to steroid in 28 subjects (Diaz-Llopis, 2012; Diaz-Llopis, 2013). Both studies demonstrated that the toxin injections provided pain relief. In a third trial (36 subjects), gastrocnemius-soleus toxin injections and stretching were compared to steroid injections in the plantar foot and stretching (Elizondo-Rodriguez, 2013). The combination of toxin injections and plantar fascia stretching exercises resulted in reduced symptoms and improved activities of daily living compared to the steroid injections alone. The fourth study evaluated (50 subjects) who received either toxin or placebo delivered by ultrasound guidance (Huang, 2010). Subjects in the toxin group experienced pain relief while subjects receiving placebo reported no change in their pain levels.

Surgery: About 10% of patients do not respond to conservative treatment modalities within six to nine months (Monteagudo, 2013; Neufeld, 2008). If conservative treatment fails and symptoms are intractable, several surgical procedures are available (Monteagudo, 2013; Neufeld, 2008). Surgical options include release of the plantar fascia at the midsection or proximally; proximal release of the plantar fascia and ostectomy of the calcaneal spur; endoscopic plantar fasciectomy; and recession of the gastrocnemius and/or soleus (Davies, 1999; League, 2008; Monteagudo, 2013; Sammarco, 1996). However, no randomized, controlled clinical trials have compared the outcomes of nonsurgical treatments with surgery, and there are insufficient clinical data to support the use of surgery (League, 2008; Neufeld, 2008).

[redacted]

Specific Aims

Heel pain associated with plantar fasciitis is produced by nociceptive foci within degenerative plantar fascia adjacent to and distal to its origin. Shortening of the plantar fascia occurs during sleep and inactivity; however, the forces precipitated by standing stress the degenerative fascia and produce pain. It is unknown whether the adaptations within the gastrocnemius-soleus complex (triceps surae) producing shortening of muscle fibers is primary or secondary; however, reestablishment of the length of the Achilles tendon decreases forces within the plantar fascia. [redacted]

The specific aims of this study are 1) to compare the safety and efficacy of DaxibotulinumtoxinA for Injection versus placebo for managing plantar fasciitis; 2) to evaluate the impact of DaxibotulinumtoxinA for Injection on function, quality of life and utility, and 3) to determine appropriate power for additional trials.

[redacted]

[redacted]

Study Design

The study is designed as a prospective, randomized, placebo-controlled, double-blinded clinical trial to compare DaxibotulinumtoxinA for Injection and placebo injections for the management of plantar fasciitis signs and symptoms.

[redacted]

Study Population

Adult male and female patients who have been diagnosed with plantar fasciitis that has not responded to conservative treatment modalities for three months will be enrolled in these clinical trials.

All patients who present with plantar fasciitis who meet the study inclusion/exclusion criteria will be asked to participate in the study. If patients agree to participate and provide informed consent, they will be enrolled in the study and randomized to one of the two study treatments.

[redacted]

Inclusion criteria

1. Written informed consent, including authorization to release health information
2. Skeletally mature, male or female patients 18 to 65 years of age with diagnosis of unilateral plantar fasciitis by physical examination and/or ultrasonography
3. Unilateral plantar fasciitis as defined as no symptoms or signs in the contralateral foot with no sought medical attention in the contralateral foot
4. Persistent heel pain for more than three months

[redacted]

Exclusion criteria

1. No previous injections of botulinum toxins
2. Entrapment of the posterior tibial, lateral plantar, or medial plantar nerve (local nerve entrapment)
3. Fixed hindfoot varus
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11. Severe osteoarthritis of the forefoot, midfoot, or ankle
12. Aminoglycoside therapy
13. Peripheral vascular disease
14. Rheumatoid arthritis

15. Poorly controlled diabetes mellitus (hemoglobin A1C greater than 8%)
16. Previous surgery on the midfoot or hindfoot
17. Spasticity
18. Neuromuscular disease
19. Systemic muscle weakness
20. Fibromyalgia
21. Allergy or sensitivity to any components of the study treatments
22. Comorbidities that confound the evaluation of the feet

[redacted]

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

Informed Consent

If a subject meets the study entry criteria, the study will be presented to them. A thorough explanation of the study will be provided to the patient, and adequate time will be allowed to ask questions about potential study participation. [redacted] Once the patient has been fully informed, they will be asked to sign the IRB approved study consent form and become a study subject.

The informed consent document will adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, as well as the elements required by the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guideline, and applicable federal and local regulatory requirements. The consent form must also include a statement that the sponsor, their designees, and auditing regulatory agencies will have direct access to the subject's records and medical history for study related purposes.

The subject will be given a copy of the signed informed consent document with the original kept on file by the Investigator. All of the above activities must be completed before any study related procedures are conducted (including any screening study procedures).

[redacted]

Sample Size Estimate

The clinical trial is designed to evaluate the safety and efficacy of DaxibotulinumtoxinA for Injection for the management of plantar fasciitis. Based upon published peer review trials, 60 subjects will be enrolled. [redacted]

[redacted]

[redacted]

Study Procedures/Study Interventions

All clinical laboratory assessments will be conducted locally at the clinical site facilities.

Screening: Subjects presenting with heel pain will be examined to verify the diagnosis of plantar fasciitis. Then, subjects with plantar fasciitis will be screened to determine if they meet the study eligibility criteria. Prospective study participants will be informed of the study, and the requirements for study participation will be explained to them. [redacted]

[redacted]

In addition, they will undergo an examination of both feet. [redacted]

[redacted]

Injection Visit: After consent and randomization, Vital signs [Blood Pressure (BP), Heart Rate (HR), Pulse and Temperature] are taken prior to and following study drug administration. [redacted]

Follow-up: [redacted] Acceptable study visit windows can be ±3 days. [redacted]

Outcome Measures

Primary safety endpoint

- Adverse events associated with the two study treatments

Primary outcome measure

- Improvement in the American Orthopaedic Foot and Ankle Score (AOFAS)

[redacted]

American Orthopaedic Foot and Ankle Score (AOFAS)

The American Academy of Orthopaedic Surgeons developed several musculoskeletal outcomes instruments to collect patient based data to use to assess the effectiveness of treatments and to study the clinical outcomes of the treatments. The AOFAS foot and ankle questionnaire was designed for use in patients 18 years old and older. This questionnaire documents patient assessments of foot and ankle conditions and improvements resulting from treatments. Disability indices for the lower limb core, global foot and ankle function, and shoe comfort can be evaluated using this instrument. The questionnaire requires about 10 minutes to complete.

[redacted]

[redacted]

Study Discontinuation

Screen failures: A screen failure occurs when a subject for whom informed consent is obtained: 1) does not meet inclusion/exclusion criteria, 2) the study randomization was not completed, or 3) the subject withdraws consent for study participation.

Subject discontinuation: Study participants may end their study participation at any time for any reason. When subjects withdraw from the study, the reason for their discontinuation will be documented. Subjects who end their study participation early will not be replaced, and the reason for their study discontinuation will be documented.

Subjects who do not complete the study who cannot be contacted and have no reason for their discontinuation will be classified as "lost to follow up." Three attempts will be made to contact the subjects by phone or email. If the subject cannot be reached, then certified mail will be used to contact them.

Adverse Events (AE)

The study will evaluate and document any adverse events associated with the use of the injectable botulinum toxin or placebo used in the clinical trial.

Illness or pre-existing conditions that are present before the study is initiated which continue to have the same severity, frequency, or duration after the toxin treatment will not be recorded as AEs. However, if there is an increase in severity or duration of the symptoms associated with the illness or pre-existing condition, these events will be reported as AEs.

[redacted]

INJECTION SITE EVALUATION

The injection sites will be evaluated at Treatment Visit (Day 0) pre- and post-treatment (to determine if there is an immediate reaction to the investigational product), Follow-up Visits (3/Wk1, 4/Wk2, 5/Wk4, 6/Wk6) and End-of-Study Visit (7/Wk16) or Early Discontinuation Visit, if applicable. The assessment will be done as a global evaluation of the injection sites (Table 1).

Table 1: Injection Site Evaluation

Assessment Descriptor	Present?	
	Yes	No
Erythema		
Edema		
Burning or Stinging (sensation as described by subject)		
Itching (sensation as described by subject)		

[redacted]

[redacted]

If a subject is experiencing any such symptoms they are to be recorded on the AE page [redacted]

[redacted]

Definitions Related to Adverse Events:

For this protocol, an **adverse event (AE)** is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, abnormal laboratory finding, injury or accident) that emerges or worsens following administration of investigational product and until the end of study participation. The untoward medical occurrence may not necessarily have a causal relationship to the administration of the investigational product. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory result), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A **pre-existing condition** is one that is present prior to treatment and is to be reported as part of the subject's medical history. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during the study.

An **unexpected AE** is one not identified in nature, severity, or frequency in the current protocol or Investigator's Brochure.

A **serious adverse event (SAE)** includes any event that results in any of the following outcomes:

- Death
- Life-threatening, (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred. It does not apply to an AE that hypothetically might have caused death if it were more severe)
- Persistent or significant disability/incapacity (i.e., the AE results in a substantial disruption of the subject's ability to carry out normal life functions)
- Requires in-patient hospitalization or prolongs hospitalization (i.e., the AE required at least a 24 hour in-patient hospitalization or prolonged a hospitalization beyond the expected length of stay. Hospitalizations for elective medical/surgical procedures, scheduled treatments, or routine check-ups are not SAEs by this criterion).

Any AE experienced by a study participant whether or not it is considered to be related to the study protocol will be documented. An AE can include subjective symptoms and/or objective findings. All AEs that occur during the study will be reported on study-specific case report forms and in the subject's electronic medical record. All AEs will be graded according to their severity (mild, moderate or severe).

Any AE that is associated with subject termination from the study protocol will be reported to the sponsor and our IRB within seven days of learning about the AE.

The investigator also will document their opinion as to whether the AE was related to the study product according to the following classification: 1) unrelated, 2) possibly related, 3) probably related, and 4) definitely related.

Study participants who have experienced an AE will be followed until the AE is resolved, the subject is lost to follow-up, or the AE is explained or stabilized.

All serious AEs will be reported immediately (within 48 hours) to the study sponsor and the IRB using a SAE form. The sponsor then will report the SAE to the medical monitor for the study. The SAE form will include the nature of the SAE, the time of onset relative to the use of the product, the duration and severity of the event, and whether or not the study was interrupted or the participant was discontinued as a result of the SAE.

Data Analysis

Data analysis will only be conducted on outcomes from subjects who were dosed. Study data will be analyzed according to each subject's randomization assignment. All evaluable data will be included in the analysis following the intent-to-treat principle. The primary analysis will focus on the improvement in the AOFAS. [redacted]

Data Management

The Department of Orthopaedic Surgery at Wake Forest School of Medicine will be responsible for data collection and data management.

Data Collection

All study data will be collected on approved case report forms (CRF). The data will be entered into a REDCap database that meets all HIPPA requirements, is backed up every 24 hours, and is located behind a firewall. Information that can be used to support the data collected on CRF's will be readily available to verify CRF entries.

[redacted]

[redacted]

Compliance with study protocol: The research coordinator will monitor the study participant compliance with the treatment protocols. Any deviations from the assigned treatment group or the actual treatment received by any study participant will be documented. Completion of follow-up visits also will be monitored. Subjects who miss study visits will be contacted and their visits rescheduled.

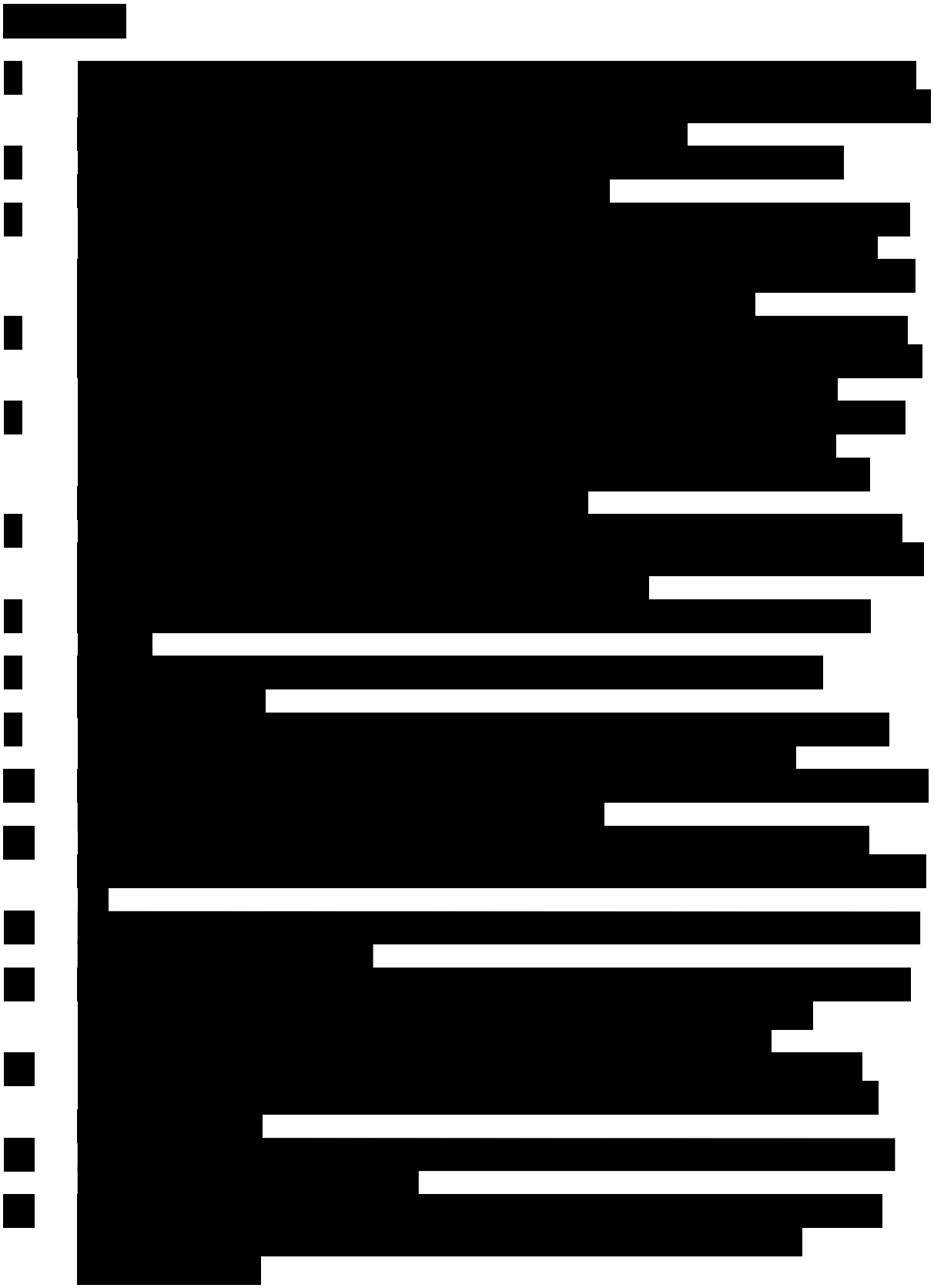
Study database: Expertise on study design, biostatistical analysis, and information management will be coordinated with the assistance of computer programmers and biostatisticians from the Department of Public Health Sciences at the Wake Forest School of Medicine.

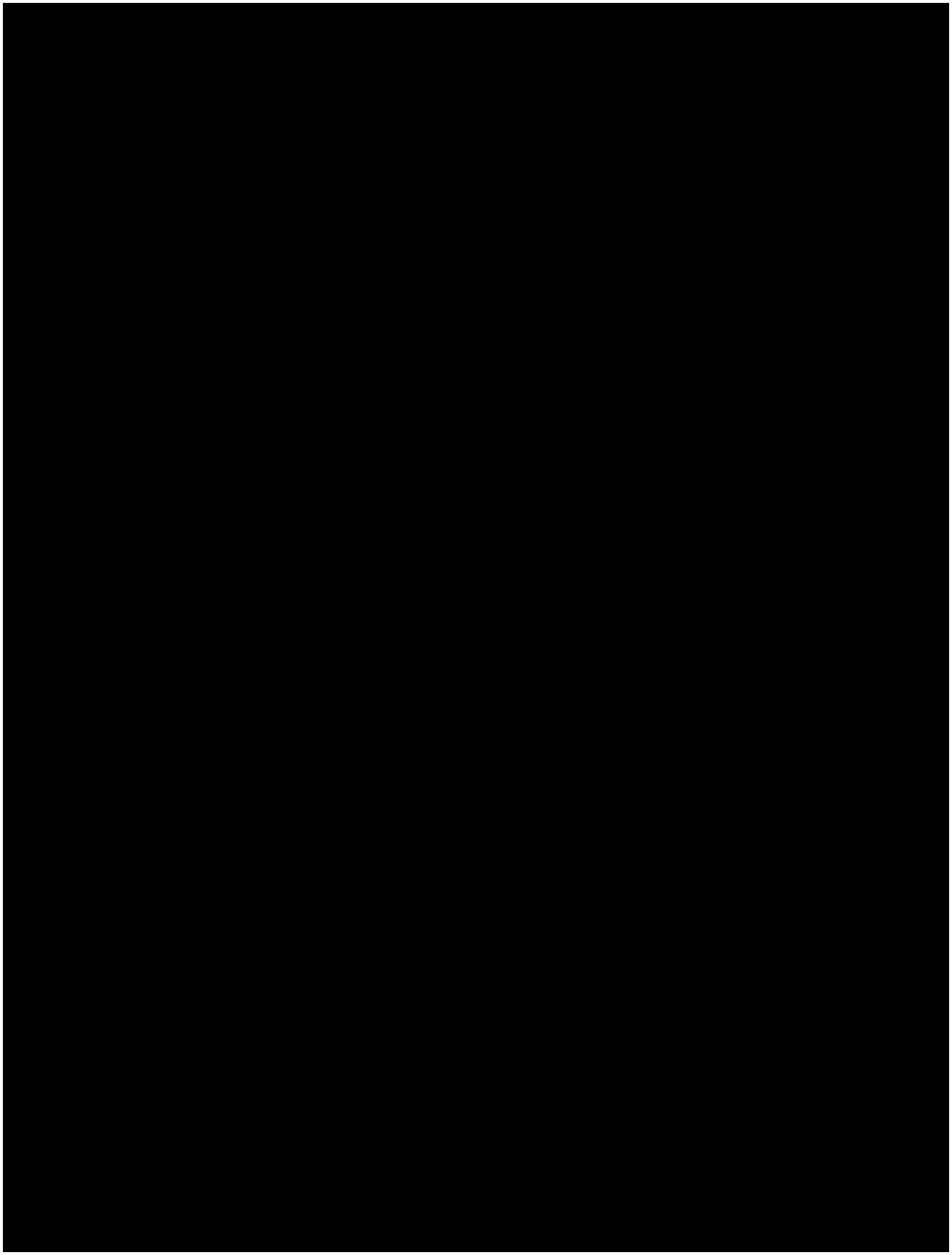
Treatment of Missing data: Some data elements will be missing in this study due to subjects who withdraw from the study, subjects who are lost to follow-up, or subjects who do not complete all study visits. The completion status of each subject will be documented (e.g., completed protocol, withdrew from study, lost to follow-up, etc.). Data from subjects for whom all study data is not complete will be included in the data analysis up until the time of

their withdrawal from the protocol. All reasonable efforts will be made by the study staff to maintain contact with the study participants during their participation in the study. The study coordinator will attempt to contact any subjects who are lost to follow-up. For subjects who are unwilling to return to clinic for follow-up, the study coordinator will attempt to contact them and to collect study data from them during a telephone call or by forms sent to them through the mail.

File Management and Records Retention: It is the responsibility of the Investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial. Documentation is subject to inspection by the sponsor and relevant regulatory agencies.

It is a sponsor requirement that all Investigators participating in clinical studies maintain detailed clinical data for one of the following periods: country-specific requirements, a period of at least two years following the last approval of a marketing application approved by a Regulatory Authority in an ICH region or until there are no pending or contemplated marketing applications in an ICH region, or a period of two years after sponsor notifies the Investigator that the data will not be submitted for review by any Regulatory Authority.





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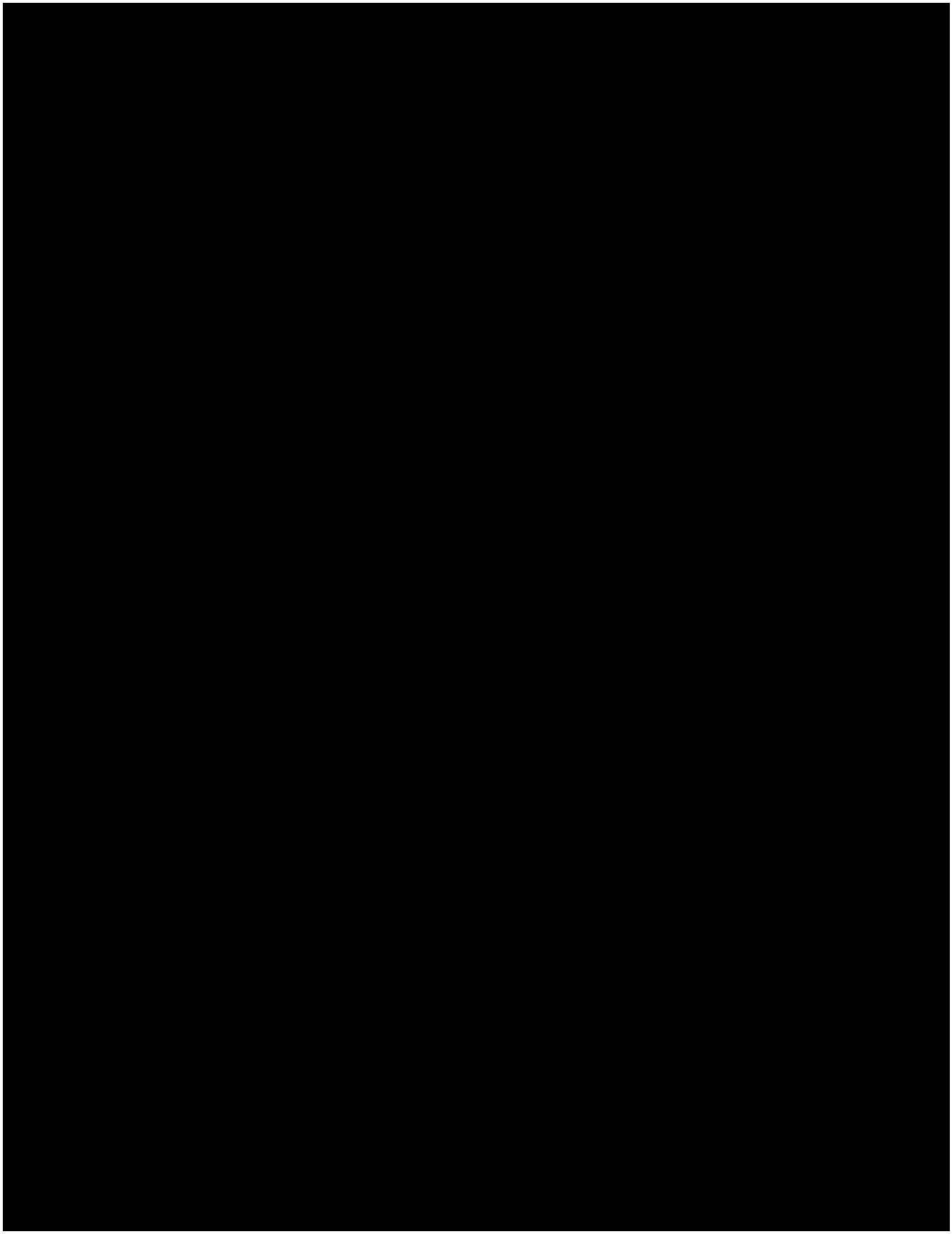

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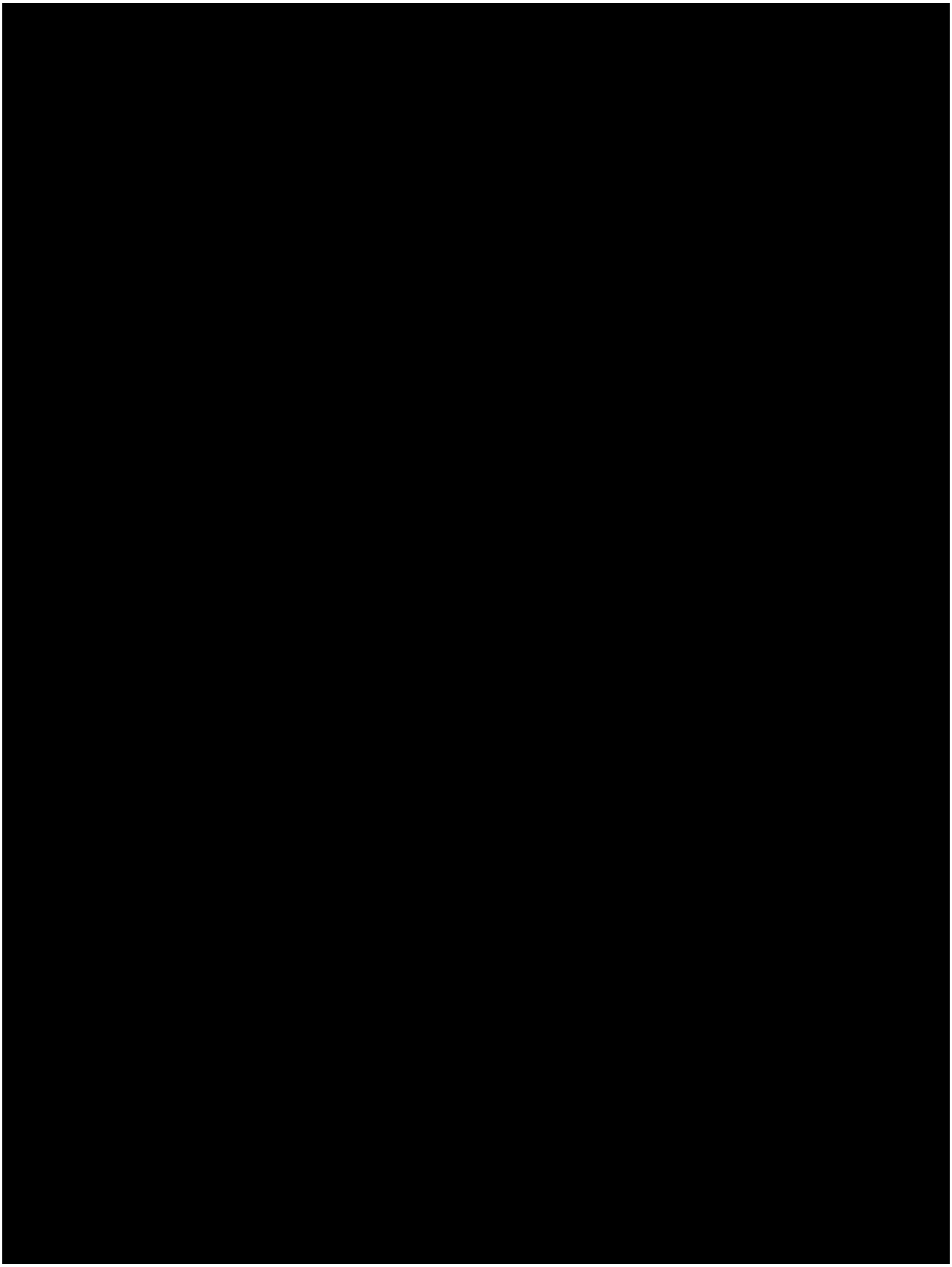

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