Boehringer Ingelheim

Clinical Study Protocol

	Document Number:	**Not applicable**
EudraCT No.: **EU Trial No:**	NA	
BI Study No.	352.2154	
BI Investigational Product:	NA	
Title	Proof of concept (proof of intervention principles) study assessing effects of Technology-Assisted Respiratory Adherence prototype version 3 (a Digital Behaviour Change Intervention, DBCI) on proximal clinical outcomes and mediators (psychological mediators, self-management behaviours) in individuals with COPD (IwCOPD)	
Lay Title	Proof of concept study assessing Technology-Assisted Respiratory Adherence prototype version 3 in individuals with COPD	
Clinical Phase	ORBIT model for behavioural treatment development: Phase IIa (R19-2270)	
Study Team Leader	[redacted] Phone: +[redacted]	
Coordinating Investigator	NA	
Current Version and Date	**Protocol Version 2.0**	**Date: 16 Sep 2021**
Original Protocol Date	**Version 1.0, 24 Feb 2021**	

CLINICAL STUDY PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	24 Feb 2021
Revision date	16 Sep 2021
BI study number	352.2154
Title of study	Proof of concept (proof of intervention principles) study assessing effects of Technology-Assisted Respiratory Adherence prototype version 3 (a Digital Behaviour Change Intervention, DBCI) on proximal clinical outcomes and mediators (psychological mediators, self-management behaviours) in individuals with COPD (IwCOPD)
Principal Investigator	NA
Study site	NA
Clinical phase	ORBIT: Phase IIa
Study rationale	On the basis of accumulated knowledge during Phase I development, the TARA development team concluded that the TARA prototype version 3 may be defined as a putative Minimum Functional Product (MFP) for the target clinical use case. As such, the development team determined that it was appropriate to move into Phase IIa of development and conduct a proof-of-concept study to determine if TARA prototype version 3 can achieve benefit on a clinically relevant target in a small, select sample. In this way, an important goal of this proof-of-concept study is to determine whether or not TARA version 3 demonstrates enough of a clinical signal to merit moving forward to conducting more rigorous testing using a randomized design in larger, more representative study population.
Study objectives	**Primary Research Questions** Is there a clinically significant reduction in breathlessness in symptomatic IwCOPD following engagement with TARA after 12 weeks? **Secondary Research Questions** **Activity Levels:** Is there an associated maintenance or increase in activities of daily living to support a positive benefit of TARA on breathlessness? **Physical Activity Experience:** Is there an improvement in the physical activity experience of the patient?
Study assessments	**Primary Assessments** • Percentage of participants who experience a clinically significant decrease in breathlessness as measured by the Chronic Respiratory Questionnaire – Self Administered Individualized (CRQ-SAI) dyspnea domain at week 12.

	• Mean change in CRQ-SAI dyspnea domain from baseline to 12 weeks. The CRQ-SAI dyspnea score ranges from 1 to 7 with higher values indicating an improvement of breathlessness. **<u>Secondary assessments</u>** **Activity Levels:** • Change from baseline in average number of steps measured by the activity tracker at week 12. • Change from baseline in average cadence (steps/min) measured by the activity tracker at week 12. **Physical Activity Experience:** • Change from baseline in the difficulty domain of the Clinical Visits PROactive Physical Activity in COPD instrument (C-PPAC) at week 12. The domain score ranges from 0 to 40 with a higher value representing a lesser degree of difficulty.
Study design	Within-subject pre-post study design
Total number of participants entered	50 IwCOPD • Cohort 1: 25 IwCOPD (non-pharmacological self-management support) • Cohort 2: 25 IwCOPD (non-pharmacological + pharmacological self-management support)
Number of participants on each treatment	NA
Diagnosis	COPD (chronic bronchitis or emphysema)
Main in- and exclusion criteria	**Key inclusion criteria** • Individuals with COPD (IwCOPD)Male or females • Age ≥ 40 years • Current or ex-smokers • mMRC Score ≥ 2 (i.e. evidence of activity-related breathlessness) • Patients must have a prescription for either Spiriva Respimat or Stiolto Respimat as per one of the below scenarios: a. Participants must have a new prescription for either Spiriva Respimat or Stiolto Respimat (this could include a patient who has never received a maintenance bronchodilator for treatment before, or a patient who was previously on an alternative maintenance bronchodilator who is being switched to Spiriva Respimat or Stiolto Respimat to help with their COPD management). OR b. Participants currently on Spiriva Respimat or Stiolto Respimat who could benefit from engagement with TARA (after discussion with their physician). • Participants must be on a short-acting bronchodilator (“rescue medication”)

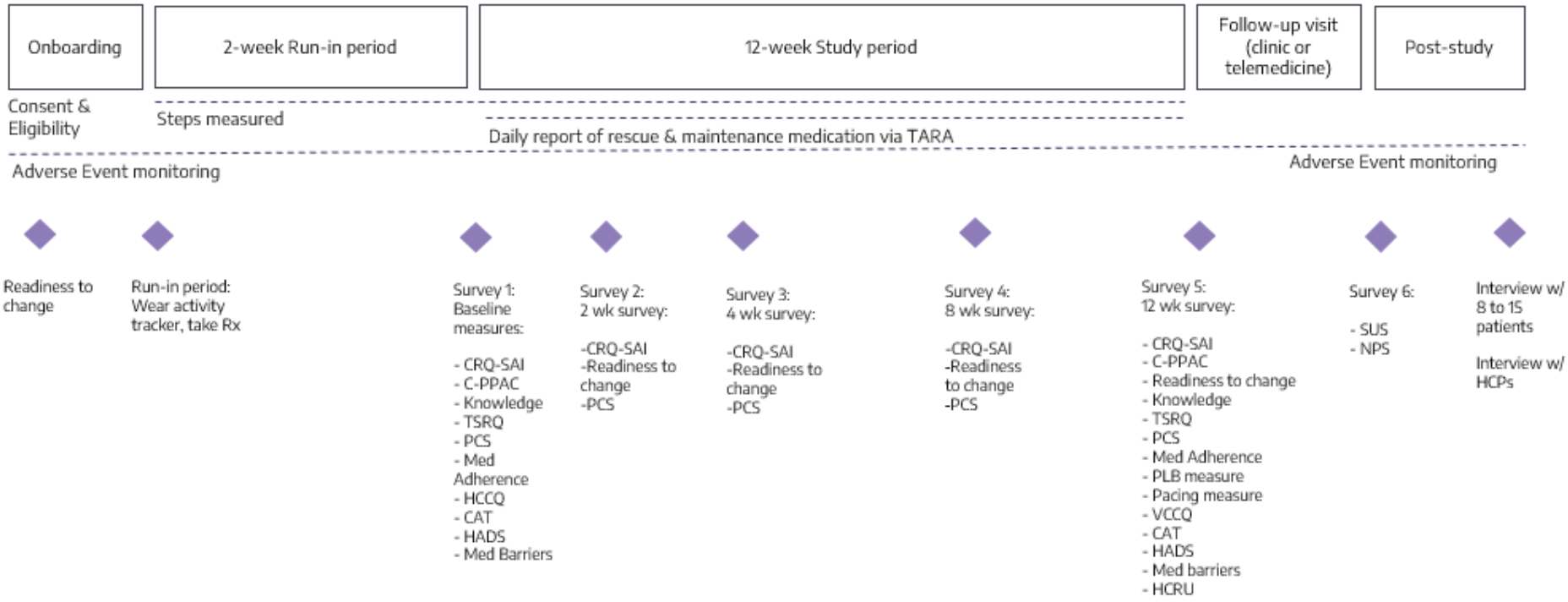
	• Participants must be willing to use the study specific activity tracker ([redacted] device) and be willing to complete all data collection requirements (within TARA plus on-line questionnaires plus possible phone interview) • Fluency in written English • Access to a Smartphone and at least one other device (desktop, laptop or tablet) with updated browsers installed (or willing to download up-to-date version for the study), and daily home access to internet • Need to have personal e-mail account that is used daily **Key exclusion criteria** • Patients with asthma as concurrent baseline condition at the time of screening • Patients with confirmed, suspected or recovered SARS-CoV-2 infection or if the patient had household or other contact with an individual with confirmed SARS-CoV-2 infection within 14 days prior to the completion of the eligibility questionnaire. • Patient with a worsening COPD episode requiring medical intervention within 4 weeks of enrolment • Patients who have completed a pulmonary rehabilitation (PR) or self-management program in the 3 months prior to enrolment or patients who are currently in a PR program • Patients prescribed inhaled COPD medications other than Spiriva Respimat plus albuterol or Stiolto Respimat plus albuterol • Patients with any contraindications for participating in the study (after discussion with their physician). • Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s) • Women who are pregnant, nursing, or who plan to become pregnant while in the study • Any self-reported medical or neuro-cognitive condition that would limit the ability of the participant to consent
Test product(s)	TARA[1] DBCI[2] prototype (version 3)
dose	NA
mode of administration	NA
Comparator product(s)	NA
dose	NA
mode of administration	NA
Duration of observation	16 weeks maximum observation period (from informed consent to post-TARA in-depth interview)
Statistical methods	**Primary Assessment Analyses** For the primary assessment, the CRQ-SAI dyspnea domain will be used to calculate breathlessness measures at baseline and week 12. Analyses to be conducted include the following:

	• The percentage of the study population who experience a clinically significant decrease in breathlessness (minimal clinically important difference (MCID) of 0.5) will be calculated. • The difference between week 12 and baseline will be calculated and compared against the criterion of minimal clinically important difference (MCID) of 0.5. **Secondary Assessment Analyses** Descriptive statistics of additional secondary endpoint variables will be explored for selection of best-fit analysis techniques. Pre-post differences in the physical activity experience will also be explored to see if TARA v3 has had a positive effect on perceived difficulty during activities. **Interim Analyses** NA

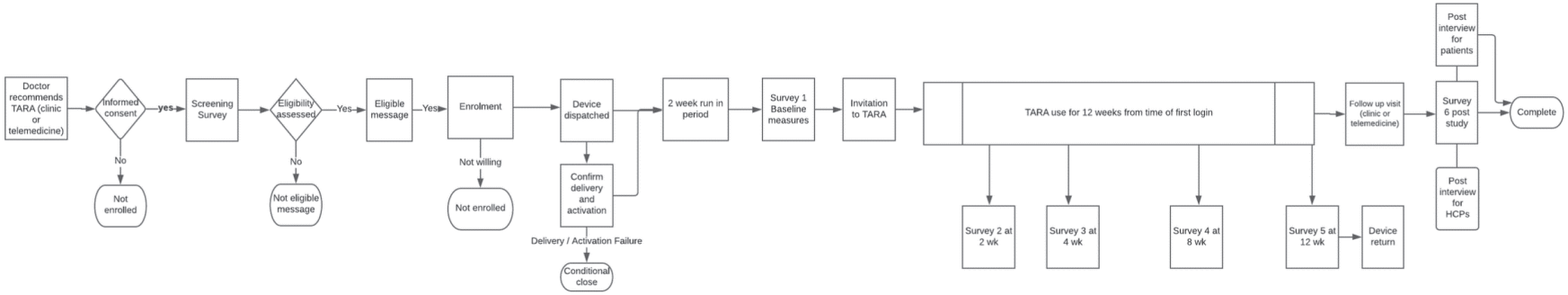
[1] TARA: **T**echnology-**A**ssisted **R**espiratory **A**dherence
[2] DBCI: **D**igital **B**ehaviour **C**hange **I**ntervention

FLOW CHART

Study Measures and Timepoints (beginning post-consent):



Individual Participant Flow:



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ABBREVIATIONS

ADR	Adverse Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
BE	Behavioural Experiment
BI	Boehringer Ingelheim
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
C-PPAC	Clinical Visit PROactive Physical Activity in COPD
CRA	Clinical Research Associate
CRQ-SAI	Chronic Respiratory Questionnaire – Self-Administered Individualized
CRO	Contract Research Organisation
CRT	Clinical Research Testing
DBCI	Digital Behaviour Change Intervention
EFL	Expiratory Flow Limitation
ER	Emergency Room
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GOLD	Global Initiative for Obstructive Lung Disease
HA	Health Authority
HADS	Hospital Anxiety and Depression Scale
HCCQ	Health Care Climate Questionnaire
HCP	Health Care Professional
ICH	International Council on Harmonisation
IDI	In-Depth Interview
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
IwCOPD	Individual with COPD
LABA	Long Acting β-Agonist

LAMA	Long Acting Muscarinic Antagonist
MC	Motivational Communication
MCID	Minimal Clinically Important Difference
MCP	Motivational Communication Practitioner
mMRC	(Modified) Medical Research Council
MFP	Minimum Functional Product
NPS	Net Promoter Survey
OCS	Oral Corticosteriods
PCS	Perceived Competence Scale
PR	Pulmonary Rehabilitation
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
SUS	System Usability Scale
TARA	Technology-Assisted Respiratory Adherence
TSRQ	Treatment Self-Regulation Questionnaire
VCCQ	Virtual Care Climate Questionnaire
WHO	World Health Organisation

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Chronic Obstructive Pulmonary Disease (COPD): medical/scientific and patient perspectives

COPD is a common, preventable and treatable disease that is characterized by expiratory flow limitation (EFL) due to airway and / or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (P19-00675). The chronic EFL characteristic of COPD is caused by a mixture of small airways disease (e.g., obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person. These changes do not always occur together but evolve at different rates over time. Chronic inflammation causes structural changes, narrowing of the small airways, and destruction of the lung parenchyma that leads to a loss of alveolar attachments to the small airways and decreases lung elastic recoil. In turn, these changes diminish the ability of the airways to remain open during expiration. A loss of small airways may also contribute to EFL, and mucociliary dysfunction is a characteristic feature of the disease. EFL is usually measured by post-bronchodilator spirometry because this is the most widely available and reproducible test of lung function (P19-00675).

The lung function impairment that characterizes COPD has significant impact on how the patient feels and functions during performance of tasks during everyday life. Patients with COPD have a variety of symptoms, including shortness of breath (breathlessness), chest tightness, wheezing, and cough with or without sputum as well as systemic symptoms such as fatigue and weakness (R19-2157). Breathlessness is a ubiquitous symptom in COPD and a key indicator used in the diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (P19-00675); it is persistent and progressive over time and identified as a major concern by patients due to its impact on daily life and emotional well-being (R19-2157).

COPD guidelines recommend that the management of stable COPD should be based on an individualised assessment, with the main treatment goals being reduction of symptoms (relieve symptoms, improve exercise tolerance, improve health status) and future risk (prevent disease progression, prevent and treat exacerbations, reduce mortality). Management strategies include pharmacological treatments complemented by appropriate non-pharmacological interventions (P19-00675).

Self-management in COPD: recent focus on adoption of healthy behaviours

Self-management is now considered a major component of the “chronic care model” for COPD. In general, self-management training aims to help patients acquire and practise the skills they need to carry out disease-specific medical regimens, to guide changes in health behaviour and to provide emotional support to enable patients to adjust their roles for optimal function and control of their disease (R19-2163, R19-2168). In addition to addressing behavioural risk factors (i.e. smoking, diet, exercise), self-management should involve patients in monitoring and managing the signs and symptoms of their disease, being adherent

to treatment (including to medications and other medical advice), maintaining regular contact with healthcare providers, and managing the psychosocial consequences of their condition (P19-00675).

Implicit in the description of self-management is the "provision of self-management support/coaching", which refers to the strategies, techniques and skills required to self-manage their disease effectively. Patients are not always motivated to adopt healthier behaviours or engage in recommended disease management strategies, even when there are clear benefits; this is often referred to as the "knowledge–behaviour" gap, and is a major challenge for chronic disease management. Patient support needs to go beyond pure education/advice-giving (didactic) approaches to help patients learn and adopt sustainable self-management skills; a motivational communication (MC) style is recommended as a means to empower patients to take greater responsibility for their health and well-being (P19-00675) and to support patients towards increased confidence (self-efficacy) that they can effectively manage their health (R19-2162; R19-2153; R19-2185).

Use of digital technology to enhance accessibility and effectiveness of self-management

Recent research has focused on development of enabling and assistive technologies that are accessible at all times to provide patients with relevant, individualised, motivational, and educational material that encourages, supports, and facilitates self-management; these interventions provide information and instruction, and facilitate goal setting and self-monitoring, relying on one or more approaches, such as video, audio, digital images, and hard or digital copies, to deliver educational and motivational content related to issues such as smoking cessation, exercise, diet, and symptom management (R19-2223; R19-2224; R19-2219; R19-2221; R19-2179; R19-2181). While a recent systematic review (R19-2220) was not able to come to a definitive conclusion about the effectiveness of smart technology as a means of supporting, encouraging, and sustaining self-management in COPD, preliminary evidence of benefits in terms of outcomes such as quality of life and physical activity up to six months warranted a recommendation for further high-quality research in this area. Key focus areas for future research include exploration of strategies that will promote long-term engagement with smart technology and inclusion of qualitative data collection to inform issues relevant to the digital divide and to reveal what influences uptake and sustained use of technology among people with COPD.

Given the central position of behaviour change support in COPD self-management training and the opportunities afforded by advances in digital technology, recommendations for designing, evaluating, and implementing digital behaviour change interventions (DBCIs) in health care may support future efforts in self-management research by identifying the scientific principles relevant to developing effective DBCIs, and supporting multidisciplinary teams of digital technologists, user experience researchers, behaviour scientists, health care professionals and patients to work together more effectively to advance research methods and advance the understanding and techniques of behaviour change through digital technology (R19-2150).

1.2 DESCRIPTION OF INTERVENTION

Background

Engaging in appropriate self-management involves a complex series of behavioural changes: addressing behavioural risk factors including smoking cessation, maintaining or increasing physical activity, and ensuring adequate sleep and a healthy diet; learning to self-manage breathlessness, energy conservation techniques, and stress/anxiety management strategies; avoiding aggravating factors, monitoring and managing worsening symptoms, having a written action plan and maintaining regular contact/communication with a healthcare professional. The patient's needs, preferences, and personal goals should inform the personalized design of the self-management training plan (P19-00675).

Within a holistic vision of a technology-enabled self-management program in COPD that supports all relevant treatment goals (P19-00675) and associated behaviours, our initial discussions prior to development of a working protype for a self-management DBCI focussed on (i) identifying one specific, relevant, patient-centric treatment goal ("clinical target"), and (ii) selecting one relevant treatment recommendation (and associated behaviour) known to be efficacious with respect to the achievement of this treatment goal (P19-00675). Activity limitation due to breathlessness is a ubiquitous burden for patients with COPD; as such, the initial DBCI development has focussed attention on treatment recommendations for breathlessness management in COPD:

- adhering to prescribed symptomatic medicines
- learning to self-manage breathlessness
- maintaining or increasing physical activity
- energy conservation techniques
- avoiding aggravating factors
- stress/anxiety management strategies

Treatment guidelines (P19-00675) place bronchodilators as the foundation of pharmacologic management of COPD and are considered central to symptom management and commonly given on a regular basis to prevent or reduce symptoms. In patients with moderate to very severe pulmonary impairment (i.e., GOLD Stage II to IV) whose symptoms are not adequately controlled with as-needed short-acting bronchodilators, adding regular treatment with one or more long-acting inhaled bronchodilators is recommended (long-acting β-agonists, LABAs; long-acting muscarinic antagonists, LAMAs). LABAs and LAMAs significantly improve lung function, dyspnea, health status and reduce exacerbation rates; combination treatment with a LABA and a LAMA increases lung function and reduces symptoms compared to monotherapy.

Therefore, based on a review of GOLD guidelines, we decided to focus our attention on the following treatment goal and associated pharmacological and non-pharmacological recommendations for management of stable COPD:

> **Treatment goal:** Reduction of symptoms in patients with COPD
> [with initial focus on breathlessness]

> **Pharmacological treatment recommendation (GOLD 2020)** (P20-00875)**:** regular (daily, as-prescribed) treatment with long-acting bronchodilators in patients whose symptoms are not adequately controlled with as-needed short-acting bronchodilators
>
> **Non-pharmacological management recommendation (GOLD 2020)** (P20-00875)**:** "…patients should be offered guidance on self-management of breathlessness, energy conservation and stress management, (and they should be given a written action plan)."

With this GOLD-specified treatment goal / recommendation as a focus, we then identified the following target behaviours to be addressed with the initial TARA[1] DBCI solution development:

> **Target behaviour:** (***sustained)*** adherence to:
> - prescribed maintenance long-acting bronchodilator medication ("pharmacological self-management support")
> - pursed lip breathing ("non-pharmacological self-management support")
> - pacing / energy conservation ("non-pharmacological self-management support")

With regards to adherence to prescribed maintenance long-acting bronchodilator medication, for the purposes of the initial solution development and research evaluation, it was necessary to restrict our focus to a limited number of once daily inhaled medications in order to reduce the content requirements within the educational component of the DBCI working prototype (e.g. education on appropriate inhaler technique); our operational focus was on patients prescribed either Spiriva Respimat (once daily) or Stiolto Respimat (once daily) as inhaled maintenance pharmacological treatment as well as short-acting β-agonist for as-needed symptom relief.

To provide additional development guidance, we focused on the following **target clinical use case** for TARA version 3 ("intended use"):

> *TARA offers patients remote breathlessness self-management support during daily life. TARA is a digital behavior change intervention intended to support patients with COPD in adopting and sustaining clinically recommended (evidence-based) self-management behaviours. TARA is intended to be used independently at home by patients using an internet-enabled device.*
>
> *Access to TARA will be achieved via a recommendation from a prescribing physician at the same time as provision of a prescription for a once daily maintenance bronchodilator (Spiriva/Stiolto Respimat)*
>
> *Appropriate patients as per GOLD recommendations (vis a vis maintenance bronchodilator treatment in combination with self-management).*

[1] **T**echnology-**A**ssisted **R**espiratory **A**dherence

The initial duration of patient engagement with TARA will be between an initial contact with an HCP and a follow-up contact with an HCP.

Summary reports from TARA can be delivered by the patient to the HCP at the follow-up clinical visit by print-out or screen-share to update the HCP on the patient's progress in symptom self-management, which may be an enabler for a robust discussion with the HCP during the follow-up visit.

Further details regarding the science behind the TARA development and a more detailed description of the TARA solution is provided in the Investigator's Brochure.

1.3 RATIONALE FOR PERFORMING THE STUDY

The early development phase of TARA has been informed by the ORBIT model for developing behavioural treatments to prevent and/or manage chronic disease (R19-2270). The ORBIT model was considered to be appropriate for a number of reasons: (i) it focuses on the early, pre-efficacy phases of behavioural treatment development; (ii) it was developed for use with a broad array of chronic diseases, (iii) it intentionally uses terminology from the drug development model.

In accordance with the ORBIT model, the goal of Phase I was to develop an intervention or 'treatment package' that is considered to contain essential components offered in an efficient way, is acceptable to the population of interest, and is likely to have a clinically significant benefit on the behavioural risk factor.

In the early stages of Phase I, the scientific foundation and the basic elements of the behavioural treatment were defined: (i) development of a hypothesized pathway by which a behavioural treatment could solve the clinical problem, (ii) specification of clinically significant milestones on the behavioural risk factor(s) being targeted, (iii) identification of appropriate target population, (iv) definition of potential treatment components, and (v) elucidation of basic behavioural and social sciences support for potential treatment components and their respective treatment targets.

Phase I focussed on the design of the essential features of the (digital) behavioural treatment: taxonomies and "mapping" strategies that characterize behavioural interventions and their components were used to select treatment elements; experimental and observational studies in the laboratory and field enabled the identification of potential treatment components and the respective biological, psychophysiological, social, environmental, and behavioural targets needed to accomplish change in them and, in turn, in the behavioural risk factor; qualitative research was conducted to develop a rich understanding of the problem from the perspective of IwCOPD; several UXR activities were conducted to inform development of components of the solution; an initial clinical research study was conducted to evaluate engagement with an early working prototype.

On the basis of accumulated knowledge during Phase I development, the TARA development team concluded that the TARA prototype version 3 may be defined as a putative Minimum Functional Product (MFP) for the target clinical use case. As such, the development team

determined that it was appropriate to move into Phase IIa of development and conduct a proof-of-concept study to determine if TARA prototype version 3 can achieve benefit on a relevant clinical target in a small, select sample. In this way, an important goal of this proof-of-concept study is to determine whether or not TARA version 3 merits more rigorous testing using a randomized design in larger, more representative study population.

TARA may be described as a complex intervention (R20-4211). An important task in describing a complex intervention is to identify the individual components that are being integrated into the holistic solution. TARA is being developed within the overarching framework of the GOLD clinical management guidelines, with specific attention paid to the GOLD classification schema of pharmacological and non-pharmacological disease management. Within this development framework, there is value in evaluating the extent to which the components contribute to the effectiveness of the holistic solution, similar to the evaluation of the contribution of the individual components of a combination drug product (P15-03349, P19-01878) drugs. As a preliminary evaluation of the effectiveness of the individual components of TARA [within the spirit of "proof of intervention principles"(R20-4212)], the present study will adopt a cohort approach within the study design: the first cohort will engage with TARA version 3.1, which includes non-pharmacological self-management support (i.e. self-monitoring, pursed lip breathing, pacing and energy conservation); the second cohort will engage with TARA version 3.2, which includes both non-pharmacological and pharmacological self-management support (i.e. additional inclusion of the medication support component).

1.4 BENEFIT-RISK ASSESSMENT

While benefit-risk assessment is standard practice within the clinical drug development paradigm, it is also increasingly recognised as an important consideration for non-pharmacological interventions in healthcare (P14-02978; R19-2769).

1.4.1 Benefits

Potential benefits of the fully developed TARA DBCI include improving knowledge of COPD and its treatments and how treatment can improve symptoms and outcomes, verifying inhaler technique, and learning new skills that may improve self-management of COPD; these same potential benefits are applicable to study participants engaging with the TARA DBCI working prototype (version 3).

1.4.2 Risks

No adverse effects have been identified during the user experience testing rounds of components of the intervention or in the first clinical study (CRT1; 352.2133).

Study 352.2154 will be the second study that IwCOPD will engage with TARA in a real-world setting. There is a potential for (disease-related) behaviour change and consequent risks associated with changes in behaviour; in light of the fact that (i) study participants will only be allowed to log-on to TARA after recommendation by their primary physician, (ii) the

medical oversight of the participant is by their primary physician and (iii) no therapeutic recommendations are being provided by the software, risks associated with engagement with TARA in this study are considered low. The time required to engage with TARA is a potential inconvenience and is mitigated by the option for study participants to disengage from TARA / study at any time.

1.4.2.1 Covid-19 related risks

Potential risks for participants due to the COVID-19 pandemic have been evaluated and the following measures have been put in place in this study to mitigate any risk:

- Participants will be under the medical oversight of their primary physician
- Participants with active or recovered SARS CoV-2 infection will be excluded from the study (Section 3.3.3.).
- The majority of study activities will be conducted remotely and the number of on-site visits has been limited in this study. However, in case of an increased risk of SARS-CoV-2 infection due to physical visits to the sites, the visits should be conducted remotely (by phone or video call) if the Investigator judges that this is the safest course of action.

1.4.3 Discussion

Study 352.2154 is designed to learn about how IwCOPD engage with TARA to allow for refinements during further solution development. If some of the underlying assumptions for the TARA development hold true, there is a potential for study participants to develop a stronger capacity to adhere to clinically recommended COPD self-management behaviours.

As such, it is acceptable to conduct this proof-of-concept study.

2. STUDY OBJECTIVES AND ASSESSMENTS

2.1 MAIN OBJECTIVE (RESEARCH QUESTIONS), PRIMARY ASSESSMENTS

2.1.1 Main objective (research question)

The main research question focusses on the following, relevant proximal clinical outcome in the context of the primary, patient-centric clinical problem addressed by TARA working prototype version 3 in consideration of the defined clinical use case (as described in Section 1.2):

> *Is there a clinically significant reduction in breathlessness in symptomatic IwCOPD following engagement with TARA after 12 weeks?*

2.1.2 Primary assessments

The primary measurement instrument (Clinical Outcome Assessment) that will be used to measure breathlessness is the dyspnea domain of the CRQ-SAI, a patient-reported outcome (PRO) with a two-week recall. The intention of TARA version 3 is to support the patient in developing skills to self-manage the breathlessness that is experienced during activities of daily life.

Primary Assessments:
- Percentage of participants who experience a clinically significant decrease in breathlessness as measured by the Chronic Respiratory Questionnaire – Self Administered Individualized (CRQ-SAI) dyspnea domain at week 12.
- Mean change in CRQ-SAI dyspnea domain from baseline to 12 weeks. The CRQ-SAI dyspnea score ranges from 1 to 7 with higher values indicating an improvement of breathlessness.

2.2 SECONDARY RESEARCH QUESTIONS, SECONDARY ASSESSMENTS

2.2.1 Secondary research questions

The secondary research question focusses on activities of daily living (amount and intensity) as well as the perceived difficulties associated with performing physical activity in daily life.

Activity Levels:
Is there an associated maintenance or increase in activities of daily living to support a positive benefit of TARA on breathlessness?

Physical Activity Experience:
Is there an improvement in the physical activity experience of the patient?

2.2.2 Secondary assessments

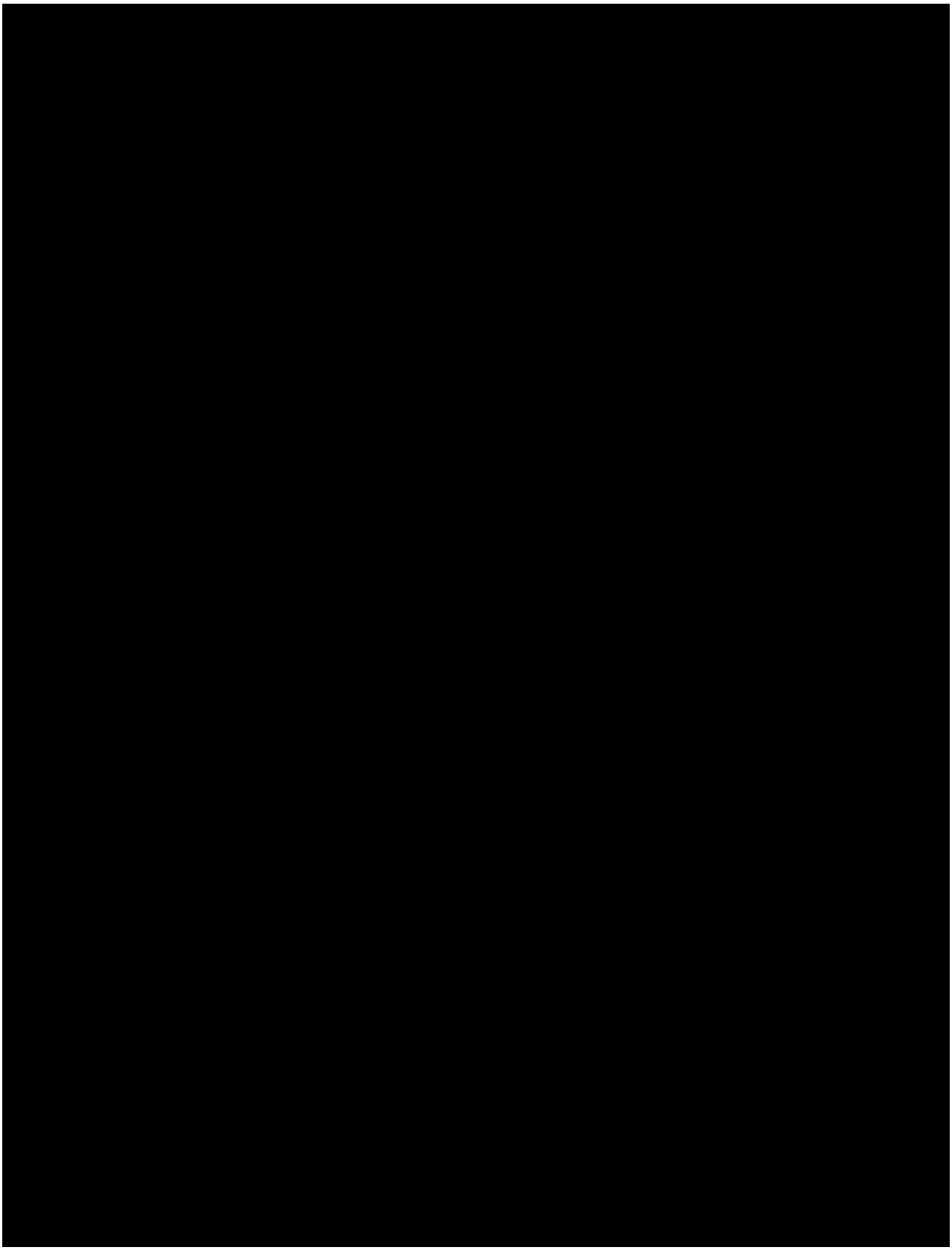
Activity Levels: Daily activity levels will be measured using the activity tracker ([redacted] for a 2-week period and an average will be taken at both timepoints to match the CRQ-SAI time frame for measurement.

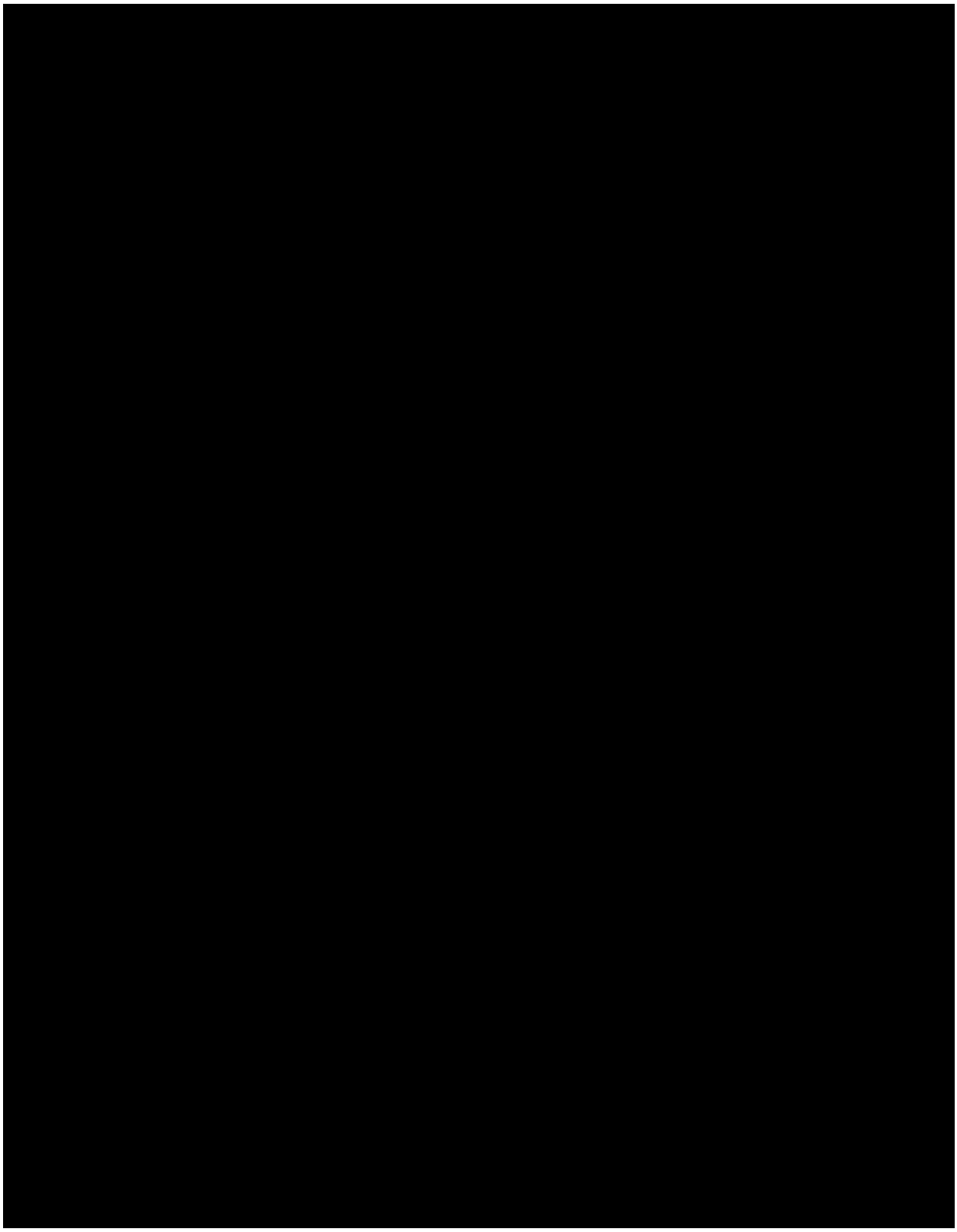
- Change from baseline in average number of steps measured by the activity tracker at week 12.
- Change from baseline in average cadence (steps/min) measured by the activity tracker at week 12.

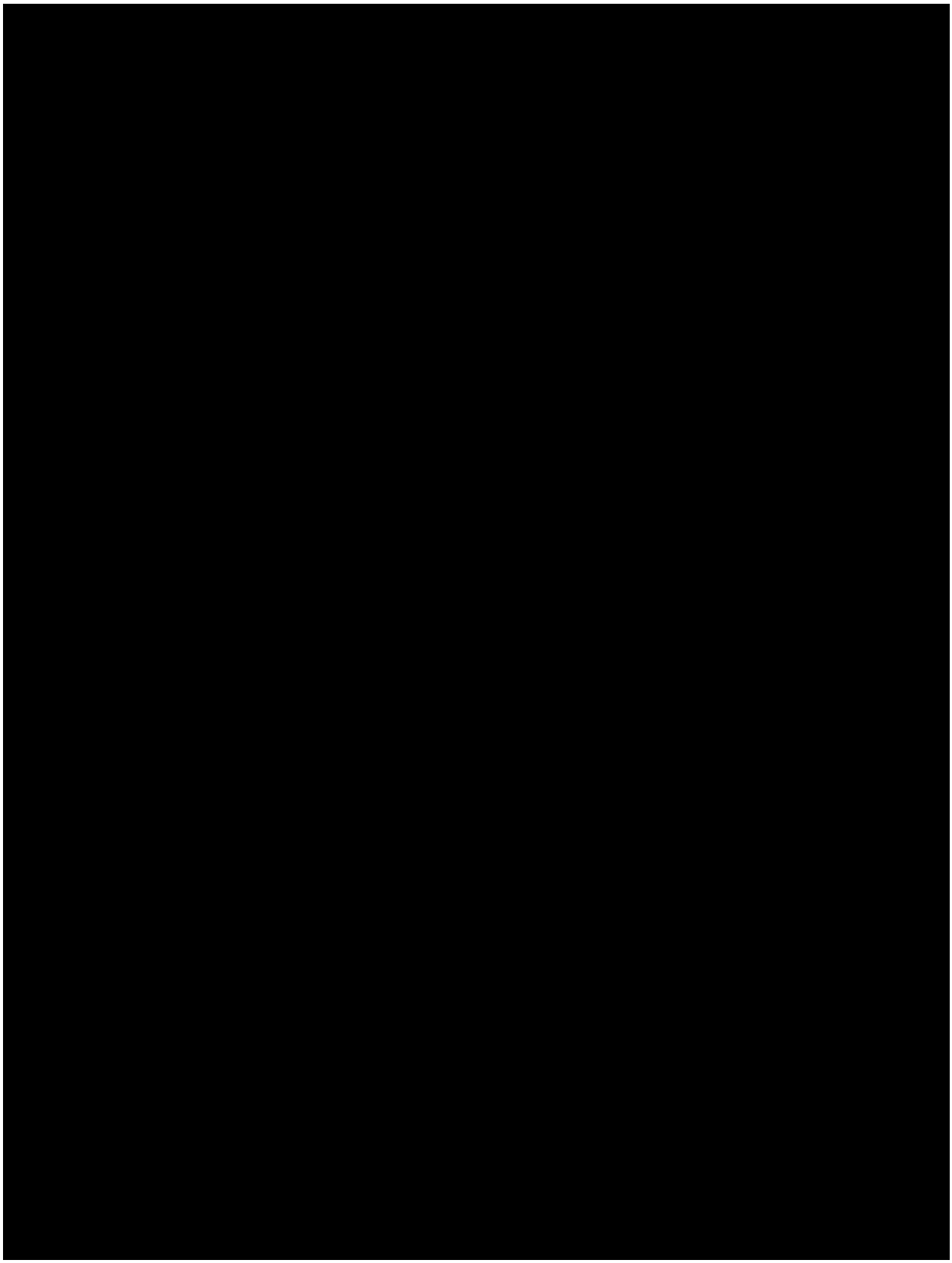
Physical Activity Experience:

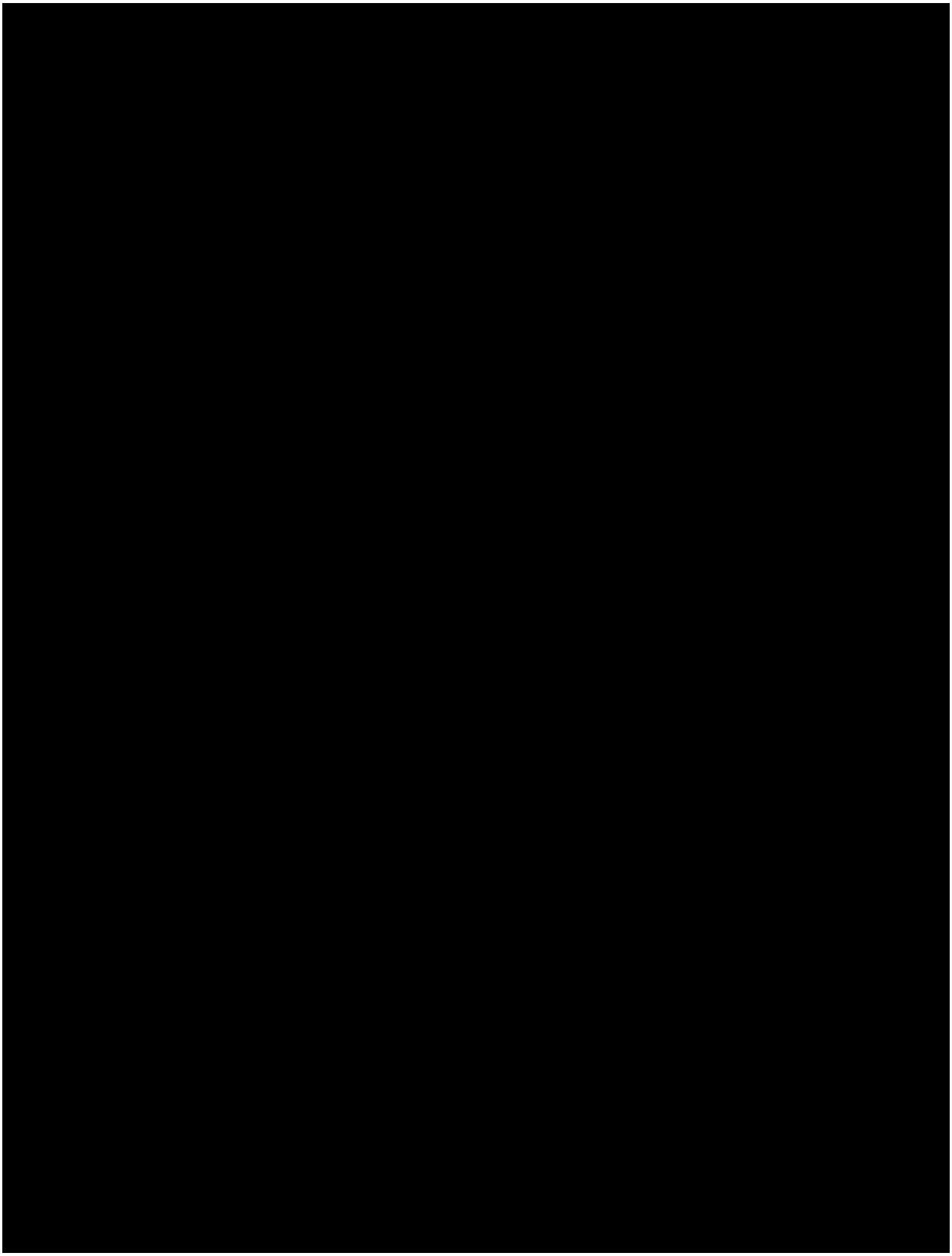
- Change from baseline in the difficulty domain of the Clinical Visits PROactive Physical Activity in COPD instrument (C-PPAC) at week 12. The domain score ranges from 0 to 40 with a higher value representing a lesser degree of difficulty.

[redacted]









3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1 OVERALL STUDY DESIGN

The study will follow a within-subject pre-post study design and will be conducted as a hybrid (clinic visit/remote) study. Participants will have clinic / telemedicine (phone or video calls) visit(s) with the clinical site and the completion of survey activities and engagement with the digital intervention TARA will take place remotely / on-line. The survey activities will be completed online via the study website at the time points outlined in the flow chart. As the TARA intervention is fully online and digital, participants in the study are free to use the intervention as much as they like for the 12-week study duration from their enrolment date.

Potentially eligible IwCOPD will be recruited from clinical sites. For participants who are receiving a new prescription for a once daily maintenance bronchodilator (Spiriva/Stiolto Respimat), the prescribing physician will recommend use of TARA to the participants at the same time as provision of the prescription. For participants who are currently on a once daily maintenance bronchodilator (Spiriva/Stiolto Respimat) but who could benefit from additional support, the physician will recommend the use of TARA for self-management alongside their existing prescription.

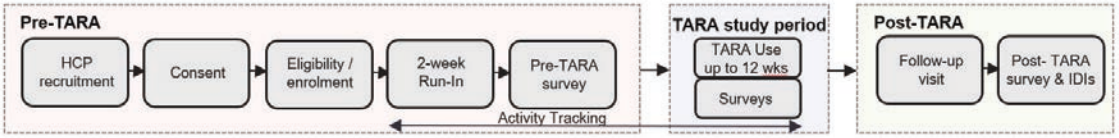
The study will have 2 cohorts of participants in order to support the evaluation of the extent that pharmacological support adds value on top of non-pharmacological support:

- The first cohort will engage with a version of TARA that includes the non-pharmacological self-management support (self-monitoring, pursed lip breathing, pacing)
- The second cohort will engage with a version of TARA that includes both non-pharmacological and pharmacological self-management support (i.e. additional inclusion of medication support component).

Recruitment into the cohorts will be conducted sequentially. The study will begin recruiting into the first cohort and once the first cohort is closed for recruitment, the second cohort will open for recruitment. This cohort strategy will support an iterative approach in the development of the digital intervention.

The study consists of three broad phases:

(1) **Pre-TARA:** study recruitment by clinic site, consent, screening, receipt of activity tracker, run-in period, and pre-TARA survey;
(2) **Intervention period (TARA delivery):** up to 12-weeks of intervention depending on the length of time of each participant's individual journey;
    i. Interim survey measures will be collected during this period via the study website at 2 weeks, 4 weeks and 8 weeks.
    ii. End of study survey measures will be collected at 12 weeks.
(3) **Post-TARA:** follow-up visit with the clinic site (in-person or telemedicine), post-TARA survey, post-TARA interview conducted in a sub-set of participants and HCP interviews.



3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Study design

According to the ORBIT model, quasi-experimental, within-subjects designs where subjects act as their own controls in a pre-post treatment comparison are appropriate in Phase IIa. The sample size can be small since clinical, not statistical, benefit is sought, and sample size calculations are unnecessary. The sample can be selected from accessible subjects, rather than be representative, because this initial test will determine only whether the treatment merits more rigorous testing. The focus of Phase IIa studies is deliberately placed on the treatment and its ability to produce clinically significant change on a behavioural risk factor to indicate that the intervention is likely to be efficacious. This is in contrast to Phase IIb studies which focus on determining the source of a treatment effect (e.g., separation of treatment effects from effects due to the passage of time) and with choosing the appropriate control group, in itself a complex undertaking.

A cohort approach has been included in the study based on the CEEBIT (Continuous Evaluation of Evolving Behavioural Intervention Technologies) methodologic framework (R20-4210) which was developed to support the evaluation of evolving versions of Behavioural Intervention Technologies (BITs).

3.3 SELECTION OF STUDY POPULATION

A sufficient number of individuals will be enrolled (sign informed consent) to ensure that approximately 50 participants with a diagnosis of COPD are entered into the intervention (TARA log-in).

Participants will be administered the Readiness to Change questionnaire at screening with the aim to enroll a higher number of participants who are not currently taking action to manage their COPD (patients who score a 1, 2 or 3 on the scale) vs. those participants who are currently taking actions to manage their COPD (participants who score a 4 or 5 on the scale). It is anticipated that these participants may need more support with managing their condition and therefore we could see a greater impact of using TARA in these participants with respect to their intention to self-manage their COPD.

An IwCOPD can only log-in to TARA (intervention entry) if they meet all eligibility criteria. A log of all participants enrolled into the study (i.e. who have signed informed consent) will be maintained irrespective of whether or not they engage with TARA (TARA log-in).

3.3.1 Main diagnosis for study entry

Outpatients with a diagnosis of COPD (chronic bronchitis or emphysema) and prescribed either Spiriva Respimat or Stiolto Respimat are eligible for inclusion if they fulfil all the inclusion criteria (Section 3.3.2) and do not present with any of the exclusion criteria (Section 3.3.3).

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with GCP (ISO 14155) and local legislation prior to admission to the study
2. Male or female patients
3. All patients must have a self-reported confirmation of a physician diagnosis of COPD (or chronic bronchitis or emphysema)
4. Age ≥ 40 years
5. Patients must be current or ex-smokers
6. Modified Medical Research Council (mMRC) Score ≥ 2 (i.e. evidence of activity-related breathlessness)
7. Patients must have a prescription for either Spiriva Respimat or Stiolto Respimat and as per one of the below scenarios:
    a. Participants must have a new prescription for either Spiriva Respimat or Stiolto Respimat (this could include a patient who has never received a maintenance bronchodilator for treatment before, or a patient who was previously on an alternative maintenance bronchodilator who is being switched to Spiriva Respimat or Stiolto Respimat to help with their COPD management).
    OR
    b. Participants currently on Spiriva Respimat or Stiolto Respimat, who could benefit from engagement with TARA (after discussion with their physician).
8. Participants must be on a short-acting bronchodilator (“rescue medication”)
9. Participants must be willing to use the study specific activity tracker ([redacted] device) and be willing to complete all data collection requirements (within TARA plus on-line questionnaires plus possible phone interview)
10. Fluency in written English
11. Access to a Smartphone and at least one other device (desktop, laptop or tablet) with updated browsers installed (or willing to download up-to-date version for the study), and daily home access to internet
12. Need to have personal e-mail account that is used daily

3.3.3 Exclusion criteria

- Patients with asthma as concurrent baseline condition at the time of screening
- Patients with confirmed, suspected or recovered SARS-CoV-2 infection or if the patient had household or other contact with an individual with confirmed SARS-CoV-2 infection within 14 days prior to the completion of the eligibility questionnaire.

- Patients with a worsening COPD episode requiring medical intervention within 4 weeks of enrolment
- Patients who have completed a pulmonary rehabilitation (PR) or COPD self-management program in the 3 months prior to enrolment or patients who are currently in a PR program (rationale: PR programs typically include a self-management component which may interfere with study objectives)
- Planned vacation or other travel during the study period that requires overnight stays away from home
- Major surgery performed within 6 weeks prior to enrolment or planned during the course of the study, e.g. hip replacement
- Patients prescribed inhaled COPD medications other than Spiriva Respimat plus albuterol or Stiolto Respimat plus albuterol
- Patients with any contraindications for participating in the study (after discussion with their physician).
- Previous enrolment in a TARA study
- Previous enrolment in this study
- Currently enrolled in another investigational device or drug study/trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s)
- Women who are pregnant, nursing, or who plan to become pregnant while in the study
- Any self-reported medical or neuro-cognitive condition that would limit the ability of the participant to consent
- Residence in State of California (rationale: new data management and privacy laws in this state present complications to an effective data analysis plan by allowing users to potentially withdraw their data from the study)

3.3.4 Withdrawal of participants from study participation

3.3.4.1 Withdrawal of consent to study participation

Participants may withdraw consent to study participation at any time without the need to justify the decision.

3.3.4.2 Discontinuation of participants

Participants will be discontinued from the study if they experience an infection with SARS-CoV-2.

3.3.4.3 Discontinuation of the study by the sponsor

Boehringer Ingelheim reserves the right to discontinue the study at any time for the following reasons:

1. Failure to meet expected enrolment goals.
2. Emergence of any new information invalidating the positive benefit-risk assessment that could significantly affect the continuation of the study.

4. TREATMENTS

4.1 INVESTIGATIONAL INTERVENTION

No IMP treatments will be administered in this study.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

There are no restrictions regarding medications for other (non-COPD) diseases.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

For a participant to be eligible for the study, they must be prescribed Spiriva plus albuterol or Stiolto plus albuterol according to the approved prescribing information. Participants that are additionally prescribed other inhaled COPD medications are not eligible.

4.2.2.2 Restrictions on diet and lifestyle

There are no restrictions regarding diet and lifestyle.

5. FURTHER DETAILS REGARDING ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Primary Assessment

Chronic Respiratory Questionnaire – Self Administered Individualized (CRQ-SAI)
The CRQ-SAI, a derivate of the original CRQ tool, is used to assess the patients' perception of their COPD and measures the impact of COPD on their life. The CRQ-SAI has 20 items over 4 domains: dyspnea, fatigue, emotional function and mastery. For dyspnea, participants are asked to select 5 activities associated with breathlessness (from a list of 26 or custom response), that they have performed in the past two weeks and that are most important to them and indicate how much breathlessness they have experienced while performing each.

The CRQ-SAI should be completed by the participants at the time points outlined in the flow chart. Details of the CRQ-SAI are provided in Appendix 10.2.1.

5.1.2 Secondary Assessments

Activity Tracker ([redacted] device)
A physical activity tracker is an accelerometer that is used to measure the overall movement of a patient. Activity trackers provide valuable information on physical activity directly from the patient's body.

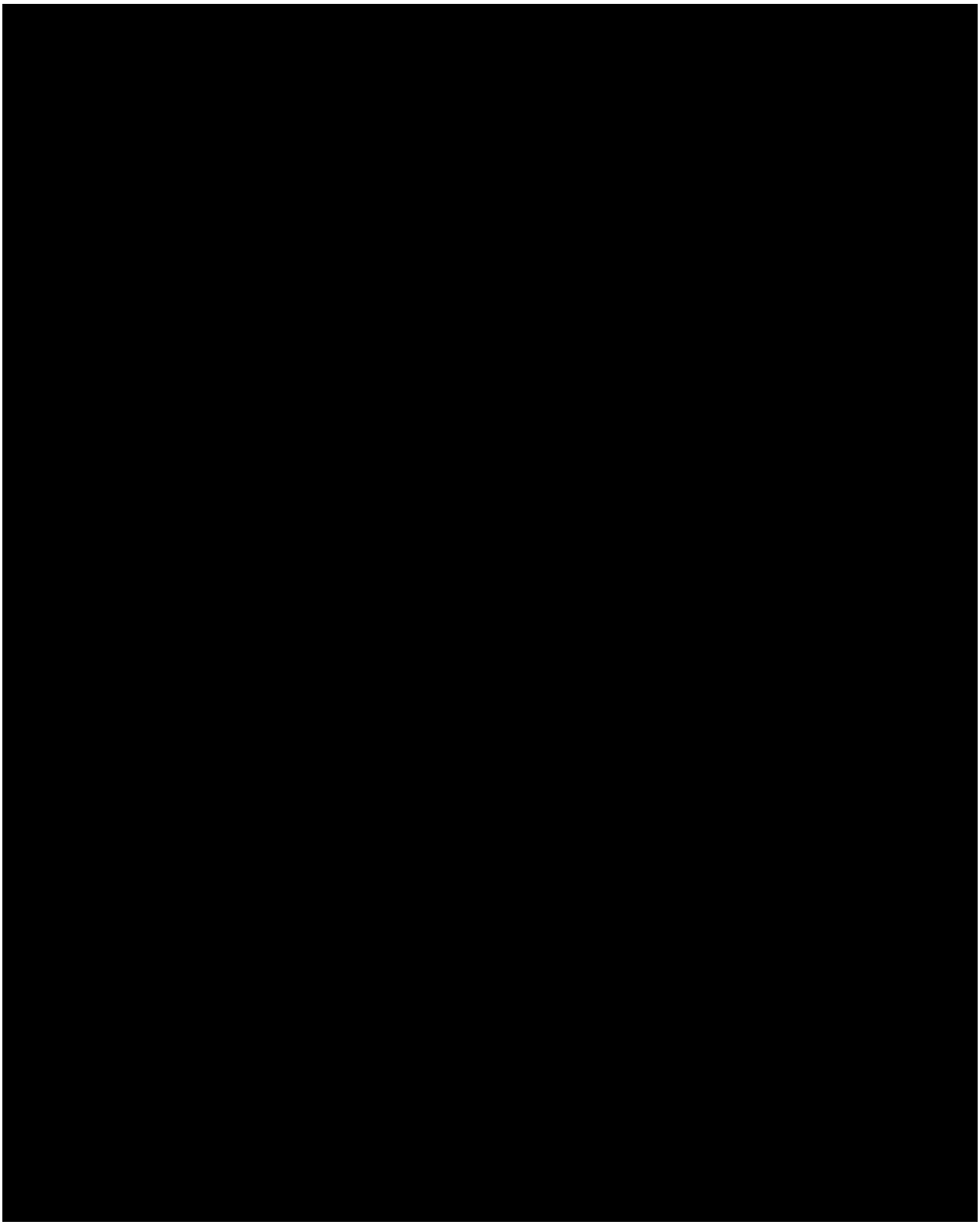
The [redacted] device will be the activity tracker used in the study to measure the amount (steps) and intensity (cadence) of daily ambulatory activities in support of the main research objective. Participants will wear the activity tracker throughout the study and the data obtained from the activity tracker will be transferred to the study database.

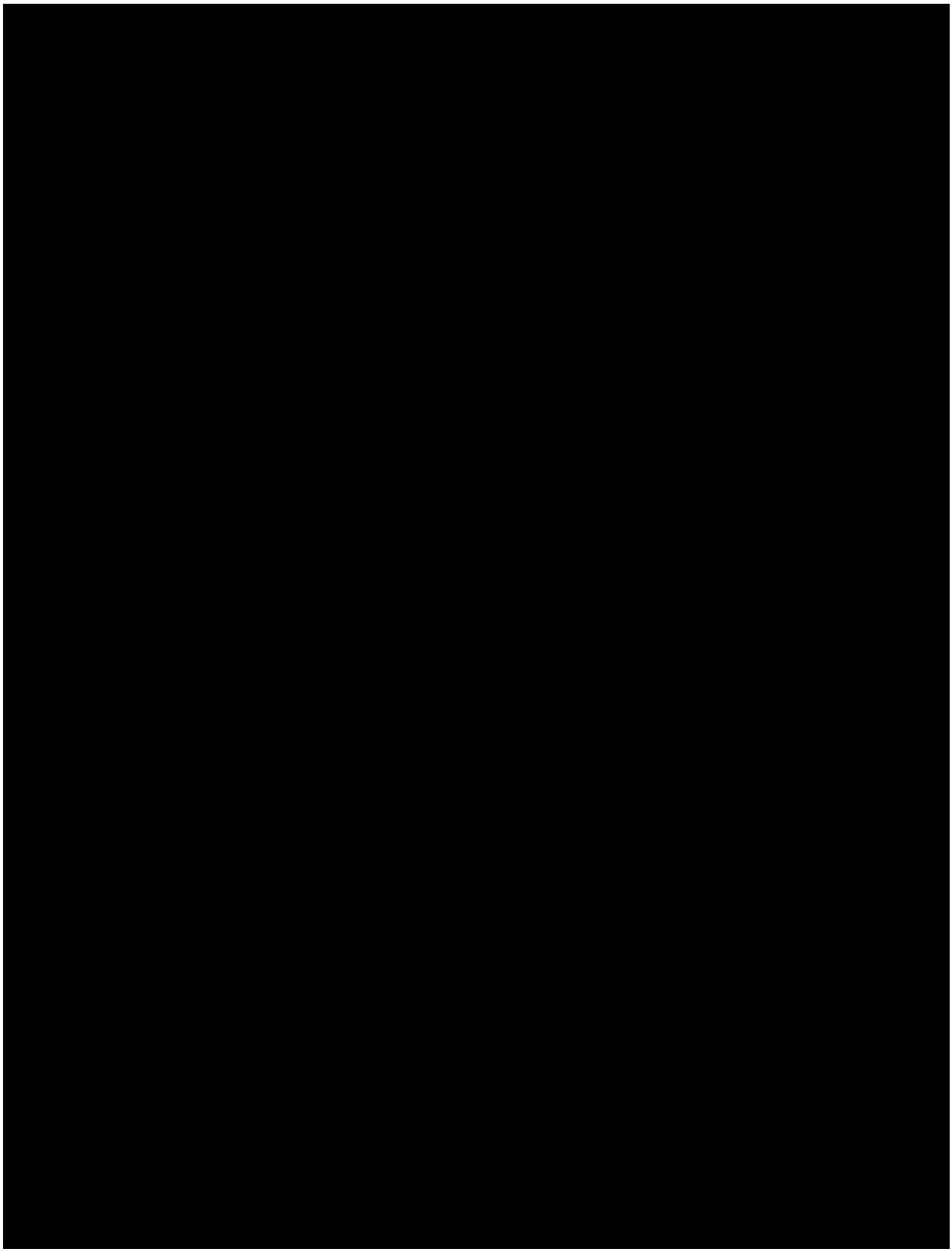
Instructions will be given to the participants on how to use the activity tracker.

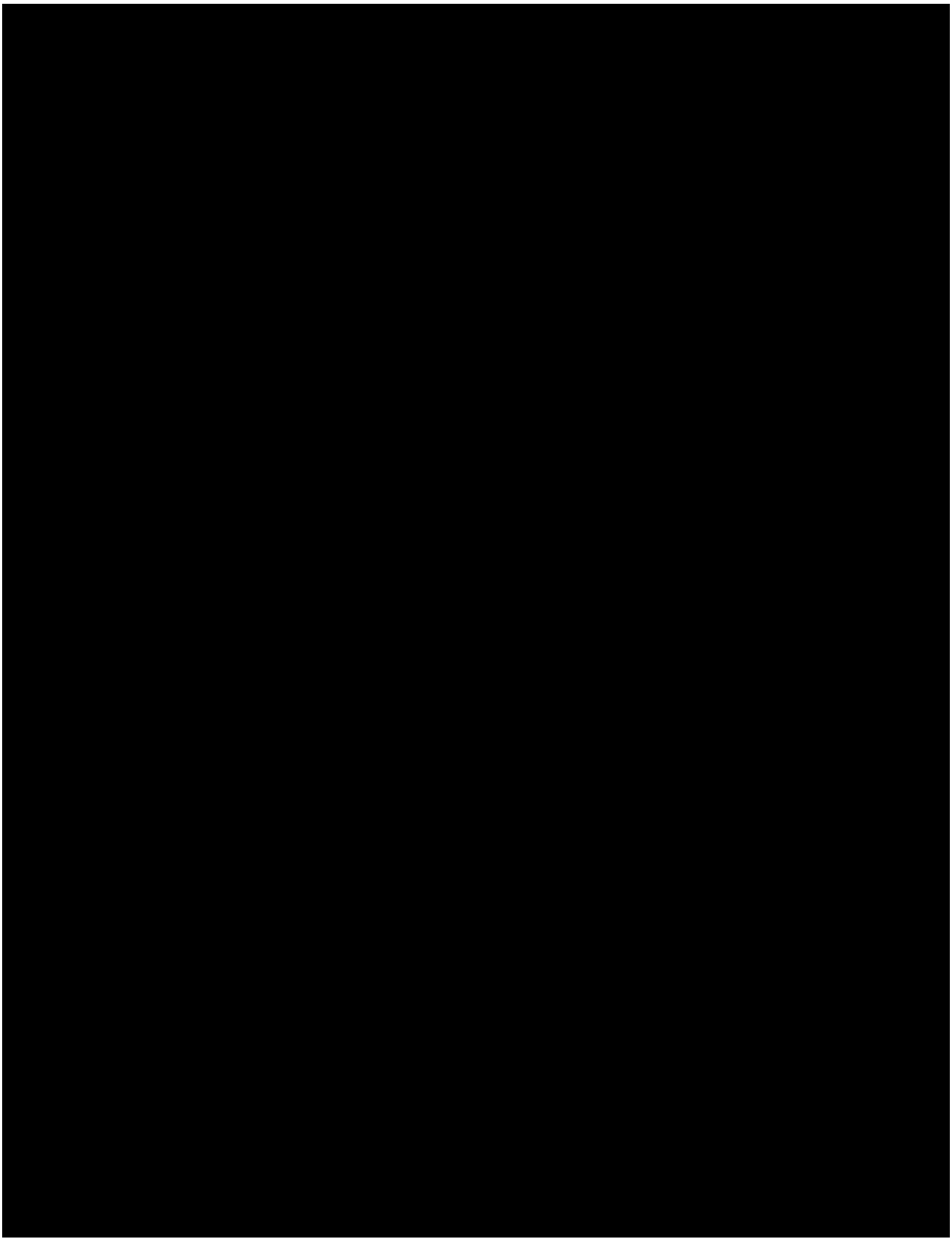
Clinical Visit PROactive Physical Activity in COPD instrument (C-PPAC)
A secondary measure of efficacy is the C-PPAC, a hybrid measurement tool incorporating a patient-reported outcome (PRO) and an activity tracker. The tool couples the difficulties associated with performing physical activity and the amount and intensity of the activities and the final instrument incorporates both a difficulty domain consisting of 10 questions and an amount domain consisting of 4 questions and 2 of these questions are based on data from the activity tracker.

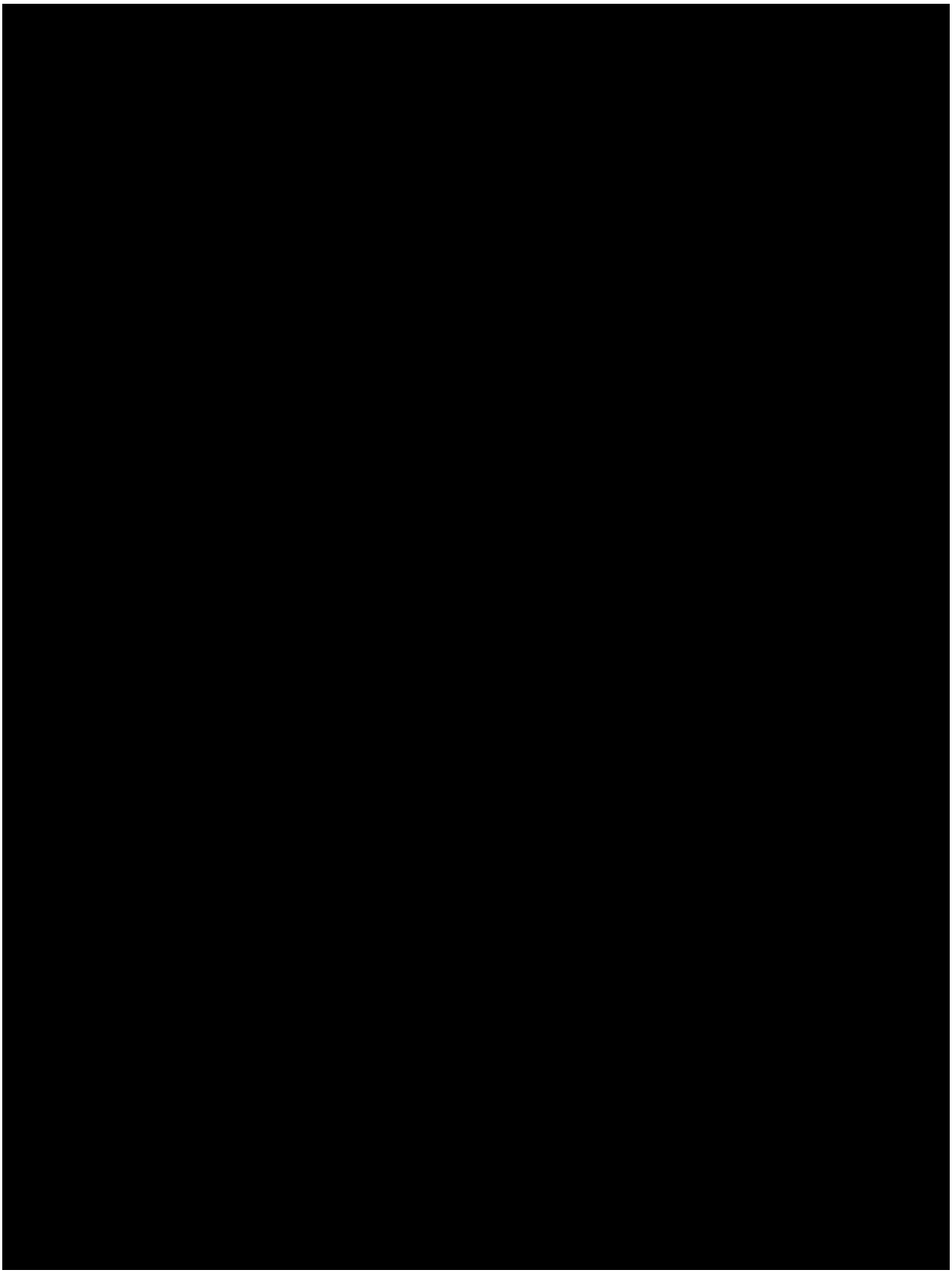
The difficulty domain includes questions related to breathlessness, but also includes questions related to other aspects of the difficulty associated with performing daily activities in IwCOPD.

The C-PPAC should be completed by the participants at the time points outlined in the flow chart. Details of the C-PPAC are provided in Appendix 10.2.2.









[redacted]

5.2 ASSESSMENT OF ENGAGEMENT AND PERCEPTIONS OF VALUE

Relevant information regarding assessment of engagement and perceptions of value is provided in Section 2.3 (Further research questions and further assessments) and in the 352-2154 Interview Guide.

5.3 ASSESSMENT OF SAFETY

5.3.1 Physical examination

NA

5.3.2 Vital signs

NA

5.3.3 Safety laboratory parameters

No safety laboratory parameters will be determined.

5.3.4 Electrocardiogram

NA

5.3.5 Other safety parameters

NA

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

5.3.6.1.1 Adverse event

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction

An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

5.3.7 Adverse Event Collection and Reporting

The investigator shall maintain and keep detailed records of all AEs in their patient files.

5.3.7.1 Collection of AEs

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a patient has been enrolled in the study and has taken study Spiriva Respimat or Stiolto Respimat, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point. See table below.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a written consent of the pregnant partner. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR, only the Pregnancy Monitoring Form and not the AE form is to be completed. If there is a serious ADR associated with the pregnancy a AE form must be completed in addition.

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug.

The following AE collection and reporting requirements have been defined:

All AEs and other safety relevant information identified via all sources used in the study have to be reported [via the study website (i.e. questionnaires), interviews, TARA platform] to the investigator for causality assessment (Section 5.3.7) and reporting to sponsor regardless of causal relationship.

5.3.7.2 Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance

Any AE or SAE must be reported to the sponsor within the timelines listed regardless of causality. The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provided to BI unique entry point:

Type of Report	Timeline
All **serious AEs**	immediately within 24 hours

All **non-serious AEs**	7 calendar days
Drug exposure during pregnancy	7 calendar days

All SAEs / AEs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the AE form.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

NA

5.5 ASSESSMENT OF BIOMARKER(S)

NA

5.6 BIOBANKING

NA

5.7 OTHER ASSESSMENTS

Modified Medication Research Council Dyspnea Scale
The mMRC Dyspnea Scale uses a simple grading system to assess a patient's level of dyspnea. All questions relate to everyday activities and are generally easily understood by patients. Score range from 0 (none) to 4 (very severe) and are usually obtained in a few seconds. Participants will be asked to score their dyspnea as part of the screener.
Details of the mMRC are provided in Appendix 10.2.11.

5.8 APPROPRIATENESS OF MEASUREMENTS

Questionnaires
The CRQ-SAI, D-PPAC, CAT, HADS are well established and validated questionnaires (R17-2573, R16-5353).

The Readiness to Change, TSRQ, PCS, HCCQ questionnaires are widely used in the study of behaviour change in a health care setting (R20-4003).

The VCCQ is a recently validated questionnaire specific for virtual care settings (R20-3985).

The SUS is a robust and valid tool (R19-2266).

Activity Tracker
The [redacted] device will be used as an activity tracker in this study. This is an electronic device used to measure physical activity levels of the participant. The device will be used according to manufacturer's guidance.

Medication Adherence
Self-reports of daily medication adherence are commonly thought to have issues with reliability, but Stirrat et al (R19-2202) reports that "evidence indicates that self-report adherence measures show moderate correspondence to other adherence measures and can significantly predict clinical outcomes" and conclude that "self-report medication adherence measures can provide actionable information despite their limitations".

Stirrat et al suggest that the quality of self-report adherence measures "may be enhanced through efforts to use validated scales, assess the proper construct, improve estimation, facilitate recall, reduce social desirability bias, and employ technologic delivery". In keeping with this recommendation, in the current study:

- Comparisons are conducted within-subject to reduce the effect of social desirability bias
- A technological delivery of the self-report is employed to provide an always-available way to record medication taking via a smartphone device, thus helping avoid issues with recall.
- All measures are administered remotely and can be completed in privacy and without research staff being present to reduce social desirability bias

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This study is a hybrid study where participants will interact with the site via clinic / telemedicine visits as indicated in the flow chart. It is preferable that any telemedicine visits are conducted via a video call, however if this is not possible then they can be done via a phone call.

The survey activities and engagement with the digital intervention TARA will take place remotely / on-line. The survey activities will be completed online via the study website at the time points outlined in the flow chart. As the TARA intervention is fully online and digital, participants in the study are free to use the intervention as much as they like during the 12-week study duration from their enrolment date.

The majority of study activities will be conducted remotely, and the number of on-site visits has been limited in this study. However, in case of an increased risk of SARS-CoV-2 infection due to physical visits to the sites, the visits should be conducted remotely (by video or phone call) if the Investigator judges that this is the safest course of action.

Study-specific reminder algorithms will be developed for situations where the study participant has not completed tasks within a certain timeframe. Additional details regarding this follow-up are outlined in the 352-2154 Study Operational Document.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Screening Period
The clinical site will identify potential participants for the study. Participants will be approached by the clinical site for participation in the study at one of their regular clinical visits as per the clinical sites' normal practice (e.g. in-person or via telemedicine). The prescribing physician will recommend use of TARA to patients who could benefit from self-management strategies at the same time as provision of a prescription for a once daily maintenance bronchodilator (Spiriva/Stiolto Respimat).

The clinical site will inform the participant about the trial and obtain informed consent in accordance with GCP (ISO 14155) and the local legislation. Once consented, participants will be given a unique ID and a link to the study website where they will log-in to complete a screening survey to ensure all inclusion and exclusion criteria are met.

Once the participant completes the screening survey, they will get a message describing whether or not they are eligible for the study.

Rescreening will be allowed on a case by case basis after discussion between the site and the sponsor.

Activity tracker shipment
Once the participant has signed consent and is determined to be eligible for the study, the activity tracker will be shipped to the study participant. Participants will be requested to wear the activity tracker during the run-in period, for the duration of the study and until the 12-week survey is completed.

Run-in Period
Once participants receive and activate the activity tracker, they will enter a 2-week run-in period. During this time, participants will wear the activity tracker and should take their medication as prescribed.

Pre-TARA Survey 1
Following the run-in period, participants will receive an email asking them to complete the pre-TARA survey. The email will have a link to the survey which will be completed on the study website. Refer to the flow chart for details of which questionnaires will be administered as part of this survey.

Login Instructions
After completion of pre-TARA survey 1, participants will receive their TARA login instructions via email along with expectations around use. The participant will then be able to login to the TARA web application.

6.2.2 Study and TARA Intervention period

TARA DBCI
Once the login is provided, participants will be able to engage with the TARA DBCI as much as they like during the 12-week intervention period. When they click on the "get help" buttons in the COPD program, they will receive an outreach by e-mail to explore what sort of help they are looking for and to resolve any issues, if possible. If the participant is interested in speaking with an MCP coach, they will receive an email to follow-up, and they will be asked to participate in the post-study IDI to give feedback on what they might want from a coach.

Activity Tracking
During the program use, participants will be asked to wear the activity tracker for the duration of the study.

Surveys
Also, during this period, participants will be requested to complete surveys at interim timepoints throughout the 12-week duration. Specifically, at 2 weeks, 4 weeks and 8 weeks after the start of the intervention period, participants will receive an email asking them to complete surveys 2, 3 and 4 respectively. The email will have a link to the survey which will be completed on the study website and consist of the CRQ-SAI, Readiness to Change and PCS questionnaires via the study website.

Survey 5
Participants will receive an email at the end of their intervention period at 12 weeks asking them to complete the 12-week survey 5. The email will have a link to the survey which will be completed on the study website. Refer to the flow chart for details of which questionnaires will be administered as part of this survey.

6.2.3 Follow-up period (study completion)

Follow-up visit (Clinic visit or Telemedicine)
After completion of the post-TARA survey 5, participants will have a follow-up with the clinical site. This visit should be performed within 7 days of the clinical site receiving the email notification to schedule the visit. The visit can be performed in clinic, however if there are issues with scheduling, the visit can be accommodated as a telemedicine visit preferably via video call. At this visit, a summary report from TARA will be shared by the participant with the HCP to update the HCP on their progress in symptom self-management. The site should ask the participant about any AEs at this visit.

Once the participant has completed the follow-up visit, they will be requested to return the activity tracker.

Post-Study Survey 6
After the follow-up visit, participants will receive an email asking them to complete the post-TARA survey 6. The email will have a link to the survey which will be completed on the study website. This survey will assess participants' impression of TARA, their willingness to recommend it in future and the interactions with their HCPs regarding TARA.

For participants not selected for the interview, this will mark the end their participation in the study.

Post-TARA In-depth Interview (IDI)
When participants receive their end-of-study emails, a sub-set of 8 to 15 participants will be asked to schedule an in-depth interview lasting approximately 60 minutes to be conducted remotely with a member of the digital technology research team (see Appendix 10.1.2 and the interview guide for more details). The final number of participants will be decided based on the sample set at which saturation of qualitative insight is achieved (no further new information is obtainable through interviews). Priority for invitations to the IDI will be given to participants who requested an MCP coach during the course of the study in order to allow them to give feedback on what they might want from a coach. At the end of the interview, participants will be asked to return the activity tracker if they have not done so.

All HCPs will be asked to participate in an interview lasting approximately 45 minutes to be conducted remotely with a member of the digital technology research team (see Appendix 10.1.3 and the interview guide for more details).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

According to established standards for evaluating behavioural treatments for chronic disease (R19-2270), in Phase IIa proof-of-concept studies: (i) a quasi-experimental pre-post study is considered an appropriate study design, and (ii) since clinical, not statistical benefit is sought, identification of formal null and alternative hypotheses, as well as power calculations and sample size estimates are considered unnecessary.

The hypothesis for this study states that compared to baseline, IwCOPD will experience a clinically significant reduction in breathlessness after 12 weeks of receiving a digital behaviour change intervention for COPD self-management (TARA version 3).

7.2 PLANNED ANALYSES

7.2.1 General considerations

In order to conclude that engagement with TARA leads to a patient benefit with regards to changes in breathlessness, it is important to confirm that any reduction in breathlessness at follow-up compared to baseline is not a consequence of a reduction in physical activity. Therefore, a preliminary analysis will be conducted to evaluate if changes in breathlessness vary with changes in physical activity from baseline to follow-up.

Analysis will be performed separately for each cohort (Cohort 1: non-pharmacological self-management support; Cohort 2: non-pharmacological + pharmacological self-management support). Pooled analysis between the cohorts will not be performed.

All patients enrolled will be included in analysis. Additional explorative analysis will be described in statistical analysis plan.

Preliminary Analysis:

Study participants will be divided into three categories based on the level of change in their physical activity from baseline to 12-week follow-up using steps as a standard measure of activity. Each participant's activity (steps) data will be descriptively analysed and standardized. Based on the distribution of observed data, participants will then be categorized into groups using an appropriate criterion of change such as:

- Decreased activity: Activity level has decreased 1 SD or more at follow-up
- Increased activity: Activity level has increased 1 SD or more at follow-up
- No change: All other participants

Following this categorization, differences in breathlessness scores (using the CRQ-SAI dyspnea domain) will be computed for each group between baseline and 12-week follow up

and comparisons conducted between groups. This analysis will evaluate if changes in breathlessness continue to be seen regardless of changes in physical activity.

7.2.2 Primary assessment analyses

For the primary assessment, the CRQ-SAI dyspnea domain will be used to calculate breathlessness measures at baseline and week 12. Analyses to be conducted include the following:

- The percentage of the study population who experience a clinically significant decrease in breathlessness (minimal clinically important difference (MCID) of 0.5) will be calculated.
- The difference between week 12 and baseline will be calculated and compared against the criterion of minimal clinically important difference (MCID) of 0.5.

7.2.3 Secondary endpoint analyses

Descriptive statistics of additional secondary endpoint variables will be explored for selection of best-fit analysis techniques. Pre-post differences in the physical activity experience will also be explored to see if TARA v3 has had a positive effect on the perceived difficulty during activities.

7.2.5 Safety analyses

Standard BI summary tables and listings will be produced. All adverse events with an onset between informed consent signature and end of the post-TARA IDI will be assigned to the study period for evaluation.

All study participants will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

7.2.6 Other Analyses

NA

7.2.7 Interim Analyses

NA

7.3 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.
For the primary endpoint analysis, imputation of missing values will not be performed. Patterns of missing data will be analyzed descriptively and summarized. Further sensitivity analyses to assess the robustness of the results on the primary endpoint may be performed and will be described in the TSAP. For further endpoints, rules for handling of missing data will be specified in the TSAP if necessary. With respect to safety evaluations, it is not planned to impute missing values.

7.4 RANDOMISATION

NA

7.5 DETERMINATION OF SAMPLE SIZE

As per section 7.1, sample size power calculations are not required for ORBIT Phase IIa studies. Based on a literature review of similar ORBIT Phase IIa proof of concept studies, as well as consultation with behavioural science experts, a sample size of 25 subjects per cohort (50 subjects overall) was deemed appropriate for an initial evaluation of whether engagement with TARA results in a clinically significant change in breathlessness at 12-week follow-up compared with baseline. This study will be further used to generate the data needed to perform sample size power calculations in future studies.

The following number of participants will be recruited into each cohort:

- Cohort 1: up to a maximum of 25 IwCOPD (non-pharmacological self-management support)
- Cohort 2: up to a maximum of 25 IwCOPD (non-pharmacological + pharmacological self-management support)

8. INFORMED CONSENT, STUDY RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The study will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki and relevant BI Standard Operating Procedures (SOPs).

In addition, the study will be carried out in accordance with principles of the Medical Devices Directive (93/42/EEC), as far as possible in this early stage of development, and the following relevant aspects of the ISO document "Clinical Investigation of Medical Devices for Human Subjects – good clinical practice" (ISO 14155, current version):

- Protection of the rights, safety and well-being of human subjects
- Assurance of the scientific conduct of the clinical investigator
- Definition of the responsibilities of the sponsor and principal investigator.

Investigators and site staff must adhere to these principles. Deviation from the protocol, applicable principles or applicable regulations will be treated as "protocol deviation".

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the participant.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the study participants against any immediate hazard, as well as of any serious breaches of the protocol or of GCP (ISO 14155) (see Appendix 10.5).

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a rule, no study results should be published prior to finalisation of the study report.

8.1 STUDY APPROVAL, PARTICIPANT INFORMATION, INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient according to GCP (ISO 14155) and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the

informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this study may be conducted by the sponsor. The quality assurance auditor will have access to the investigator's study-related files and correspondence, and the informed consent documentation of this study.

8.3 RECORDS

8.3.1 Source documents

- electronic record is the source document)electronic record is the source document)In accordance with regulatory requirements, the investigator and digital technology research team should prepare and maintain adequate and accurate source documents and study records that include all observations and other data pertinent to the investigation on each study participant. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

8.3.2 Direct access to source data and documents

The investigator will allow site study-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access must be provided to all source documents/data, including progress notes, which must be available at all times for review by the CRA, auditor and regulatory inspector. They may review all informed consents. Where appropriate, the accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will monitor compliance with the protocol and GCP (ISO 14155).

8.3.3 Storage period of records

Study site:
The study site must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the study (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of participant data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual participant data obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalised treatment data may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare. Data generated at the site as a result of the study need to be available for inspection on request by the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 STUDY MILESTONES

The **start of the study** is defined as the date when the first participant in the whole study signs e-informed consent.

The end of the study is defined as the date of the last visit of the last participant in the whole study ("Last Participant Completed"). **Early termination of the study** is defined as the premature termination of the study due to any reason before the end of the study as specified in this protocol.

Temporary halt of the study is defined as any unplanned interruption of the study by the sponsor with the intention to resume it.

Suspension of the study is defined as an interruption of the study based on a Health Authority (HA) request.

8.7 ADMINISTRATIVE STRUCTURE OF THE STUDY

The study is sponsored by Boehringer Ingelheim (BI).

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Study Team Lead, responsible for coordinating all required activities, in order to

- manage the study in accordance with applicable regulations and internal SOPs,
- direct the study team in the preparation, conduct, and reporting of the study
- ensure appropriate training and information of the investigator.

The organization of the study in the participating countries will be performed by a Contract Research Organization (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical study.

The web-based platforms used to capture data collected in the study and for TARA will be developed by a digital technology provider with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical study.

Data Management and Statistical Evaluation will be done in collaboration with an external consultant

Tasks and functions assigned in order to organise, manage, and evaluate the study are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

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9.2 UNPUBLISHED REFERENCES

Not applicable

10. APPENDICES

10.1 DETAILS OF EX-TARA ASSESSMENT TOOLS

10.1.1 Baseline, Interim and Follow-up Survey Assessments

The baseline survey will be provided to participants before they have access to the TARA program. See flow chart for a complete list of survey timepoints.

Survey 1 will be administered at the end of the run-in period and will contain the following elements:

- Chronic Respiratory Questionnaire – Self Administered Individualized (CRQ-SAI)
- Clinical Visit PROactive Physical Activity in COPD Instrument (C-PPAC)
- A Knowledge assessment for COPD self-management
- Treatment Self-Regulation Questionnaire (TSRQ)
- Perceived Competence Scale (PCS)
- Health Care Climate Questionnaire (HCCQ)
- Medication adherence questions
- COPD Assessment Test (CAT)
- Hospital Anxiety and Depression Scale (HADS)
- Questions assessing barriers to medication adherence

Interim surveys during the TARA usage period include the following.

Surveys 2, 3 and 4 will be administered at 2, 4 and 8 weeks from start of study respectively and will contain the following elements:

- Chronic Respiratory Questionnaire – Self Administered Individualized (CRQ-SAI)
- Readiness to change
- Perceived Competence Scale (PCS)

Survey 5 will be the 12-week survey and will contain the following elements:

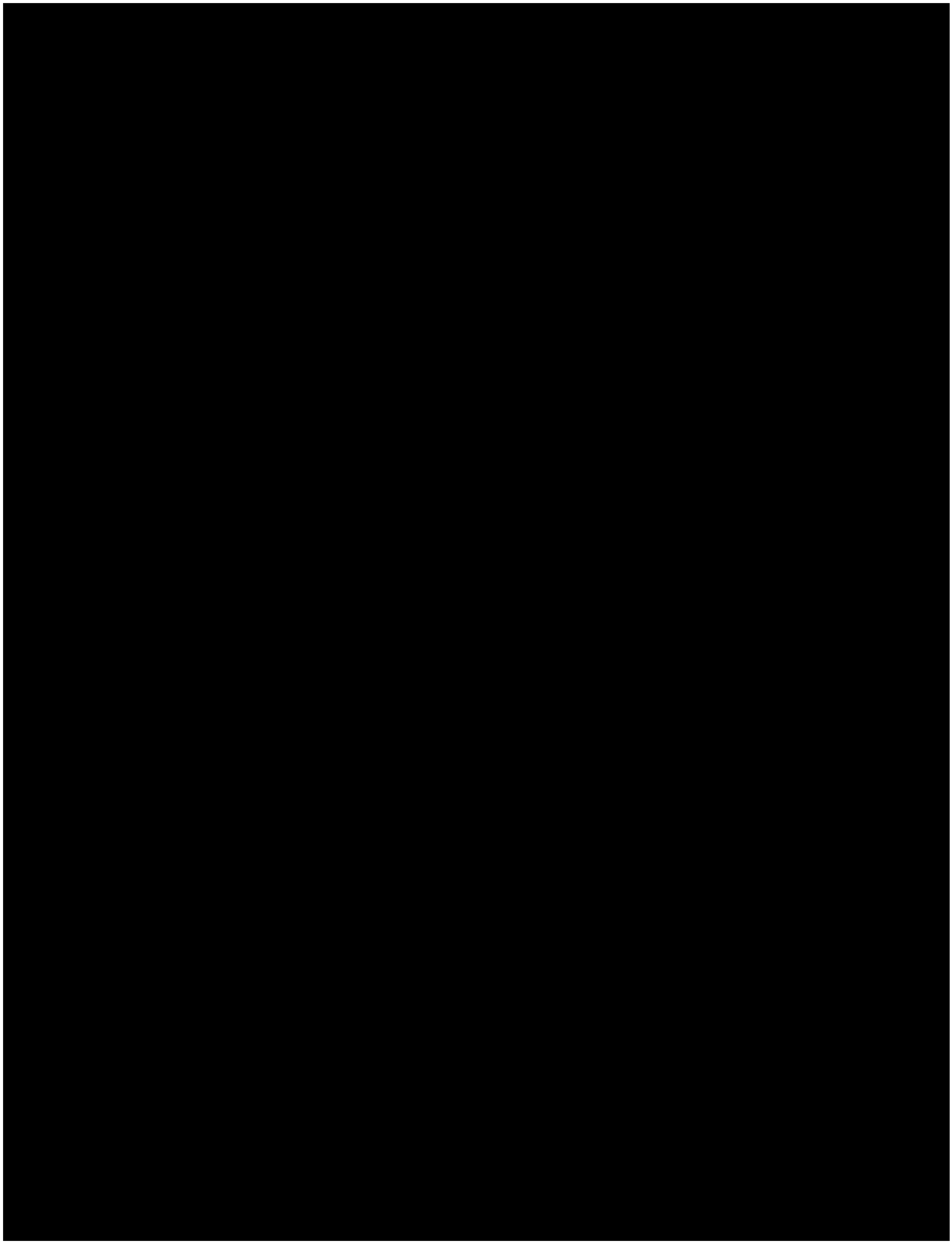
- Chronic Respiratory Questionnaire – Self Administered Individualized (CRQ-SAI)
- Clinical Visit PROactive Physical Activity in COPD Instrument (C-PPAC)
- Readiness to change
- A Knowledge assessment for COPD self-management
- Treatment Self-Regulation Questionnaire (TSRQ)
- Perceived Competence Scale (PCS)
- Virtual Care Climate Questionnaire (VCCQ)
- Questions measuring medication adherence, PLB and pacing
- COPD Assessment Test (CAT)
- Hospital Anxiety and Depression Scale (HADS)
- Questions assessing barriers to medication adherence
- Healthcare resource utilization

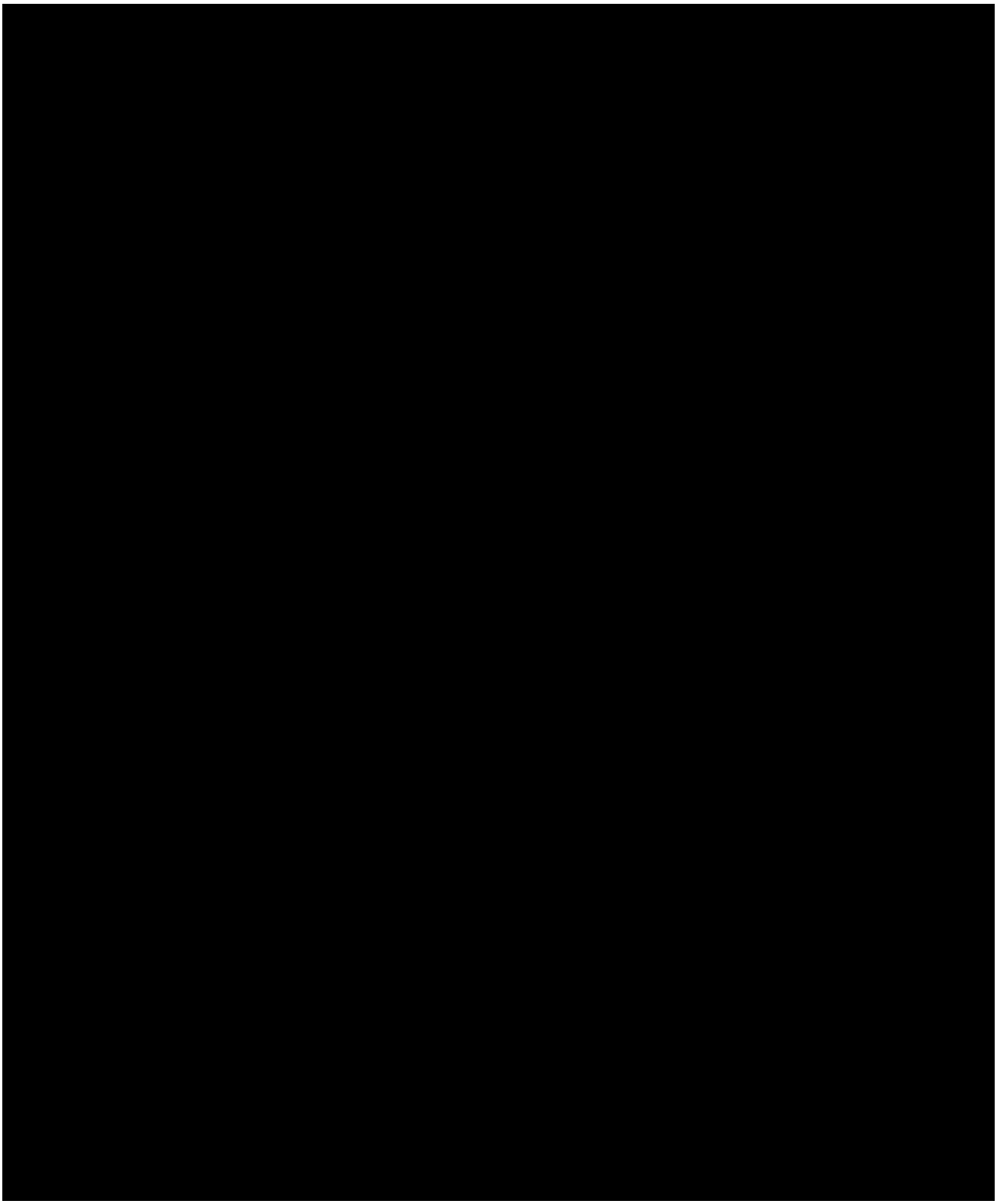
Survey 6 will be the final survey administered after the follow-up clinic visit and will contain the following elements:

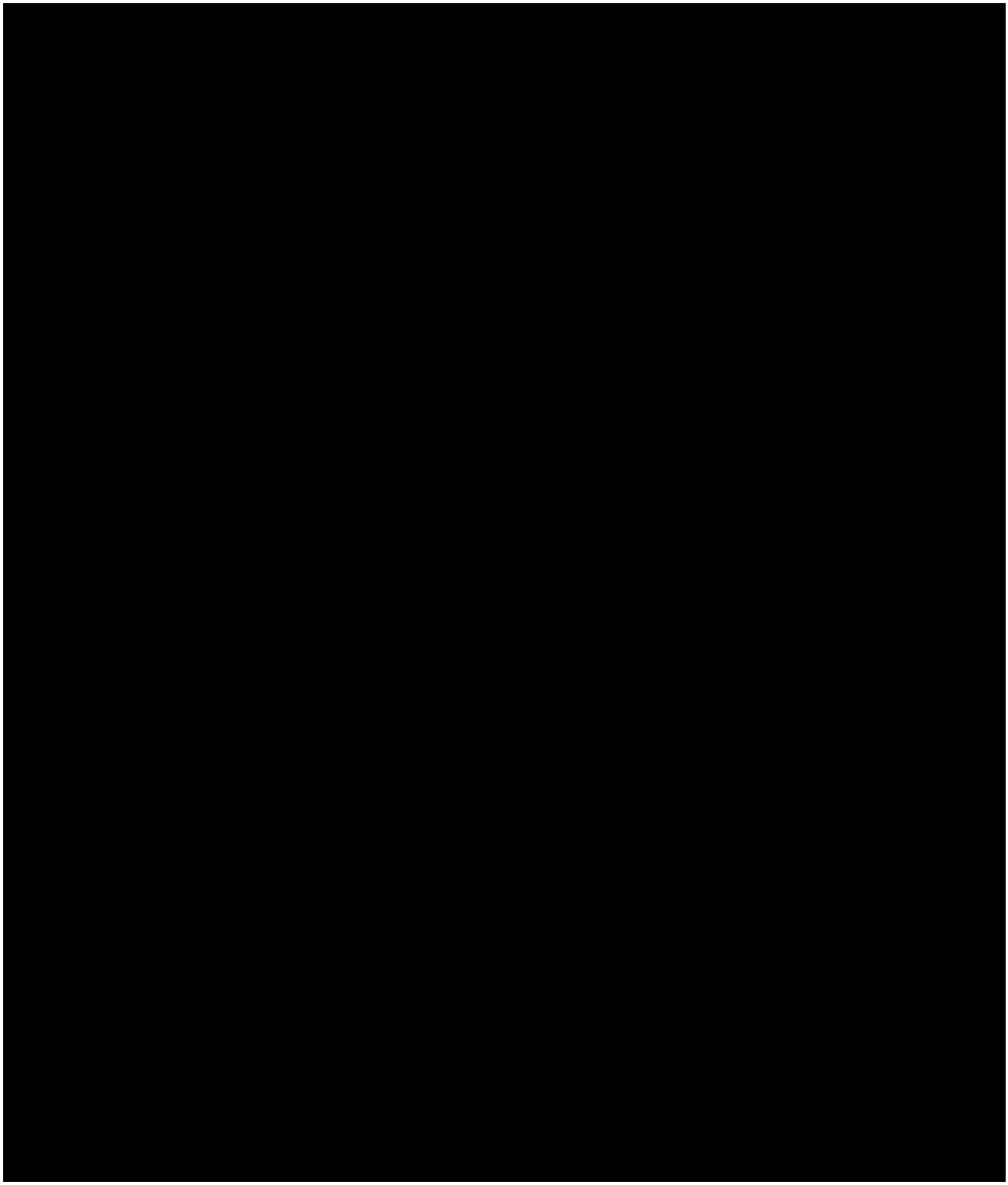
- System Usability Scale (SUS) https://measuringu.com/sus/

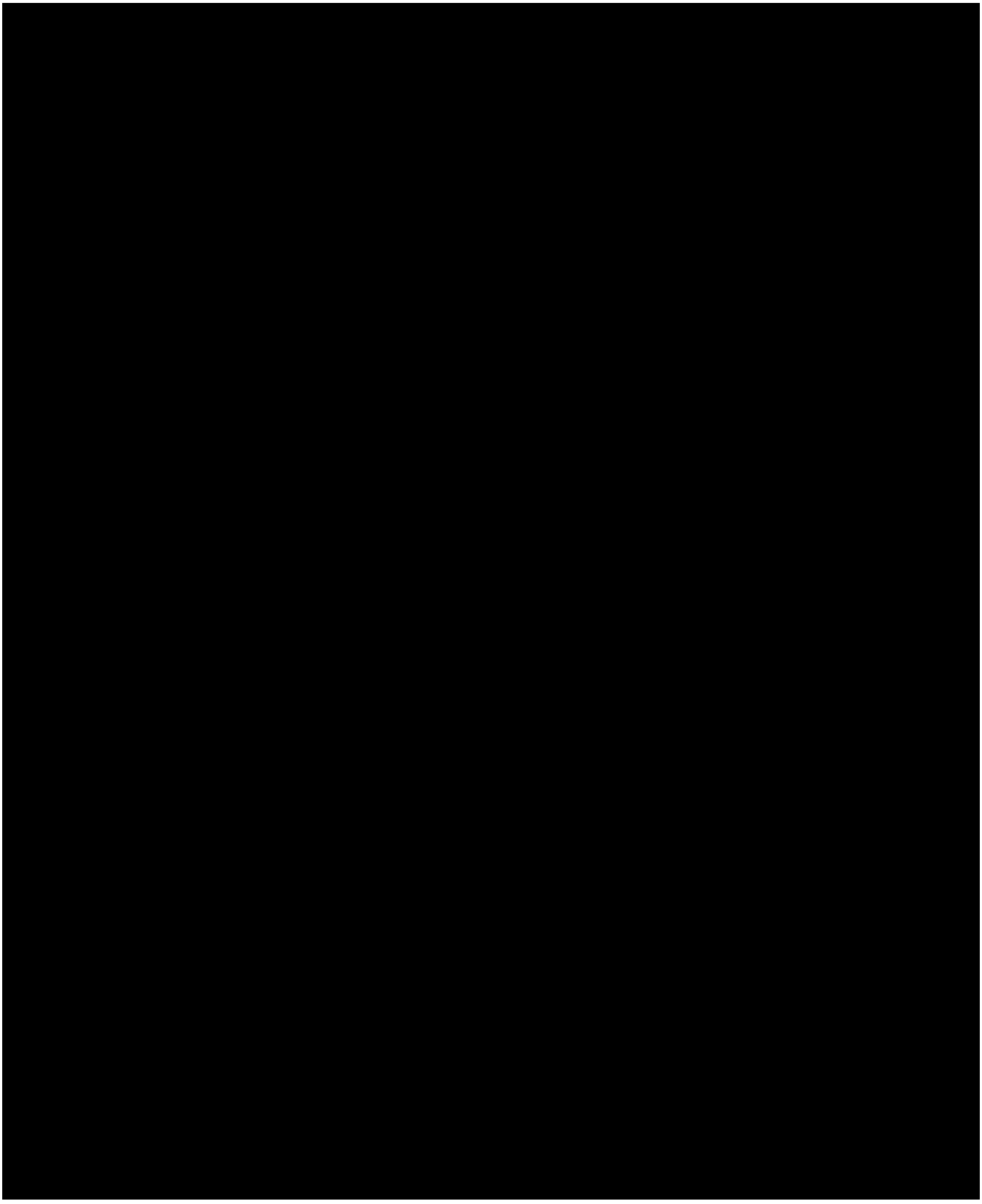
- 'Perceived value and satisfaction of TARA' Questions
    - These questions will explore participants satisfaction and willingness to recommend TARA (from Net Promoter Score (NPS) Survey)

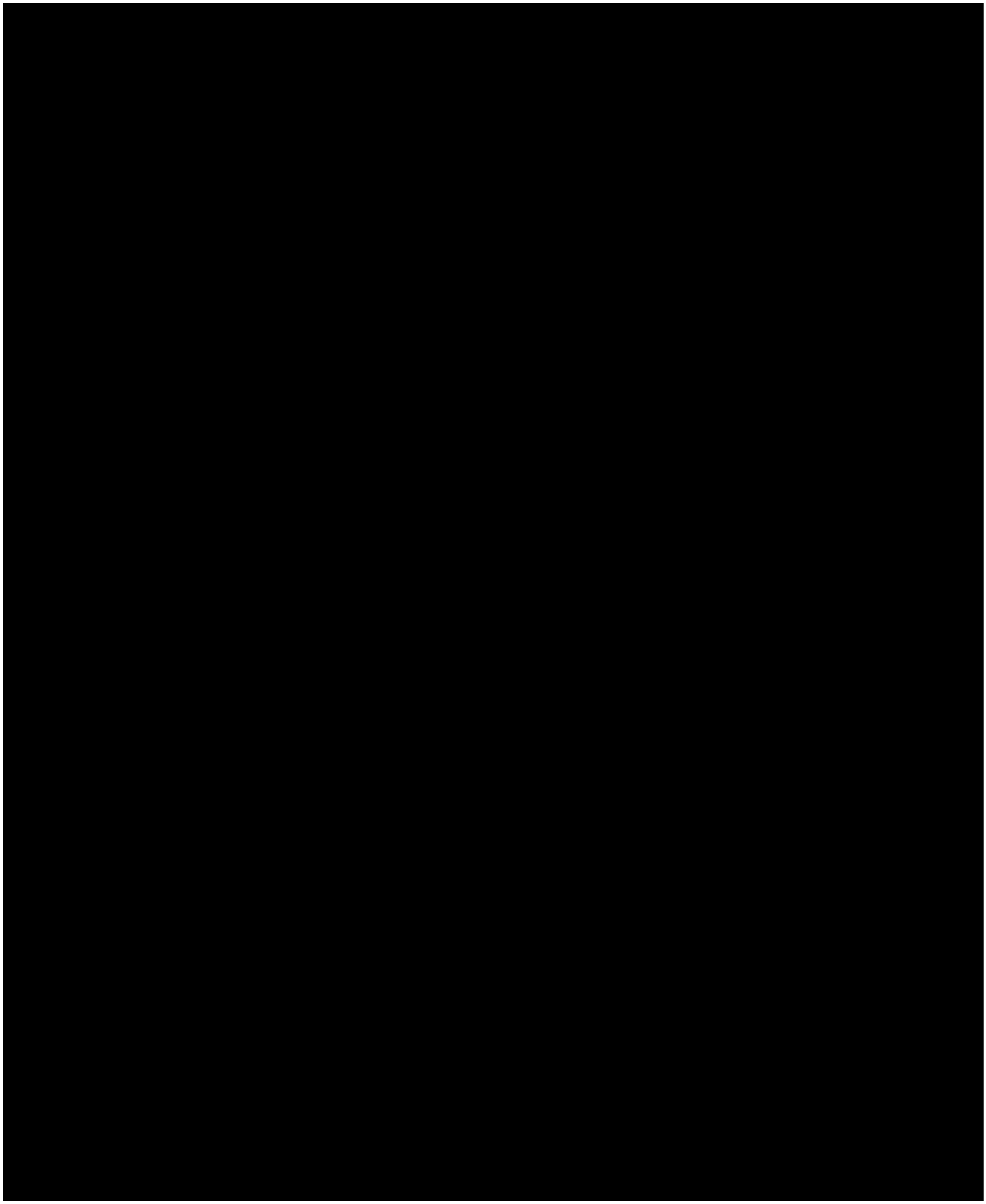
[redacted]

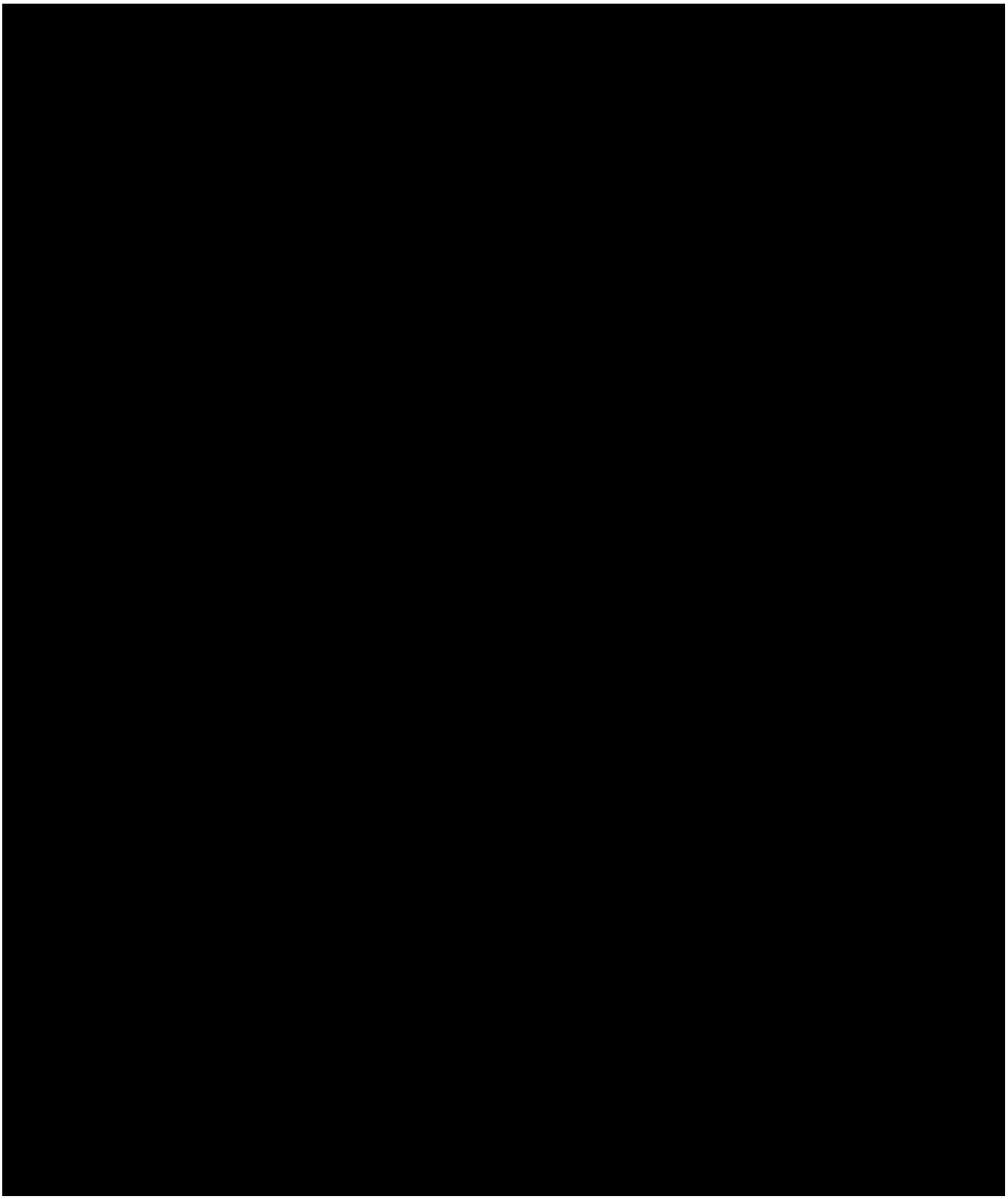


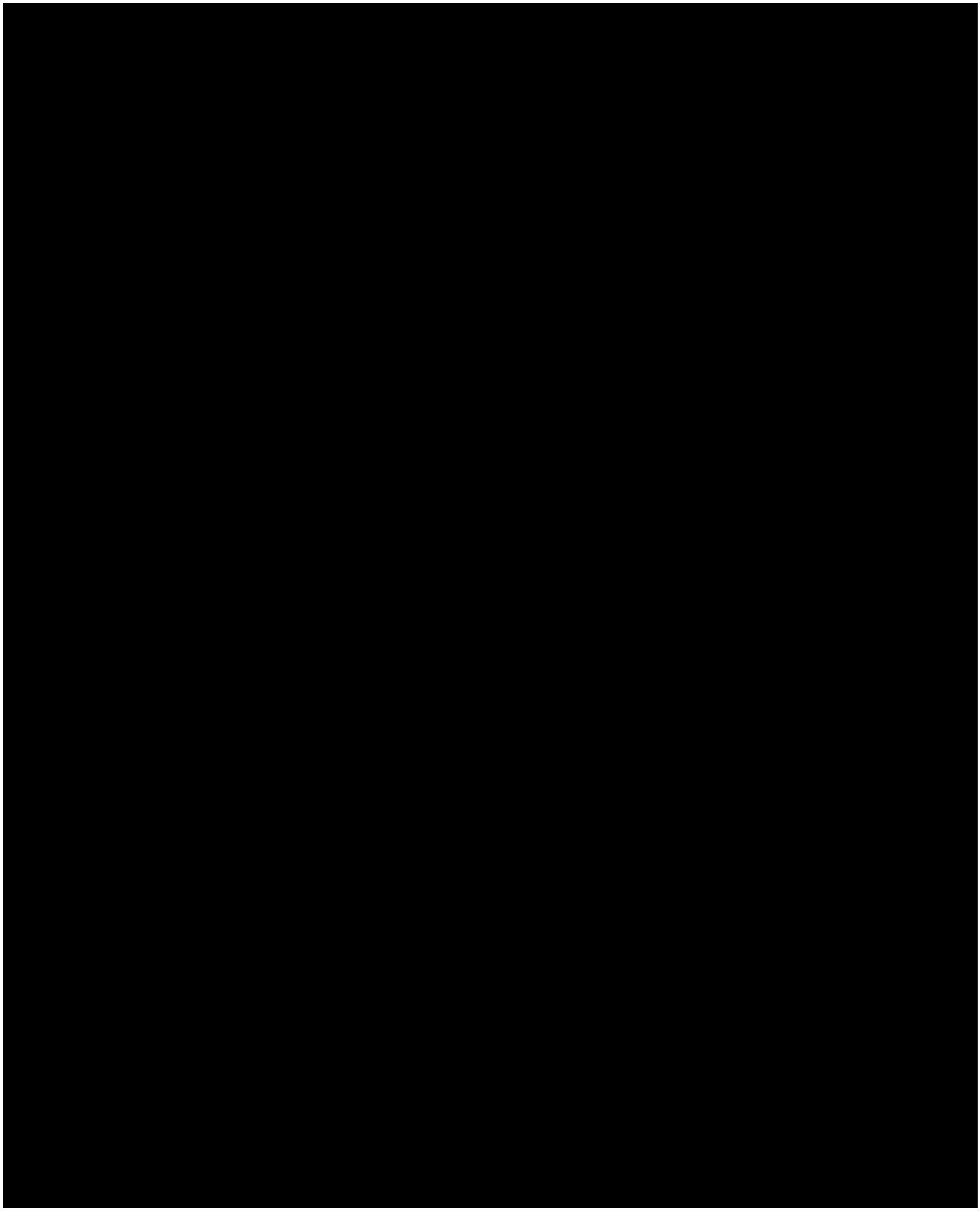


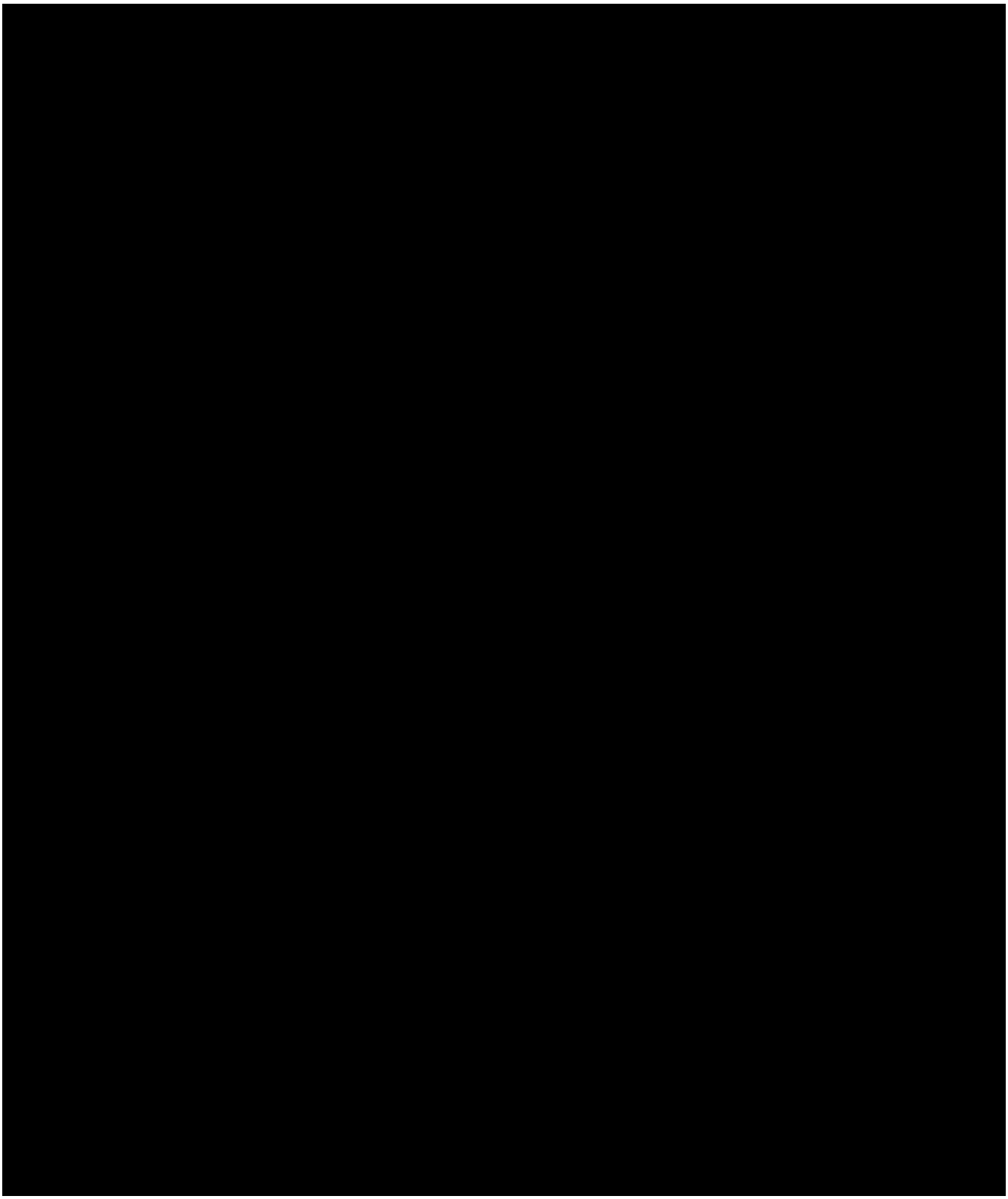


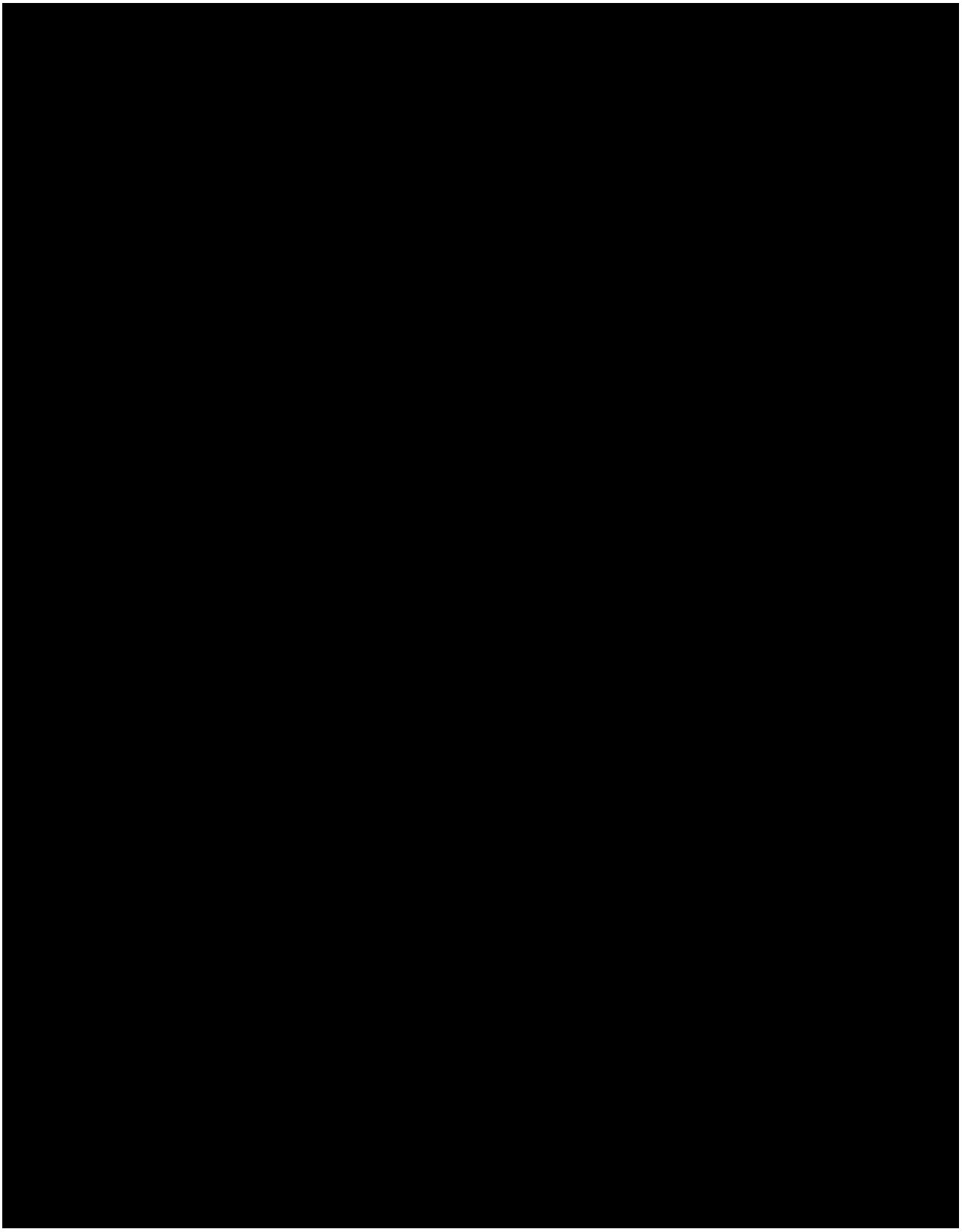


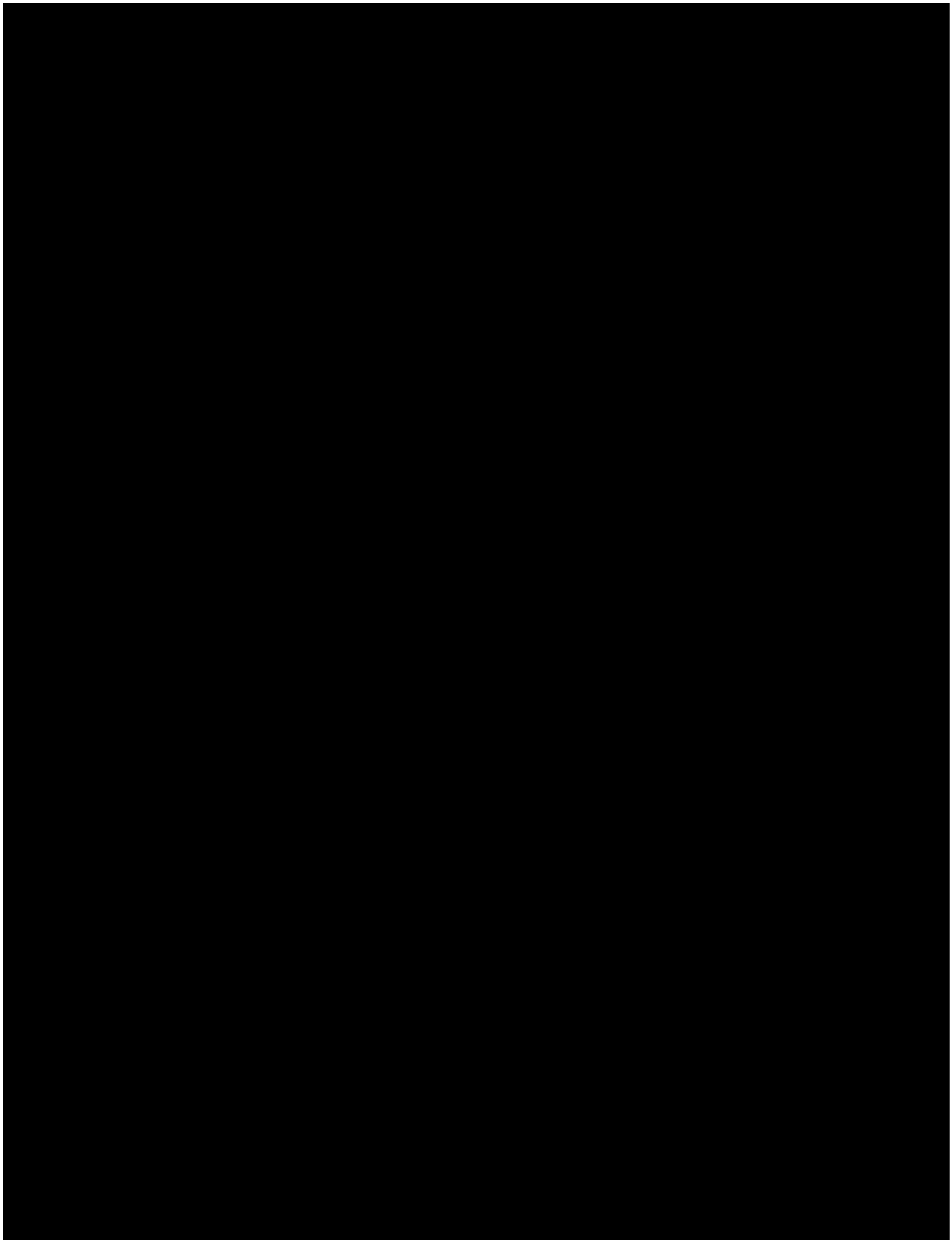


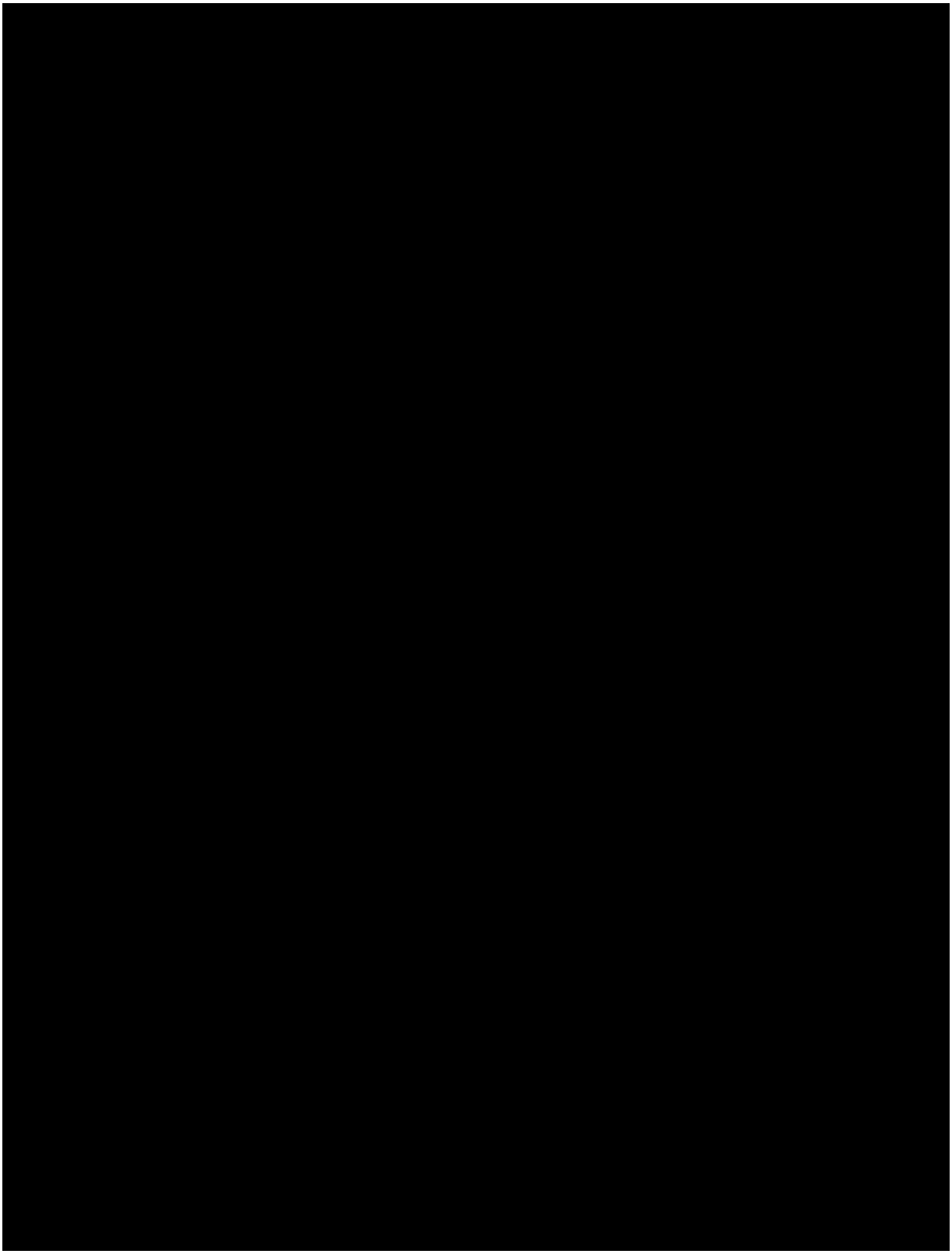


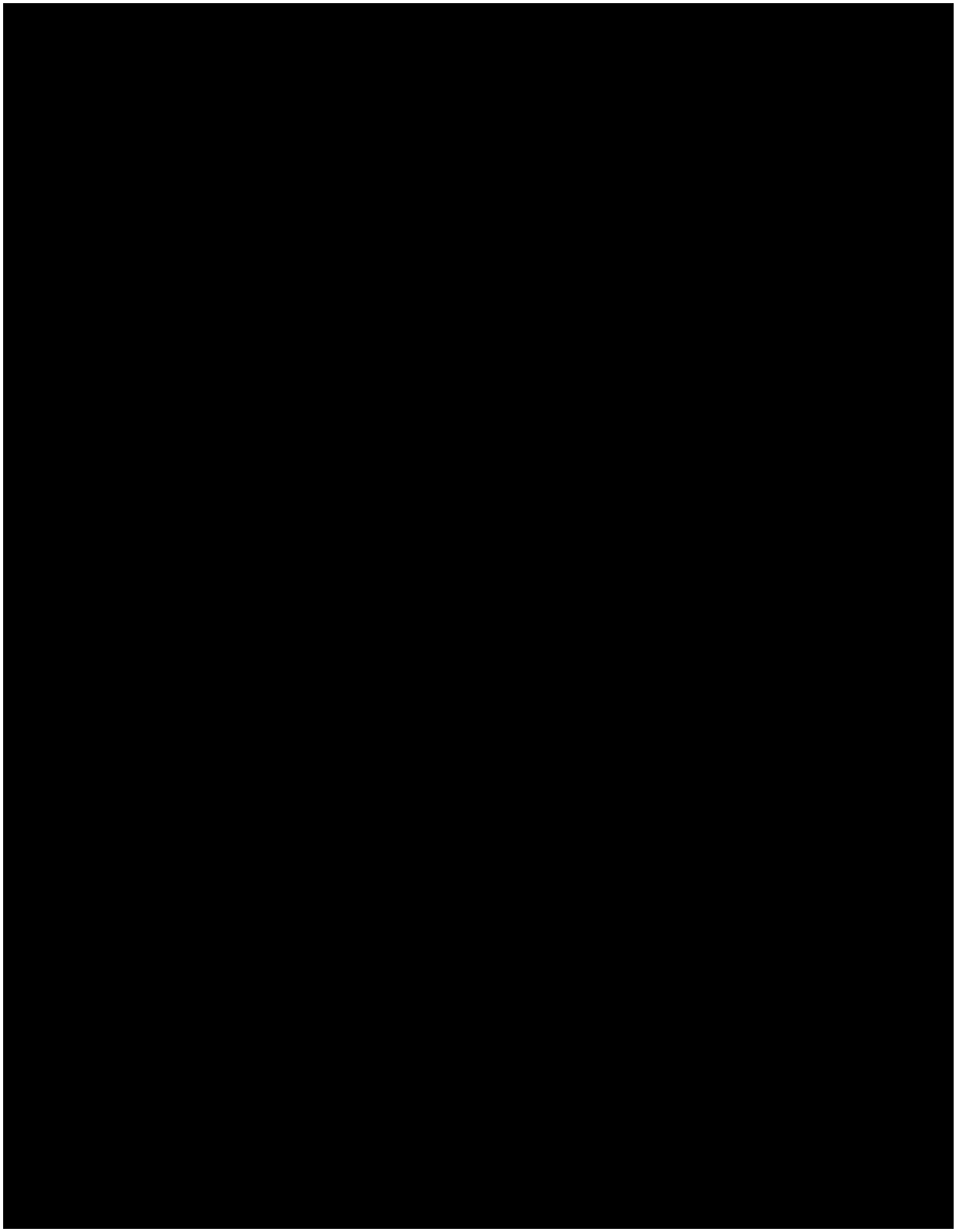


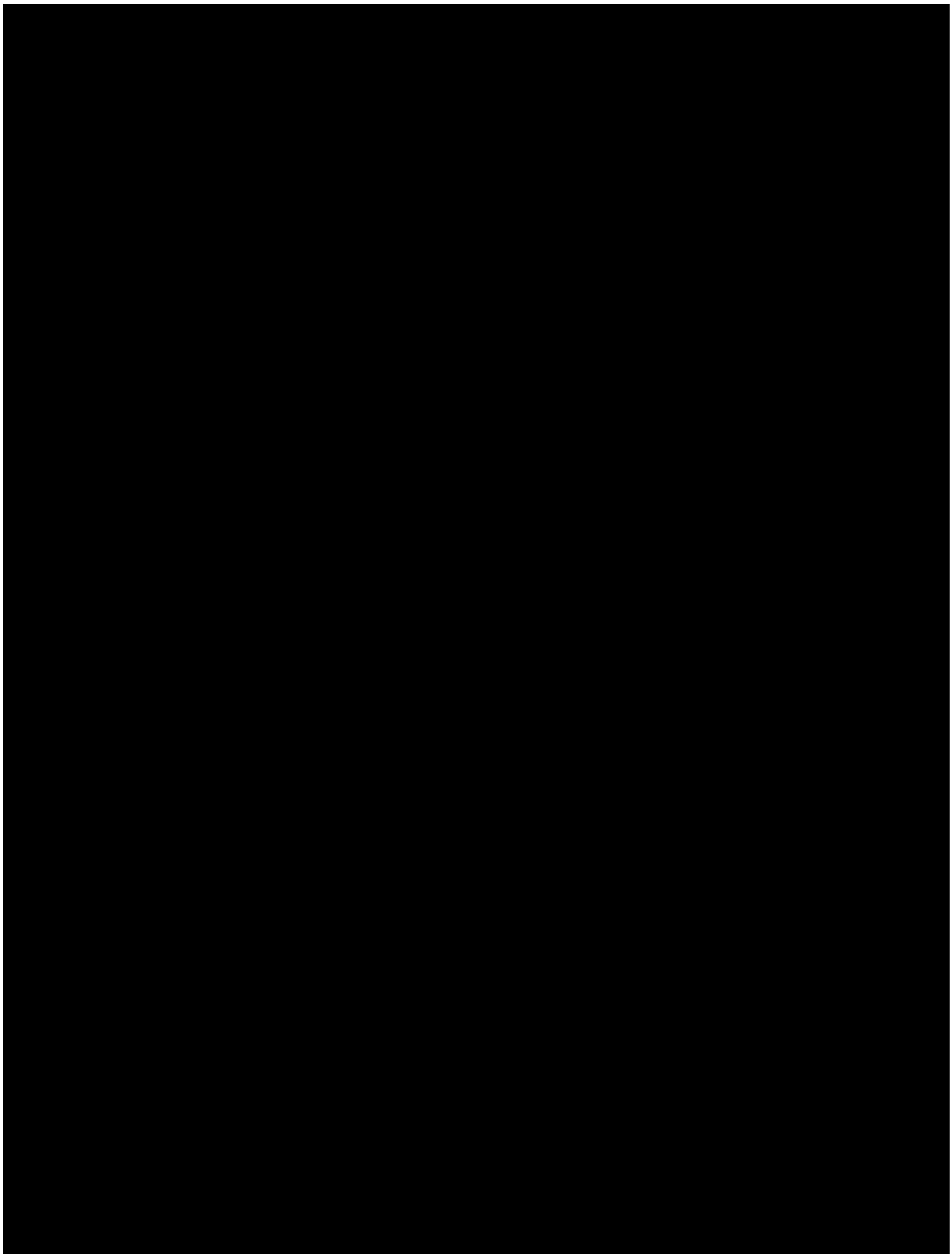


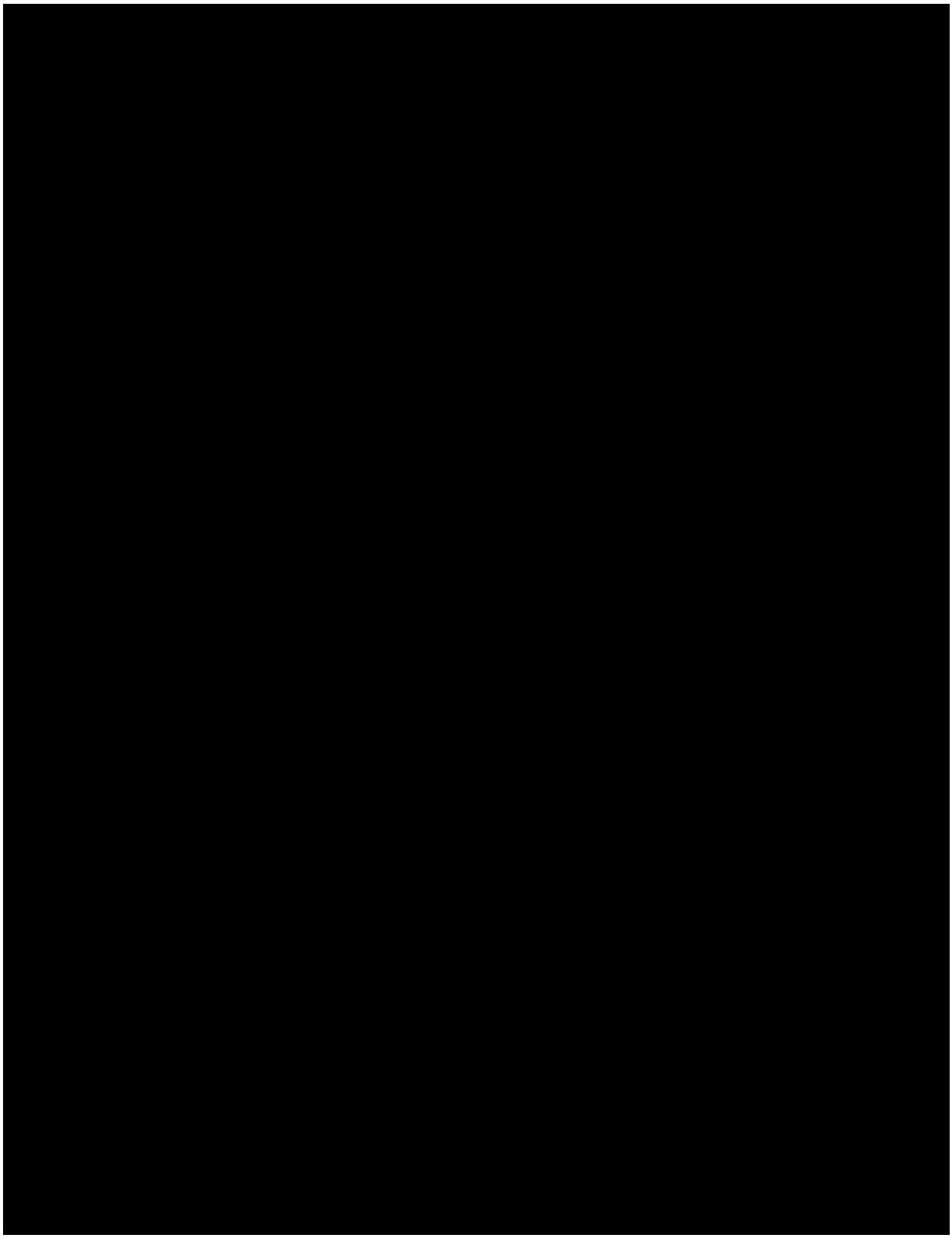


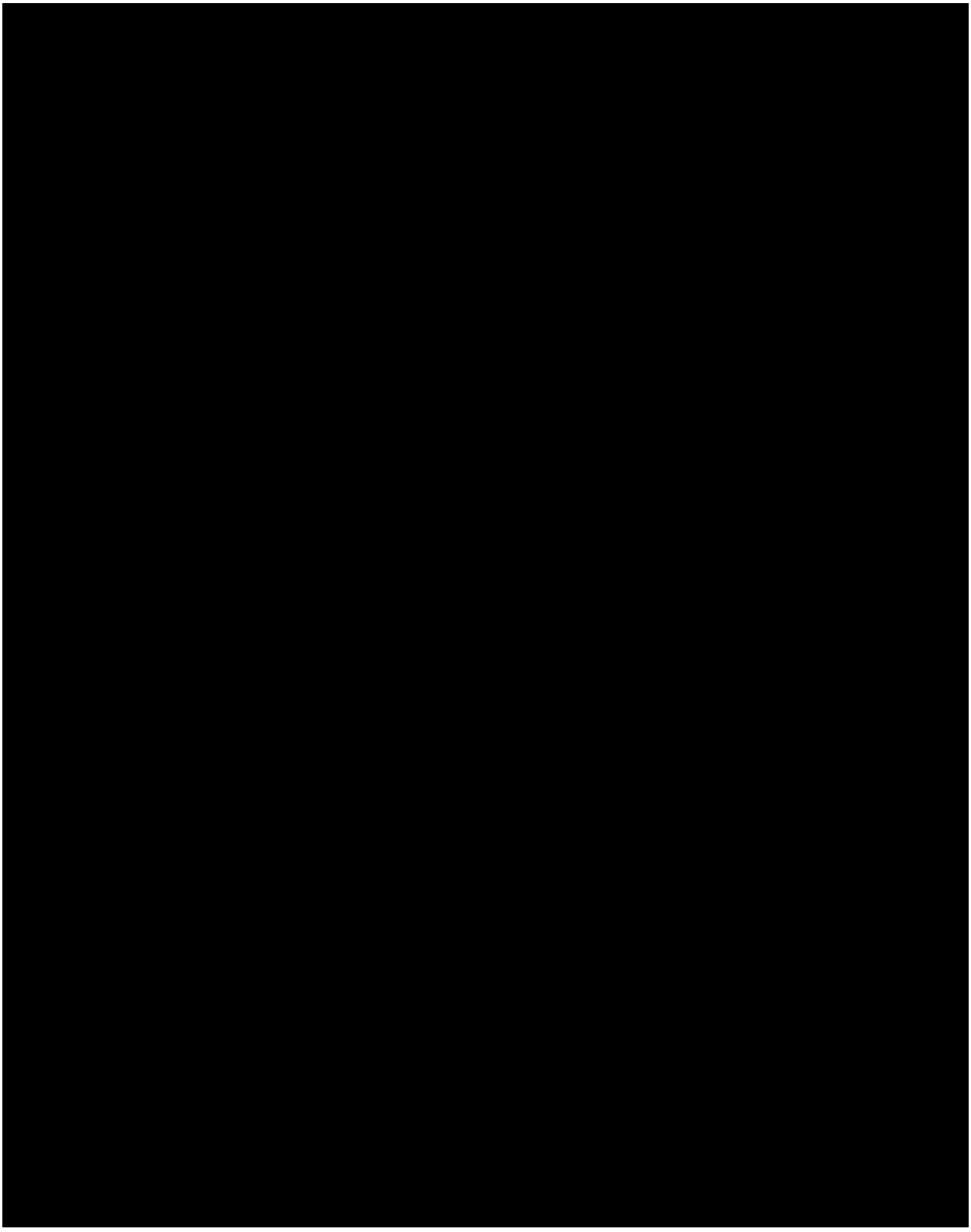


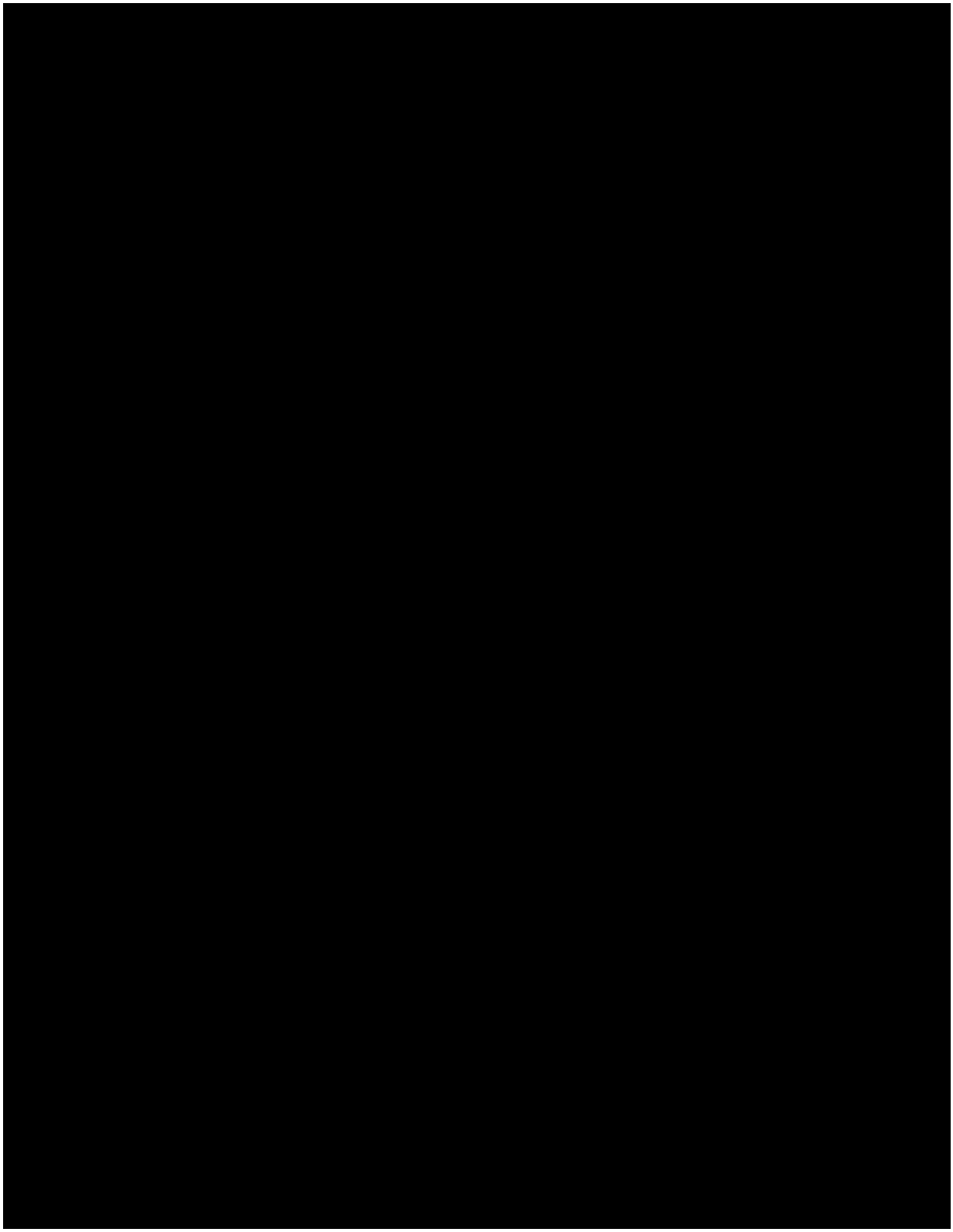


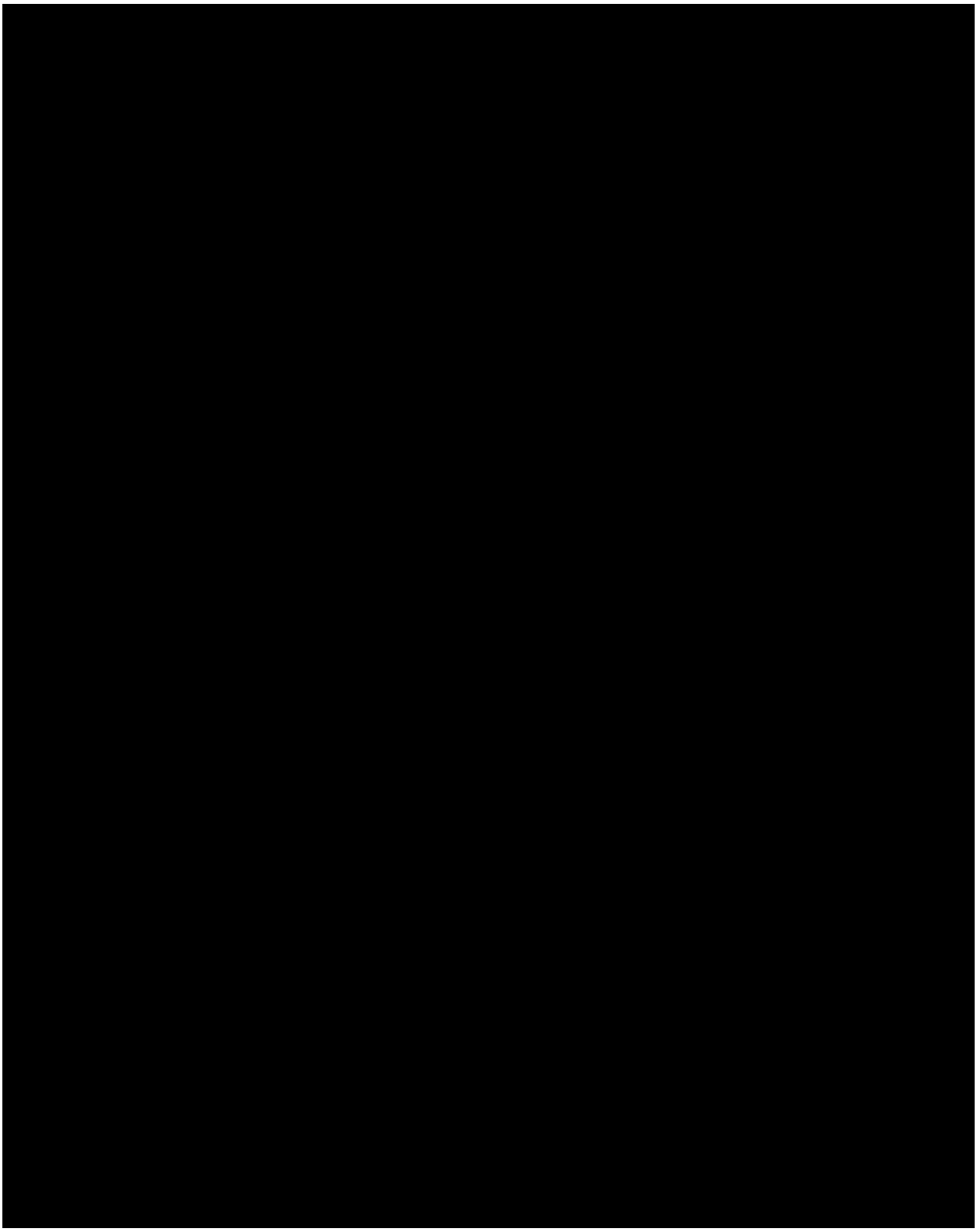


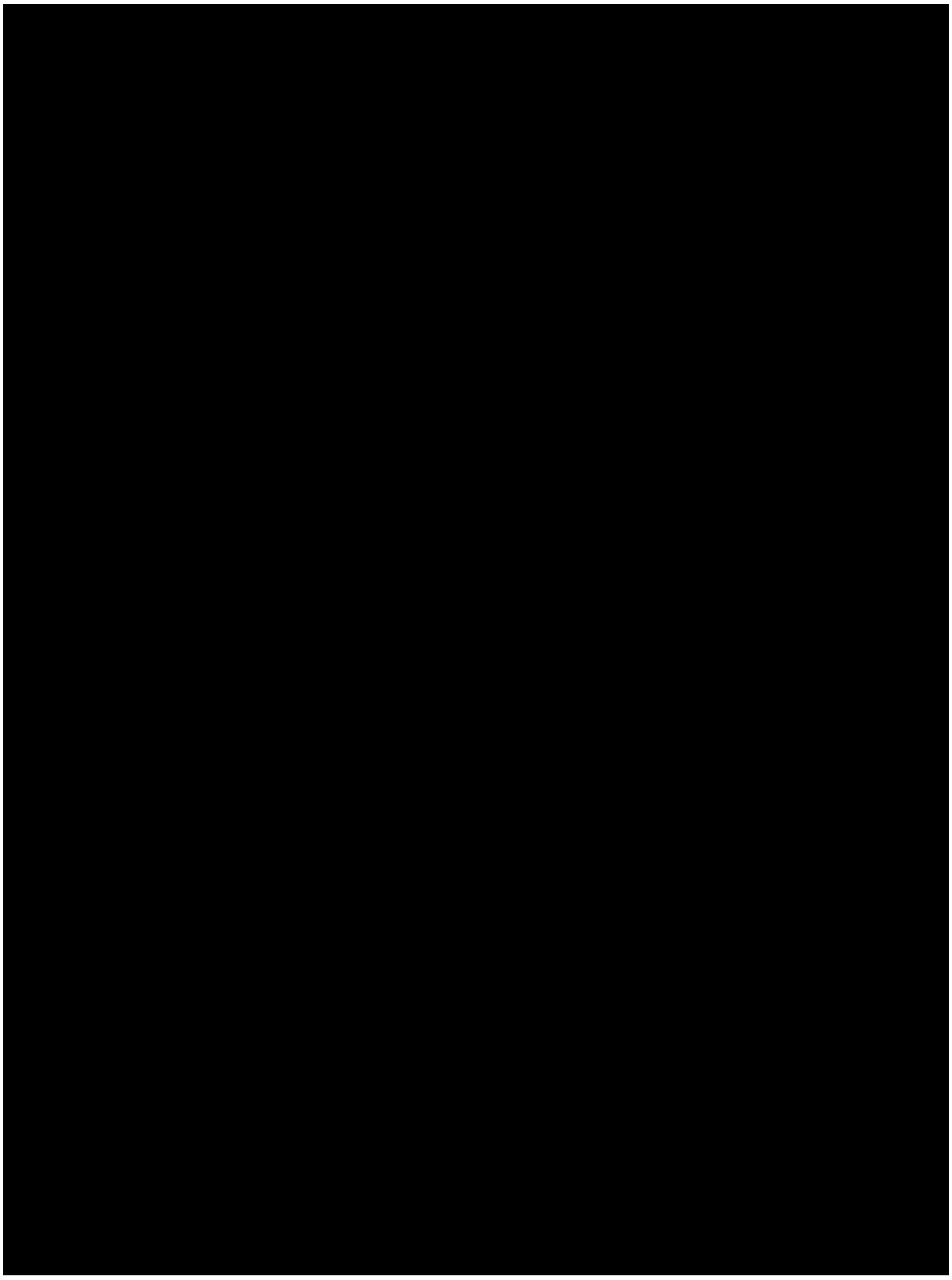


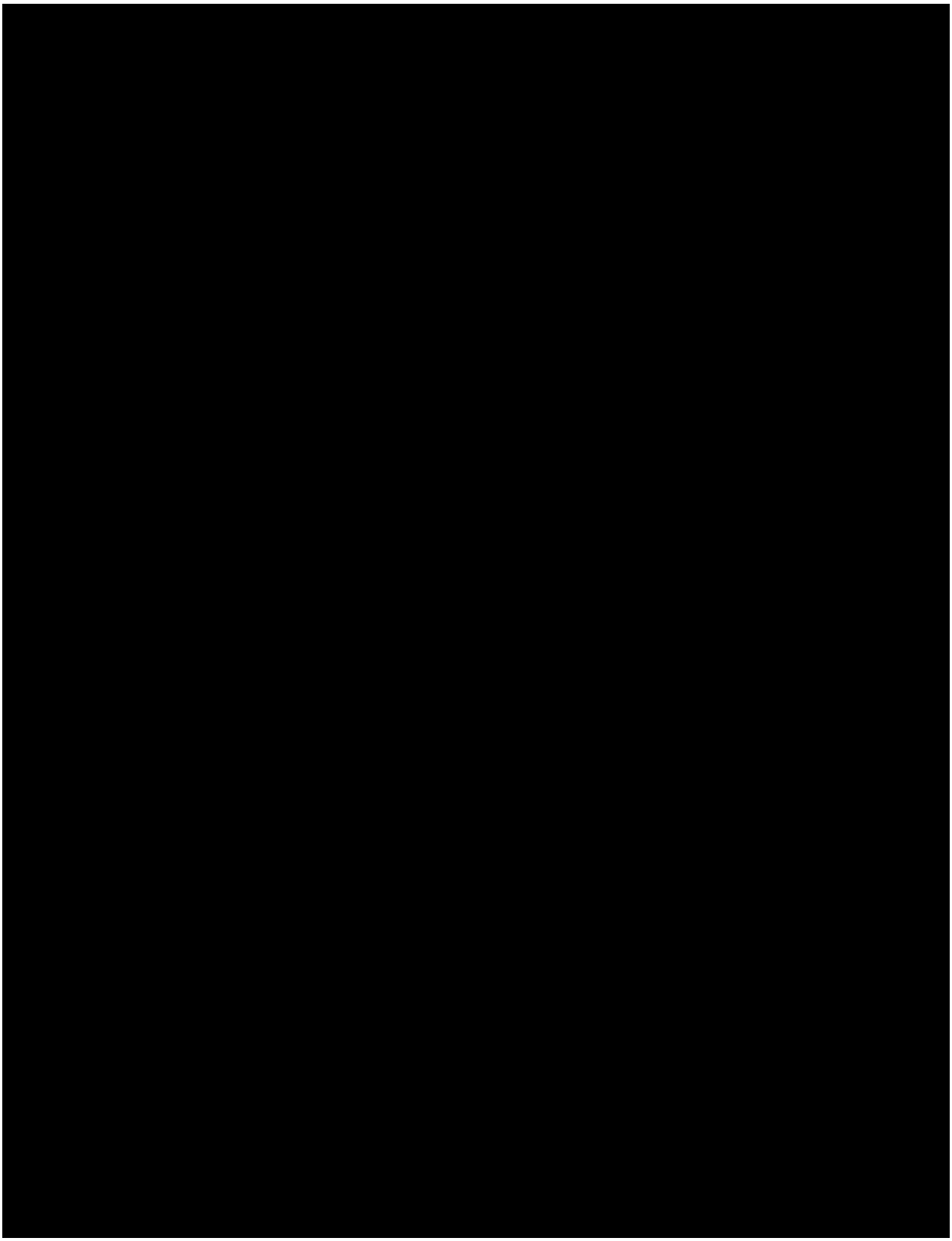


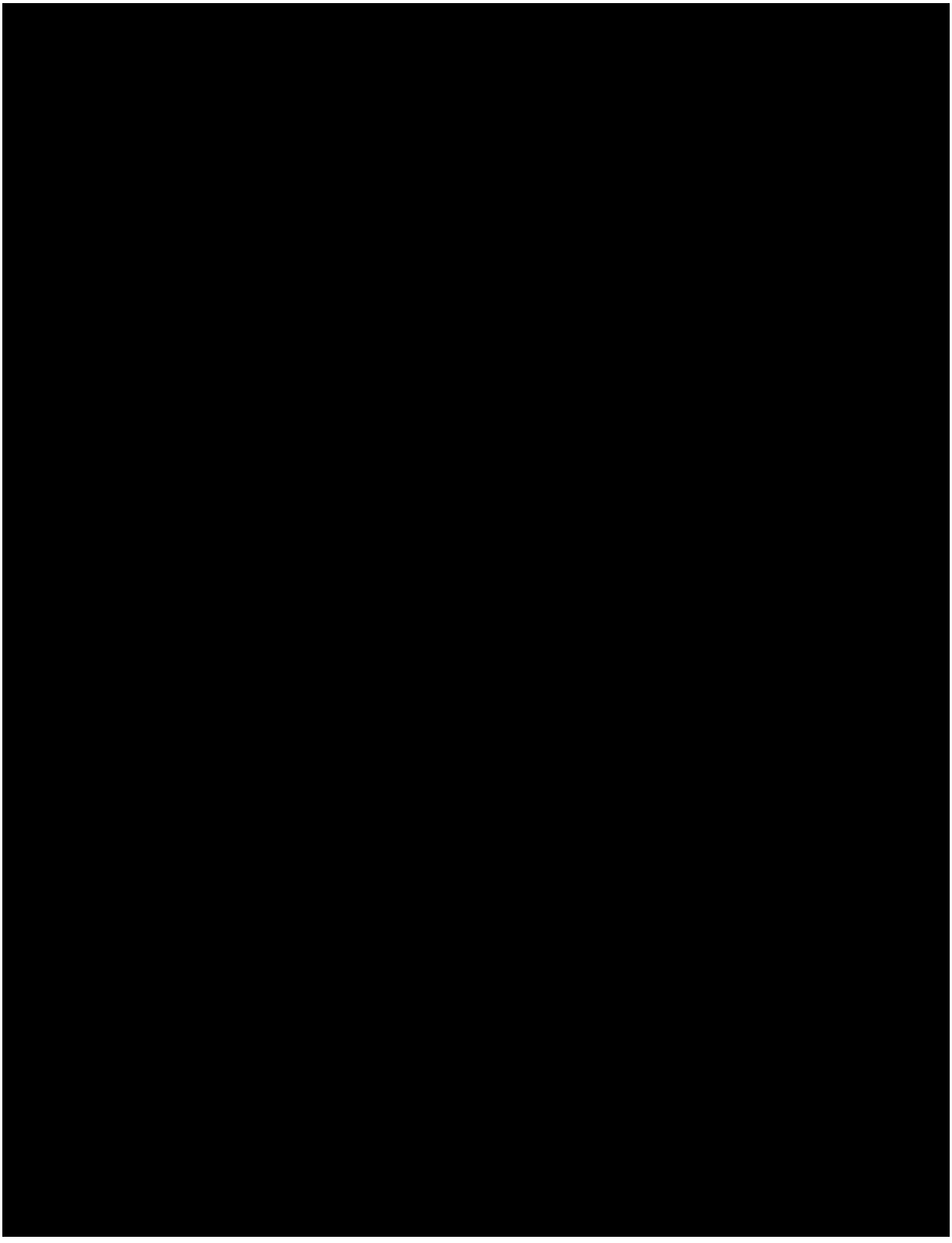


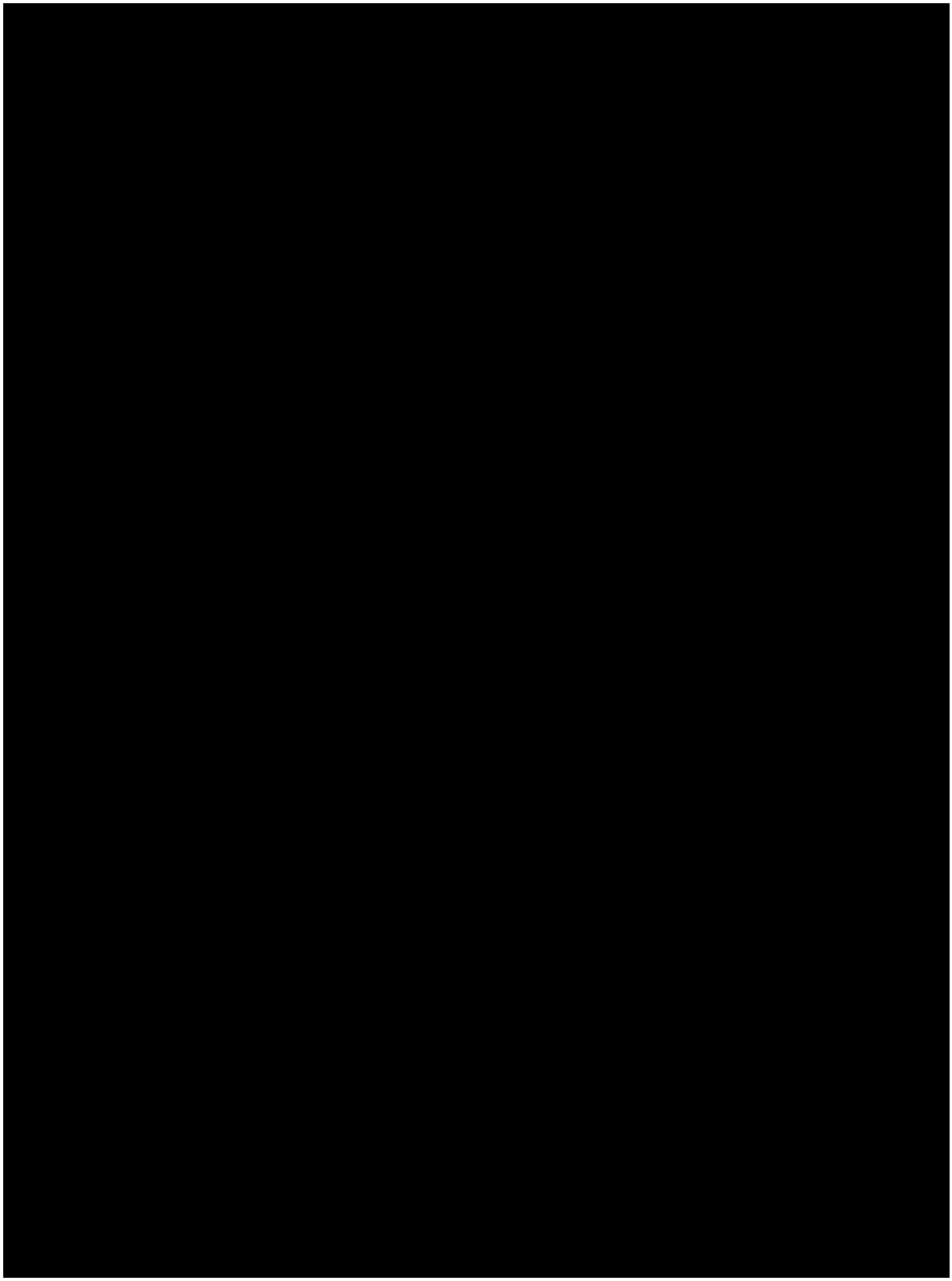


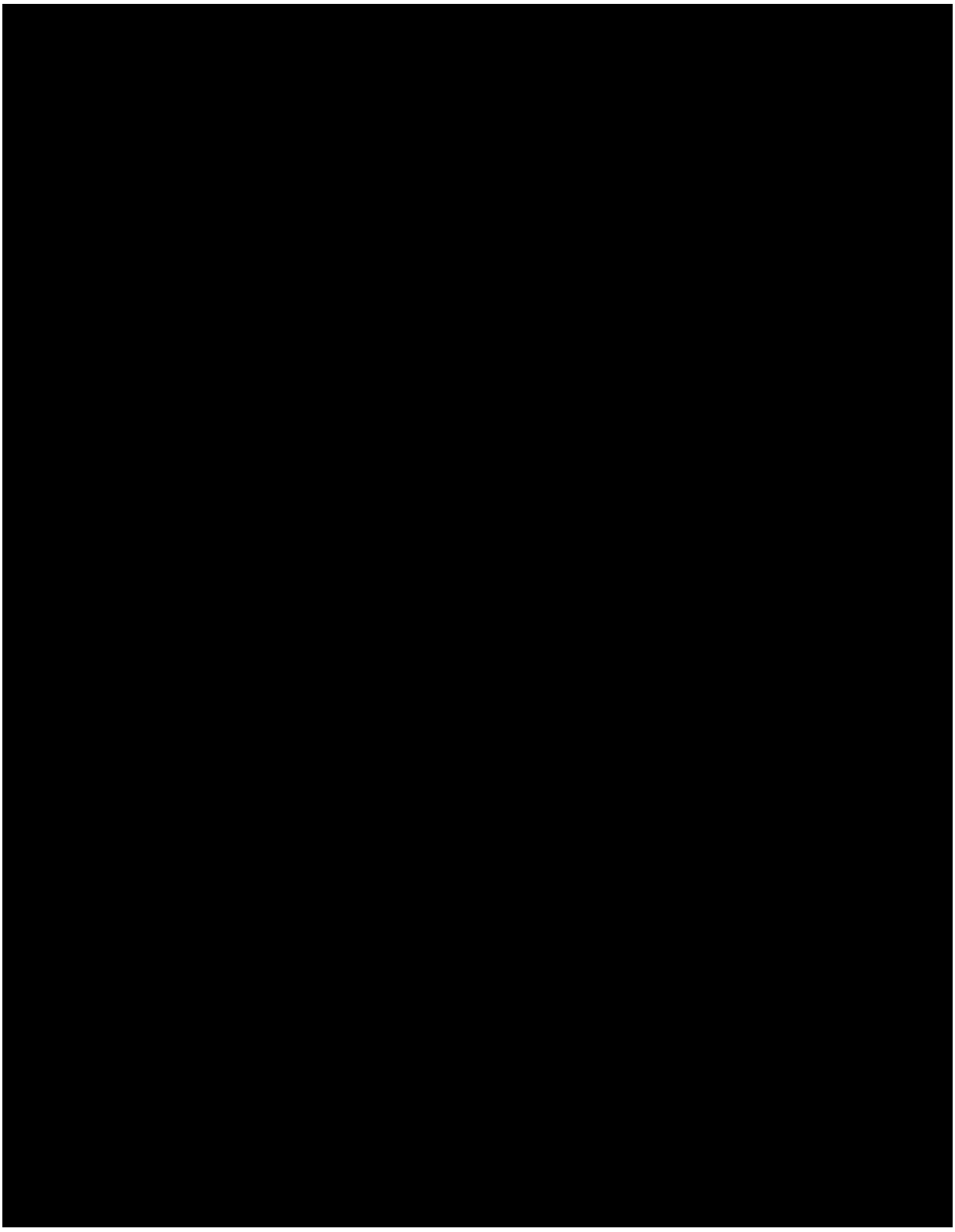


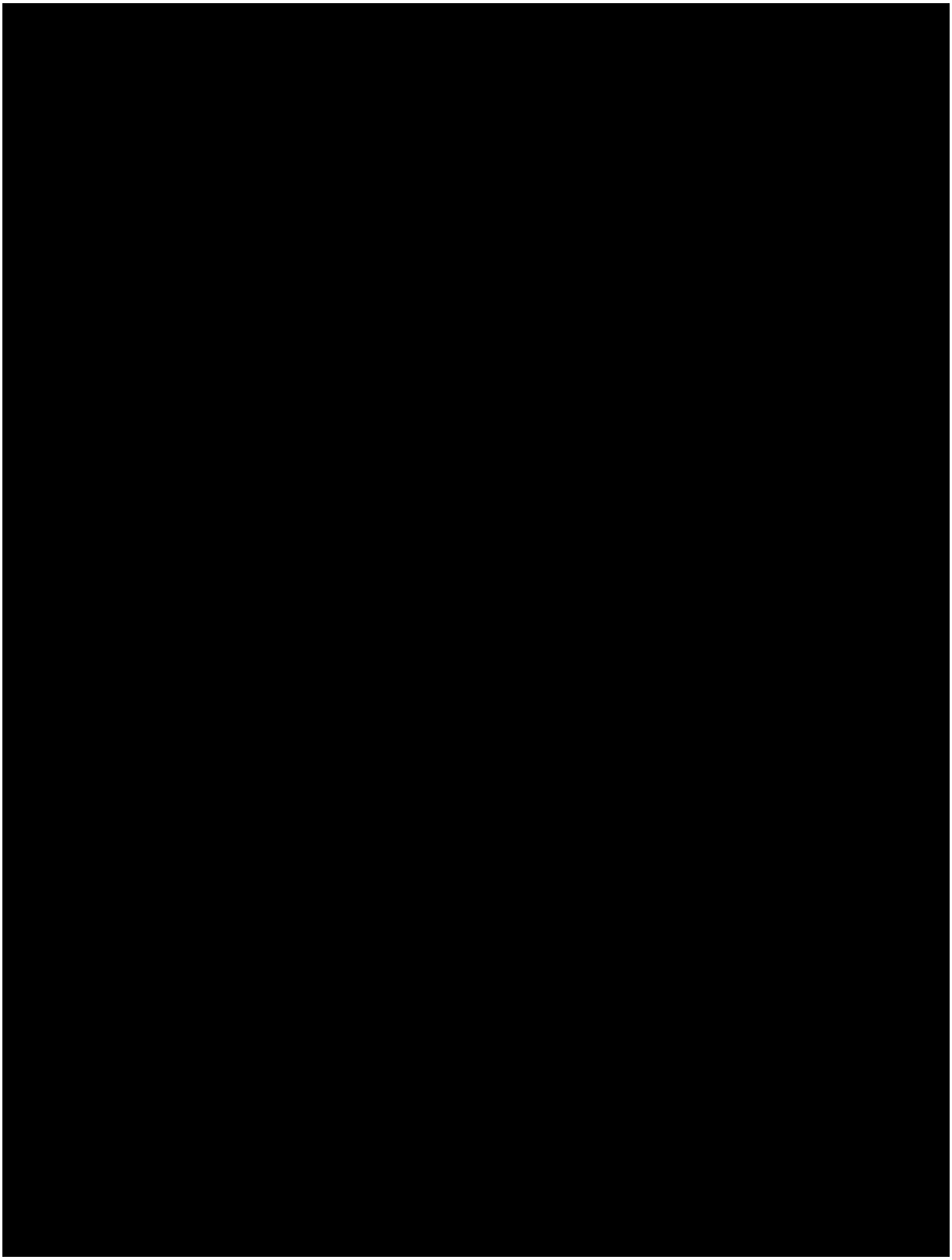


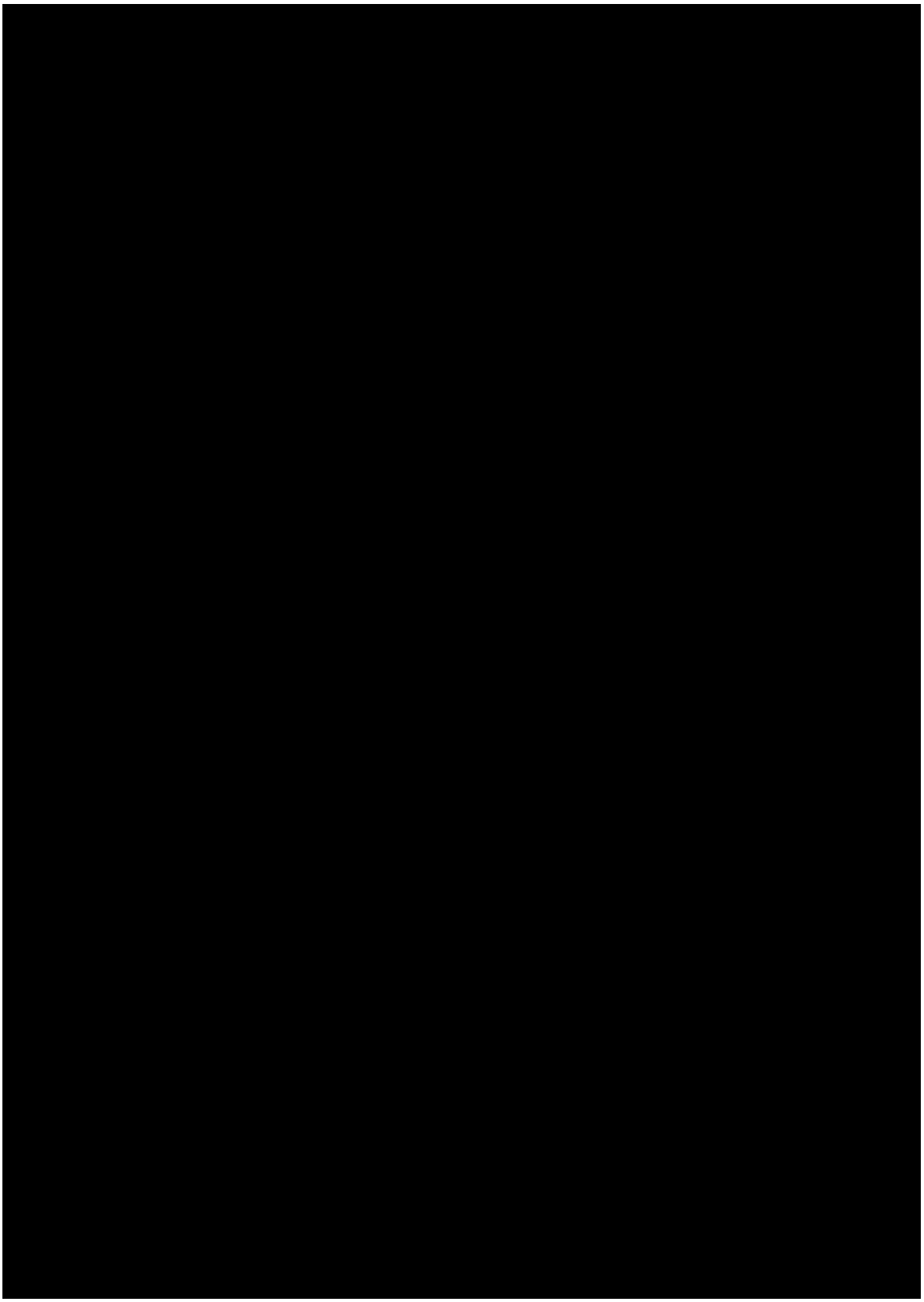


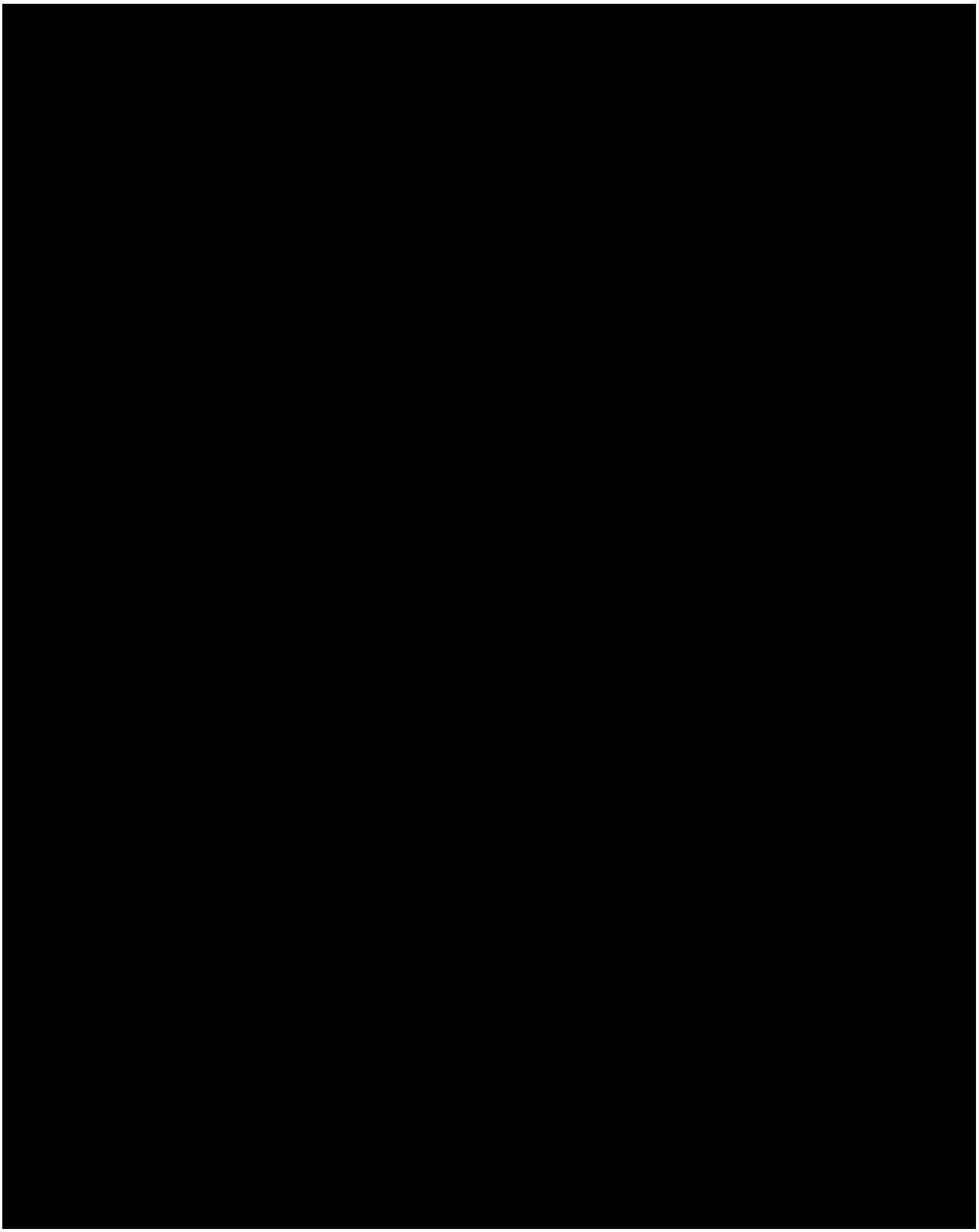


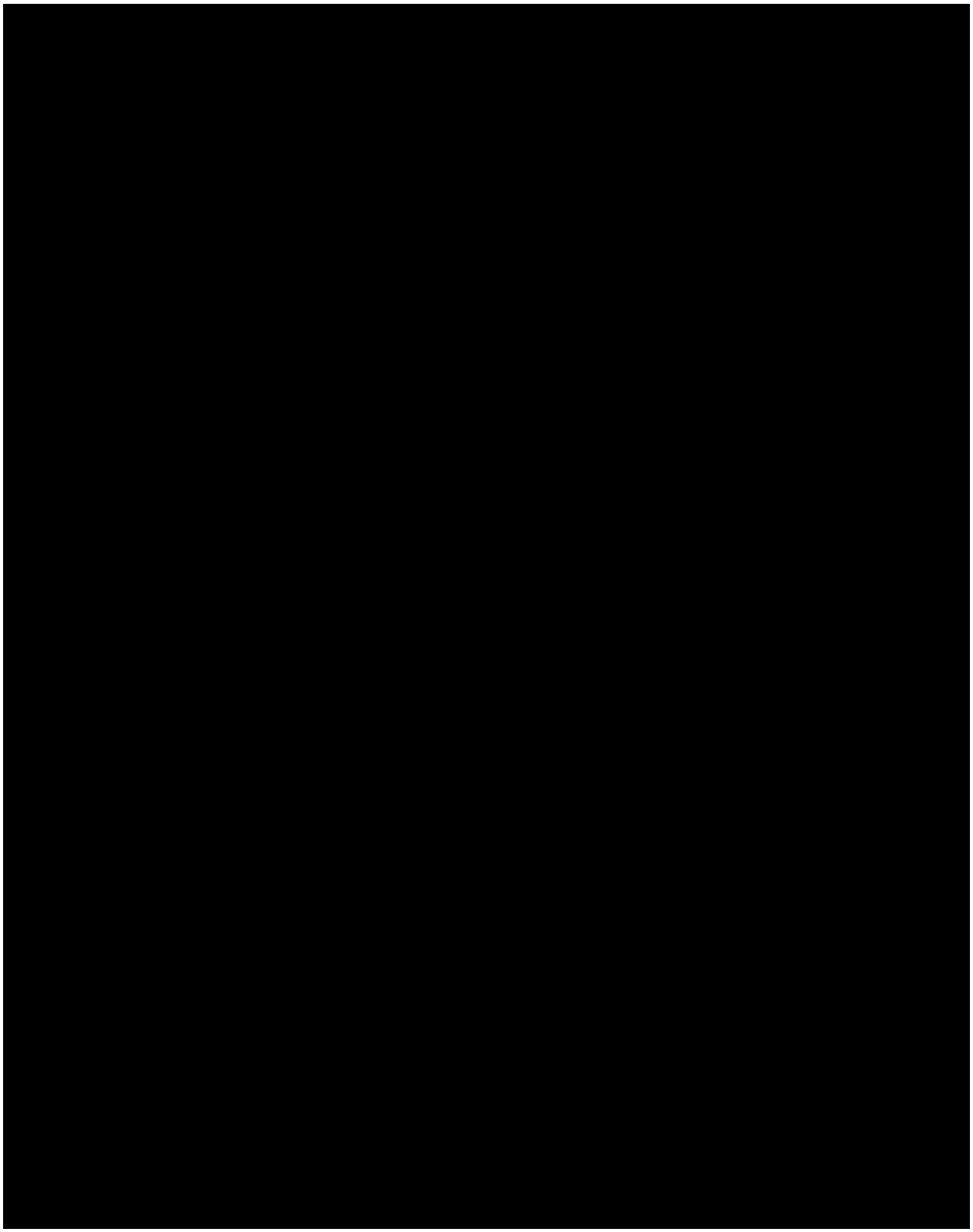












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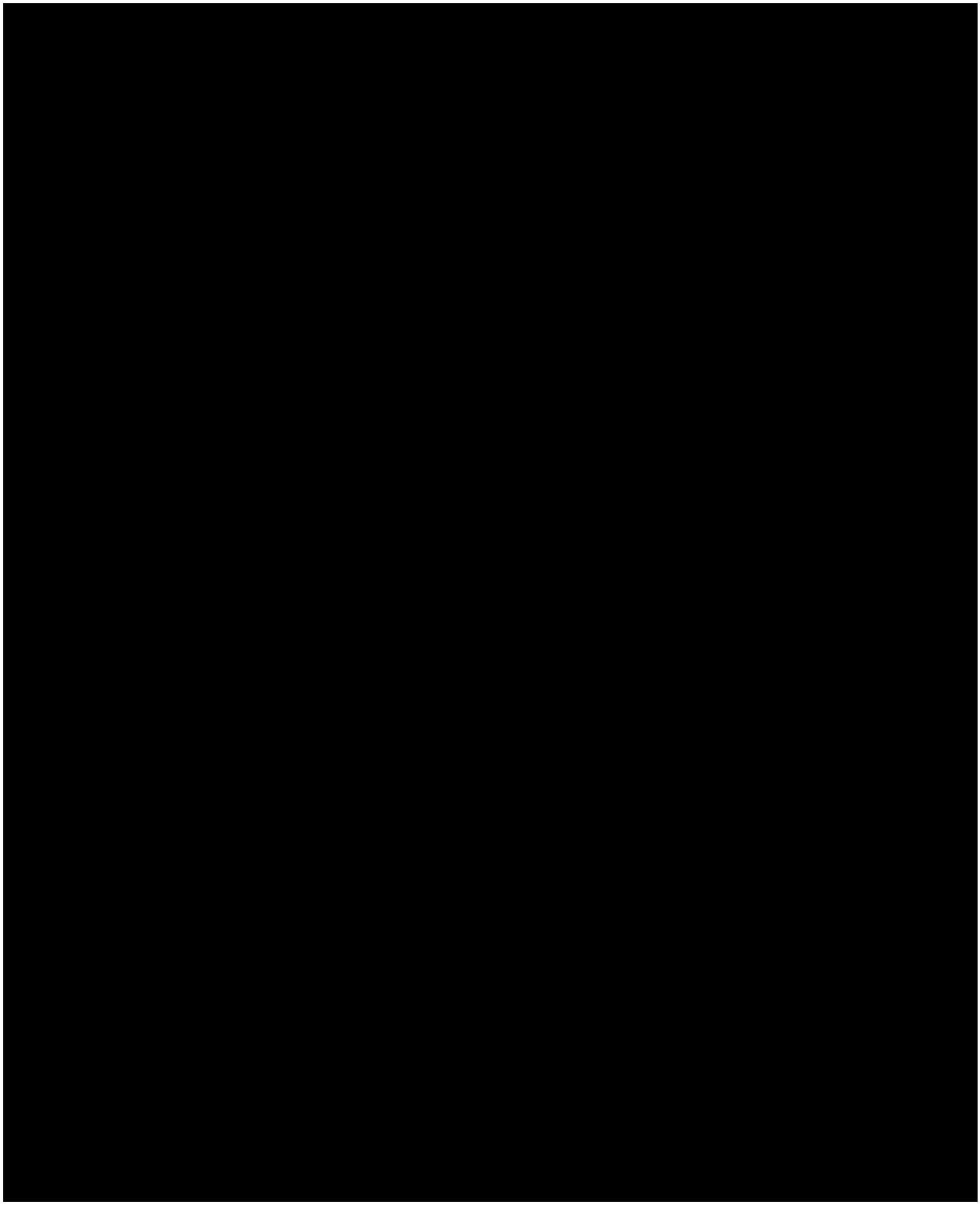

10.3 QUALITATIVE INTERVIEW SAFETY PROTOCOL

In all contacts between interviewers and study participants, the content of the discussion will be monitored for Adverse Events as detailed in Section 5.3.6.

During a qualitative interview, the participant may disclose information about unmet needs, personal risks, changes they have made (or intend to make) to medication taking behaviours or health concerns, and the interviewer has a responsibility to recommend the participant consults their personal physician or other relevant agencies.

If the participant discloses the following kind of information during the interview, the interviewer has a responsibility to refer the participant to an appropriate healthcare provider or agency or support group as follows:

1. Participant discloses information about possible medical condition, side-effect, change to medication taking that is not in line with their physician's instructions, or symptom: interviewer to recommend participant to consult their personal physician or emergency service
2. Participant discloses information about physical or mental harm or abuse, or the risk of harm or abuse, to themselves or others: interviewer to recommend participant to contact social services or police.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 AMENDMENT 1

Date of amendment		16 Sep 2021
EudraCT number **EU number**		NA
BI Trial number		352-2154
BI Investigational Medicinal Product(s)		TARA DBCI prototype (version 3)
Title of protocol		Proof of concept (proof of intervention principles) study assessing effects of Technology-Assisted Respiratory Adherence prototype version 3 (a Digital Behaviour Change Intervention, DBCI) on proximal clinical outcomes and mediators (psychological mediators, self-management behaviours) in individuals with COPD (IwCOPD)
Global Amendment due to urgent safety reasons		
Global Amendment		x
Section to be changed		Title page
Description of change		Allocation of new CTL
Rationale for change		Change in CTL
Section to be changed		Sections 2.3, 5.1.3.1, 10.1.1, 10.2.5.
Description of change		[redacted]
Section to be changed		Synopsis, Section 3.3.3
Description of change		Exclusion criterion 1 – updated from “patients with asthma” to “Patients with asthma as concurrent baseline condition at the time of screening”
Rationale for change		Clarification to all enrolment of patients with a historical diagnosis of asthma
Section to be changed		Synopsis, Section 3.3.3
Description of change		Exclusion criterion 2 - updated to include a timeframe for contacts with an infected person prior to the completion of the eligibility questionnaire.

Rationale for change		Updated to allow the enrolment of patients who have been in contact with persons infected with SARS COV-19, but are not infected themselves
Section to be changed		Section 5.3.7
Description of change		All AEs and SAEs are to be reported to BI GPV regardless of causal relationship to Spiriva Respimat or Stiolto Respimat
Rationale for change		Clarification of AE reporting requirements to ensure all identified events will be evaluated and reported accordingly.
Section to be changed		Synopsis, Sections 3.1, 7.2.7
Description of change		Removal of interim analysis
Rationale for change		Based on the observed TARA use by the first enrolled patients of cohort 1, an interim analysis between cohort 1 and cohort 2 is no longer expected to provide meaningful results.
Section to be changed		Section 7.2.1
Description of change		Clarification that cohorts 1 and 2 will be analysed separately and definition of analysis data set
Rationale for change		Further clarification on planned data analysis
Section to be changed		Section 7.2.5.
Description of change		Confirmation that all patients will be included in the safety analysis and that frequency, severity and causal relationship of adverse events will be reported.
Rationale for change		Additional clarification on planned safety analysis
Section to be changed		Section 7.3
Description of change		Confirmation that no imputation of missing data will occur.
Rationale for change		Clarification on the handling of missing data

APPROVAL / SIGNATURE PAGE

Title: Proof of concept (proof of intervention principles) study assessing effects of Technology-Assisted Respiratory Adherence prototype version 3 (a Digital Behaviour Change Intervention, DBCI) on proximal clinical outcomes and mediators (psychological mediators, self-management behaviours) in individuals with COPD (IwCOPD)

Protocol Version 2.0, 16 Sep 2021

Signatures:

Author:
Clinical Study [redacted]

DocuSigned by:
[redacted]

Date: 16-Sep-2021

Approval:
TARA Research Program [redacted]

DocuSigned by:
[redacted]

Date: 19-Sep-2021

Approval:
Study Statistician

DocuSigned by:
[redacted]

Date: 17-Sep-2021

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