NI PASS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**HEMLIBRA SURVEY TO PRESCRIBERS AND PATIENTS/CARERS TO EVALUATE AWARENESS, KNOWLEDGE AND COMPLIANCE TO ADDITIONAL RISK MINIMISATION MEASURES**
PROTOCOL NUMBER:	BO40853
VERSION NUMBER:	3.0
AUTHOR:	[redacted] F. Hoffmann-La Roche AG Grenzacherstrasse 124, 4070 Basel, Switzerland [redacted] *Hoffmann-La Roche Limited* *7070 Mississauga Rd* *Mississauga, ON L5N 5M8 Canada* Dr. [redacted], MD IQVIA 17 bis place des Reflets, TSA 64567 92099 La Defense Cedex, France
DATE FINAL:	See electronic date stamp below

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
31-Aug-2020 06:57:31	Deputy EU QPPV	[redacted]
31-Aug-2020 17:20:25	CMD	[redacted]

CONFIDENTIAL

EU PAS REGISTER NUMBER:	*EUPAS30451*
ACTIVE SUBSTANCE:	ATC code: B02BX06: Emicizumab
STUDIED MEDICINAL PRODUCT:	Hemlibra®
PRODUCT REFERENCE NUMBER:	Not applicable
PROCEDURE NUMBER{S}:	HEMLIBRA MEA/PRO 002
JOINT PASS:	No
RESEARCH QUESTION AND OBJECTIVES:	The aim of this study is to evaluate the awareness, knowledge, and adherence of prescribers and patients/carers to the additional Risk Minimisation Measures (RMM) for Hemlibra®. <u>Prescriber (HCP) survey</u> ○ Assess prescriber awareness of the Hemlibra® educational program • Assess prescriber knowledge of: ○ the identified risks (Thrombotic microangiopathy [TMA] and thrombotic events [TEs]) ○ the potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests • Assess prescriber self-reported adherence to the additional RMMs <u>Patient/carer survey</u> • Assess patient/carer awareness of the Hemlibra® educational program • Assess patient/carer knowledge of: ○ the identified risks of TMA and TE ○ the potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests • Assess patient/carer self-reported adherence to the additional RMMs

COUNTRIES OF STUDY POPULATION:	UK, Italy, Germany, Spain, France, Belgium, Netherlands, Poland, Austria, Portugal, Czech Republic, Hungary, Romania
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany
MAH CONTACT PERSON:	*Dr.* [redacted] *EU Product Development Regulatory* *Phone:* [redacted] *Fax:* [redacted] *Email:* [redacted]

PROTOCOL HISTORY

Protocol	
Version	***Date Final***
1	*(not approved)*
2	*27 March 2019*

PROTOCOL AMENDMENT, VERSION 3:

RATIONALE

Version 3 of protocol BO40853 has been amended from Version 2 primarily to extend timelines for study conduct to enable the collection of a sufficient number of completed HCP and patient questionnaires across different European regions to ensure representativeness and fulfil the planned data analysis. Version 2 of the protocol was the first version approved by PRAC. The changes to the protocol, along with the rationale for each change, are summarized below:

- The aim of this survey study is to evaluate the awareness, knowledge, and adherence of prescribers (HCPs) and patients/carers to the additional risk minimisation measures (aRMMs) for Hemlibra®. A sample size of 40 HCPs and 70 patients were planned to be surveyed in three European geographic regions. As of the 28th of July 2020, 107 HCPs and 46 patients have completed the respective questionnaires, with a majority of respondents coming from Northern and Western Europe. The number of completed patient questionnaires obtained thus far is smaller than planned and their distribution across the surveyed EU countries is not balanced. The PRAC Rapporteur has requested to extend data collection by 3 months. Consequently, the end of data collection date in the protocol has been moved from Q3 2020 to Q4 2020 (end December 2020) and the availability of the final study report has been moved to Q3 2021 (Section 4; 5; 8.1 and 8.4.2).
- The possibility to recruit patients and carers through HCPs who have not completed the HCP Questionnaire has been added to the protocol. As per the initial protocol, HCPs who have completed the HCP Questionnaire were offered to share Patients Questionnaire and Carer Questionnaire with their patients treated with Hemlibra®, or their carers, respectively. During submission of the protocol to ethics committees in some of the participating countries, lead physicians were provided with the protocol and HCP Questionnaire, which has made them ineligible for participation in the study. In fact, prior exposure would cause an information bias due to the pre acknowledgement of a number of facts that we are asking in the survey. Consequently, access to the patients of these physicians was impeded which had an impact on Patient and Carer Questionnaires data collection. In order to compensate for the loss of patients caused by the above, the protocol has been modified to allow HCPs to share the Questionnaires with patients/carers without prior requirement for HCPs to complete the HCP Questionnaire (Section 8.1; 8.1.1; 8.4.1 and 8.5.2).
- Geographic grouping of countries was originally suggested as the main criterion for grouping for the analysis. The statistical analysis section (Section 8.7.1) was updated to allow for other criteria of grouping which may also be used for results presentation e.g., Euro Health Consumer Index. The Euro Health Consumer Index is a commonly used index for assessing the performance of national health systems and it enables grouping of countries based on quality of healthcare as assessed by patients. In addition, the section about analysis of

response rate (Section 8.7.3) was updated to match the Statistical Analysis Plan and reflect the actual various groupings that result from the recruitment operations (see Section 8.4.1).

Additional minor changes, including updates in administrative information, have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
aPCC	Activated Prothrombin Complex Concentrate
aPTT	Activated Partial Thromboplastin Time
CHMP	Committee for Medicinal Products for Human Use
EC	Ethics Committee
EDC	Electronic data capture
EMA	European Medicines Agency
EphMRA	European Pharmaceutical Marketing Research Association
EU	European Union
EUHANET	European Haemophilia Network
GVP	Good Pharmacovigilance Practices
HCP	Health care provider
IRB	Institutional Review Board
MAH	Marketing authorization holder
PRAC	Pharmacovigilance Risk Assessment Committee
RMM	Risk minimisation measures
SAP	Statistical Analysis Plan
SOP	Standard operating procedure
TE	Thrombotic events
TMA	Thrombotic microangiopathy

2. RESPONSIBLE PARTIES

Protocol Development Responsible

[redacted], Clinical Scientist Associate, Product Development Oncology

F. Hoffmann-La Roche AG, Grenzacherstrasse 124, 4070 Basel, Switzerland

[redacted]

[redacted]

Hoffmann-La Roche Limited, 7070 Mississauga Rd, Mississauga, ON, L5N 5M8, Canada

[redacted]

Scientific Responsible

[redacted], *Senior Medical Director, Product Development Oncology*

Genentech, Inc., 1 DNA Way, South San Francisco, California, USA 94080

[redacted]

3. SYNOPSIS

TITLE:	**HEMLIBRA SURVEY TO PRESCRIBERS AND PATIENTS/CARERS TO EVALUATE AWARENESS, KNOWLEDGE AND COMPLIANCE TO ADDITIONAL RISK MINIMISATION MEASURES**
PROTOCOL NUMBER:	BO40853
VERSION NUMBER:	3.0
DATE OF SYNOPSIS:	See electronic stamp on the cover page
EU PAS REGISTER NUMBER:	*EUPAS30451*
STUDIED MEDICINAL PRODUCT:	Hemlibra®
SCIENTIFIC RESPONSIBLE	[redacted], *Genentech*
MAIN AUTHOR	[redacted], F. Hoffmann-La Roche
PHASE:	IV, non-interventional study
INDICATION:	For routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors and patients with severe haemophilia A without factor VIII inhibitors
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 79639 Grenzach-Wyhlen Germany

Rationale and Background

Hemlibra® (Emicizumab) is a humanized bispecific antibody targeting factors IX (FIX) and X (FX). In patients with haemophilia A, Hemlibra® bridges activated FIX and FX to restore the function of missing activated factor VIII (FVIII) that is needed for effective haemostasis. Hemlibra® received a marketing authorisation valid throughout the European Union (EU) on 23 February 2018 for the indication: routine prophylaxis of bleeding episodes in patients of all age groups with haemophilia A with FVIII inhibitors. On 31 January 2019, the Committee for Medicinal Products for Human Use (CHMP) adopted a favourable opinion on the expansion of the indication of Hemlibra® to patients of all age groups with severe haemophilia A without FVIII inhibitors. In patients with haemophilia A receiving Hemlibra®, concomitant use of activated prothrombin complex concentrate (aPCC) averaging a cumulative amount of >100U/kg/24 hours for 24 hours or more is associated with the following important identified risks: thrombotic microangiopathy [TMA] and thromboembolic events [TEs]). In addition, an important potential risk is life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with Hemlibra®. To manage these risks, additional Risk Minimisation Measures (RMMs), including the following educational materials were developed: healthcare professional guide, patient/carer guide and patient alert card. To assess prescribers' (health care providers [HCPs]) and patients' or their carers' awareness of the Hemlibra® educational program, knowledge of identified and potential life-threatening risks associated with Hemlibra® use, and adherence to additional RMMs Roche plans to conduct a non-interventional Post-Authorisation Safety Study in the form of a survey.

Research Question and Objectives

The aim of this study is to evaluate the awareness, knowledge, and adherence of prescribers and patients/carers to the additional RMMs for Hemlibra®.

Objectives

To evaluate whether prescribers and the patients/carers have understood the requirements of and report adherence with the additional RMMs associated with Hemlibra®. The objectives of the study are as follows:

Prescriber (HCP) survey

- Assess prescriber awareness of the Hemlibra® educational program by evaluating the proportion of targeted prescribers who acknowledge having received and read the relevant educational materials.
- Assess prescriber knowledge of:
    - the important identified risks of TMA and TEs that may occur if a cumulative amount of >100U/kg/24 hours for 24 hours or more of aPCC is used concomitantly with Hemlibra® by patients and
    - the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which may be unreliable in patients treated with Hemlibra®,

  by evaluating the proportion of targeted prescribers with correct responses to risk knowledge questions.
- Assess prescriber adherence to the additional RMMs, by evaluating the proportion of targeted prescribers whose responses to the practice-related questions are consistent with the Guide for Healthcare Professionals.

Patient/carer survey

- Assess patient/carer awareness of the Hemlibra® educational program by evaluation the proportion of patients who acknowledge having received and read the Patient/Carer Guide and Patient Alert Card.
- Assess patient/carer knowledge of:
    - the important identified risks of TMA and TEs that may occur if a cumulative amount of >100U/kg/24 hours for 24 hours or more of aPCC is used concomitantly with Hemlibra® by patients and

    - the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which may be unreliable in patients treated with Hemlibra®,

  by evaluating the proportion of patients/carers with correct responses to risk knowledge questions.
- Assess patient/carer adherence to the additional RMMs, which will be evaluated by evaluating the proportion of patients/carers whose responses to questions are consistent with the Patient/Carer Guide and Patient Alert Card.

Study Design

The study will utilize anonymous, cross-sectional, multi-national, surveys conducted among HCPs and patients or carers in 13 European countries, using primary data collection in the form of online questionnaires.

Description of Study

The study will be conducted between Q1 and Q4 2020. The surveys to prescribers (HCP) and patients/carers will assess their awareness of the Hemlibra® educational program, knowledge of important identified risks (TMA and TEs) and important potential life-threatening risk of bleeding due to misinterpretation of the standard coagulation tests associated with Hemlibra® use, and adherence to additional RMMs. To ensure that only relevant HCPs are targeted, the survey will only include HCPs that have treated haemophilia patients with Hemlibra® outside of clinical trials at least once. Patients or their carers will be recruited via *their* physicians.
The questionnaires will include multiple-choice and closed-ended questions as appropriate.
The surveys will be conducted in a web-based format as a standard for both HCPs and patients/carers and guided by phone if preferred by the participating HCPs.

Population

The study population is HCPs who have prescribed Hemlibra® outside of the clinical trials and patients with haemophilia A who have been or are currently being treated with Hemlibra®, both of whom must meet the following inclusion/exclusion criteria:

Inclusion

HCPs

- HCPs who prescribed Hemlibra® at least once outside the context of a clinical trial to patients with haemophilia A with FVIII inhibitors or patients with severe haemophilia A without FVIII inhibitors
- HCPs who are willing to participate in this survey

Patients/Carers

- Patients who received at least 4 doses of Hemlibra® within the last 6 months, including patients on ongoing therapy, or their carers
- Patients who are willing to participate in this self-administered survey, or their carers (parent or legal guardian) if the patient is under the age of 18

Exclusion

HCPs

- HCPs who may have conflicts of interest with the study (e.g., HCPs employed by Roche or IQVIA)

Patients/Carers

- Patients/carers who may have conflicts of interest with the study (e.g., patients/carers employed by Roche or IQVIA)
- Patients who have participated in a Hemlibra® clinical trial
- Patients with non-severe haemophilia A without FVIII inhibitors

Variables

Prescriber (HCP) survey

- Variables related to HCP participation
    - Response rate
    - Refusal rate
- Variables related to HCP practice information:
    - Location (city/country)
    - HCP primary specialization
    - Years practicing as a physician
    - Practice setting (Haemophilia Comprehensive Care Centre, haemophilia treatment centre, hospital haematology department, other)
    - Past experience with Hemlibra® (overall number of patients, number of patients with inhibitors, and severe patients without inhibitors treated)
    - Participation as a Hemlibra® clinical trial investigator
    - Last time prescribing Hemlibra®
    - Makeup of patient population (adults or children)
- Variables related to HCPs' awareness of the Hemlibra® educational program
    - Receipt of each of the RM tools (Patient Alert Card, Patient/Carer Guide, Guide for Healthcare Professionals) (yes/no)
    - Reading of the Guide for Healthcare Professionals (yes/no)
- Variables related to the HCPs' knowledge of the risks associated with the use of Hemlibra®, as described in the educational materials:
    - Knowledge of guidelines on the use of bypassing agents in their patients receiving Hemlibra® prophylaxis, particularly for TMA and TE with concomitant aPCC use (true/false statements)
    - Knowledge of laboratory coagulation tests which have their reliability affected by Hemlibra® and associated recommendations (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
    - Knowledge of time period to follow dosing and laboratory testing guidelines (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
- Variables related to the HCPs' self-reported adherence to the educational measures by correct implementation of the additional RMMs:
    - Distribution of Patient Alert Cards and Patient/Carer Guides to patients receiving Hemlibra® prophylaxis (or their carers) (tick boxes listing frequency of distribution of RM tools to patients)
    - Counselling of patients or their carers to carry the Patient Alert Card for 6 months after their last dose of Hemlibra (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
    - Use of activated partial thromboplastin time (aPTT) test results in patient who receive Hemlibra® (yes/no)
    - Precautions followed when prescribing Hemlibra® (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
    - Bypassing dosing guidance in their patients receiving Hemlibra® prophylaxis (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)

Patient/carer survey

- Variables related to the patients treated with Hemlibra®:
    - Completion by patient or carer
    - Patient age (years)
    - Time since last dose of Hemlibra® (tick boxes with ranges of treatment duration in months)
    - Diagnosis with FVIII inhibitors (yes/no)
        - Severity of disease (mild/moderate/severe)

    - Receiving at least 4 doses of Hemlibra® in the last 6 months (yes/no)
- Variables related to the patients' awareness of the Hemlibra® educational program, or the awareness of their carer if the patient is under the age of 18:
    - Receipt of Patient Alert Card and Patient/Carer Guide (tick boxes for receipt)
    - Discussion with HCPs of risks associated with the use of Hemlibra® (yes/no)
    - Reading of the received educational materials (yes/no)
- Variables related to the patients' knowledge about the risks of Hemlibra®, or the knowledge of their carer if the patient is under the age of 18:
    - Knowledge of risks associated with the use of Hemlibra® (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
    - Knowledge that the Patient Alert Card should be carried at all times (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
    - Knowledge that Hemlibra® use can affect laboratory tests on blood clotting (true/false)
    - Knowledge of aPCC dosing and risks of concomitant use with Hemlibra® therapy (true/false statements)
- Variables related to the patients' self-reported adherence to the educational measures by correct implementation of the additional RMMs, or the self-reported adherence of their carer if the patient is under the age of 18:
    - Showing the Patient Alert Card to health care professionals (yes/no)
    - For patients taking aPCC while taking Hemlibra®:
        - Taking a first dose of aPCC of <50U/kg
        - Contacting their HCP before increasing the dose of aPCC above 50U/kg (yes/no/not applicable)
        - Not taking >100U/kg/24 hours for 24 hours or more (yes/no)

Data Sources

The study is a survey using primary data collection conducted through HCP and patient/carer questionnaires administered online, with an option to be guided by phone for HCPs and is planned to be conducted in 13 European countries.

Study Size

A sample size of 40 HCPs will be surveyed. Since the response rate in some similar surveys has been as low as 10%, the questionnaire will be sent to at least 400 potential prescribers of Hemlibra in 13 European countries.

HCPs will be asked to distribute up to 18 survey kits to their patients or carers. Assuming 15-20% of HCPs agree to distribute the survey and that 20-40% of patients/carers respond, our target sample size is 70 patient questionnaires, including 25-35 from patients with inhibitors or their carers.

Data Analysis

The statistical analysis will be conducted using the SAS software V9.4 on Windows™ (SAS Institute, North Carolina, USA).

Results will be presented, overall and by geographic region. *Other criteria for grouping may also be used for results presentation e.g., Euro Health Consumer Index.* Continuous variables will be described by the number of valid cases and missing data (if applicable), mean, standard deviation, median, first quantile (Q1), third quantile (Q3), minimum, and maximum. No missing data will be imputed. Categorical variables will be described as the total number and relative percentage per category. Confidence intervals of 95% will be estimated when relevant.

Individual awareness, knowledge, and adherence values will be calculated as the percentage of correctly answered survey questions; values will range from 0 to 100% with 100% representing the percentage of all knowledge questions and behaviour questions being answered correctly, respectively.

Analysis will be done on questions common to all HCPs and patients/carers as well as on a limited number of questions presented to the subgroup of patients with concomitant use of aPCC (FEIBA) and Hemlibra® (or their carers).

Potential selection bias will be assessed by comparing the distributions of available characteristics (e.g. region, type of practice and speciality) between respondent and non-respondent HCPs, if applicable and feasible.

Success on the educational materials for additional risk minimisation measures will be defined a priori as achieving overall scores of ≥75% for awareness and adherence and ≥60% for knowledge for HCPs and ≥60% in all areas for patients/carers. Overall success is defined as success on all three measures for both HCPs and patients/carers (see Section 8.7).
The planned analyses will be fully described in the Statistical Analysis Plan (SAP) to be developed after protocol approval by the European Medicines Agency (EMA).

4. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

When applicable, approval will be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: *Protocol version 3 was issued in order to extend the timelines for study conduct by 3 months.*

5. MILESTONES

Study milestones are given in Table 1 and are based on current estimates.

Table 1 Study Milestones

Milestone	Planned Date
Registration of protocol in the EU PAS register	After approval of the protocol and before start of data collection
Start of data collection (Prescriber survey)	Q1 2020
Start of data collection (Patient survey)	Q2 2020
End of data collection	$Q4$ 2020
Final report of study results	$Q3$ 2021
Registration of the results in the EU PAS register	After approval of the final study report

EU = European Union; PAS = post-authorization study

6. RATIONALE AND BACKGROUND

6.1 STUDY RATIONALE

Haemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with haemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013). Three severity levels of the disease are distinguished based on the percentage of the normal FVIII plasma procoagulant levels, mild (>5% - <40%), moderate (1% - 5%), and severe (<1%) (White et al. 2001).

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of haemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial haemorrhage, leading to frequent bleeding events with the sequelae of musculoskeletal complications, such as arthropathy, local functional deficits, haemorrhagic shock, neurocognitive defects, or even death (World Federation of Haemophilia 2013). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (Brown et al. 2009).

Prophylactic FVIII replacement therapy (i.e., administered on a scheduled basis with the intent to prevent bleeds) has been proven to minimise bleeding events and complications (Manco-Johnson et al. 2007). Since the 1990s, recombinant FVIII concentrates have been standard-of-care treatment options for patients with haemophilia A (Kingdon and Lundblad 2002). Treatment regimens to achieve optimal prevention of bleeding events vary individually; some patients tolerate nadir FVIII levels of 1%, whereas others require higher nadir FVIII levels to achieve the desired therapeutic outcome (Ahnstrom et al. 2004; Collins et al. 2010). Current standard prophylactic regimens commonly use infusion therapy administered three times weekly; other

regimens require every other day administration, depending on the patient's needs (Shapiro 2013).

The development of inhibitory alloantibodies (inhibitors) occurs in approximately 20%−30% of patients with severe haemophilia A and in 3%−13% of those with moderate or mild disease (Franchini and Mannucci 2013). Inhibitors neutralize the activity of endogenous FVIII as well as of FVIII administered as replacement therapy. For patients with a history of a high-titre (≥ 5 BU/mL) inhibitor following a re-challenge with FVIII administration (high-responding inhibitor), the only haemostatic options currently available are pro-thrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., "bypassing agents"). Bypassing products include Factor Eight Inhibitor Bypassing Activity (FEIBA), an activated prothrombin complex concentrate (aPCC; FEIBA will be referred to as aPCC throughout this document), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]) (Srivastava et al. 2013). Both have been used as prophylaxis to prevent bleeding in patients with inhibitors against FVIII ("inhibitor patients"); however, the only available product for this indication in most countries is the aPCC FEIBA. Of note, treatment of patients with congenital haemophilia A with any severity with high-titre inhibitors is similar, and their severity, as defined at diagnosis based on FVIII activity (mild, moderate, or severe), no longer is prognostic of their clinical phenotype and risk of bleeding.

Hemlibra® (also known as emicizumab, ACE910, and RO5534262) is a recombinant, humanized, bispecific, immunoglobulin G4 (IgG4) monoclonal antibody that binds with moderate affinity to activated factor IX (FIXa) and factor X (FX).

In patients with haemophilia A, Hemlibra® bridges FIXa and FX to restore the function of missing activated FVIII that is needed for effective haemostasis. In patients with haemophilia A, haemostasis can be restored irrespective of the presence of FVIII inhibitors, as Hemlibra® shares no sequence homology with FVIII. In addition, Hemlibra offers the possibility of subcutaneous (SC) administration, removing the need for venous access. Finally, because of the expected pharmacokinetic properties of this antibody, markedly extending the dosing interval to once weekly or even less frequently, this novel compound has the potential to dramatically change the treatment of patients with haemophilia A with and without FVIII inhibitors who are in need of effective, safe, and convenient prophylactic therapy.

Hemlibra® received a marketing authorisation valid throughout the EU on 23 February 2018 for the indication: routine prophylaxis of bleeding episodes in patients with haemophilia A with FVIII inhibitors. On 31 January 2019, the CHMP adopted a favourable opinion on the expansion of the indication of Hemlibra® to patients with severe haemophilia A without FVIII inhibitors. Hemlibra® can be used in all age groups.

The most clinically significant adverse drug reactions (ADRs) reported in patients receiving Hemlibra® were thrombotic microangiopathy (TMA) and thrombotic events

(TEs). All reports of TMA and TEs occurred in patients who also received activated prothrombin complex concentrate (aPCC), a bypassing agent, at an average cumulative amount of aPCC of >100U/kg/24 hours for 24 hours or more (Oldenburg et al. 2017). Additionally, an important potential risk is life-threatening bleeding due to misinterpretation of standard coagulation tests, which are unreliable in patients treated with Hemlibra® (Hemlibra® Summary of product characteristics 2018).

To facilitate the management of these risks, additional risk minimisation measures (RMMs) have been put in place, including the following educational program materials:

- Guide for Healthcare Professionals
- Patient Alert Card
- Patient/Carer Guide

6.2 STUDY BACKGROUND

Treatment with Hemlibra® when administered concomitantly with aPCC is associated with the following important identified risks: TMAs and TEs. Important potential risks include life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with Hemlibra®. To facilitate the management of these risks, additional RMMs are put in place which include the materials for Hemlibra® educational program.

According to the guidelines on good pharmacovigilance practices (GVP) Module V, VIII, and XVI, effectiveness of risk minimisation activities should be assessed (European Medicines Agency 2012a, 2012b, 2014). Therefore, Roche propose to conduct a Non-Interventional Post-Authorisation Safety Study in the form of a survey to prescribers (HCP) and patients/carers to assess their awareness of the Hemlibra® educational program, knowledge of important identified (TMA and TEs) and potential life-threatening bleeding risks (due to misinterpretation of the standard coagulation tests) associated with Hemlibra® use and adherence to additional RMMs.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The aim of this study is to evaluate the awareness, knowledge, and self-reported adherence of prescribers and patients/carers to the additional RMMs for Hemlibra®.

7.2 OBJECTIVES

To evaluate whether prescribers and the patients/carers have understood the requirements of and report adherence with the additional RMMs associated with Hemlibra®. The objectives of the study are as follows:

Prescriber (HCP) survey

- Assess prescriber awareness of the Hemlibra® educational program by estimating the proportion of targeted prescribers who acknowledge having received and read the relevant educational materials.
- Assess prescriber knowledge of:
    - the important identified risks of TMA and TEs that may occur if a cumulative amount of >100U/kg/24 hours for 24 hours or more of aPCC is used concomitantly with Hemlibra® and
    - the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which may be unreliable in patients treated with Hemlibra®,

  by estimating the proportion of targeted prescribers with correct responses to risk knowledge questions.
- Assess self-reported prescriber adherence to the additional RMMs, by estimating the proportion of targeted prescribers whose responses to the practice-related questions are consistent with the Guide for Healthcare Professionals.

Patient/carer survey

- Assess patient/carer awareness of the Hemlibra® educational program by estimating the proportion of patients who acknowledge having received and read the Patient/Carer Guide and Patient Alert Card.
- Assess patient/carer knowledge of:
    - the important identified risks of TMA and TEs that may occur if a cumulative amount of >100U/kg/24 hours for 24 hours or more of aPCC is used concomitantly with Hemlibra® and
    - the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which may be unreliable in patients treated with Hemlibra®,

  by estimating the proportion of patients/carers with correct responses to risk knowledge questions.
- Assess patient/carer self-reported adherence to the additional RMMs, which will be evaluated by estimating the proportion of patients/carers whose responses to the questions are consistent with the Patient/Carer Guide and Patient Alert Card.

The objectives for the survey will be aligned with any key elements to be addressed in these studies provided by the Pharmacovigilance Risk Assessment Committee (PRAC).

8. RESEARCH METHODS

8.1 STUDY DESIGN

The study will utilize cross-sectional, multinational, surveys conducted among prescribers (physicians) and patients or their carers in European countries in the form of online questionnaires.

The physician part of the survey will be conducted first. The physician will initially be contacted by email or phone calls. The survey will be conducted in a web-based format and guided by phone if the participating HCPs prefer it (see Section 8.4.2).

To conduct the patient/carer part of the survey, *contacted* HCPs will be asked to propose the online survey to their patients. *HCPs will be able to propose the online survey to their patients even if they have not participated in the HCPs survey.*

Start Date of Study

The anticipated study start date for the HCP survey is Q1 2020. The anticipated patient/carer survey start date is Q2 2020.

End of Study

The end of the study will be the date from which the last data collected from the last survey recorded in the study database. The anticipated study completion is *Q4 2020.*

8.1.1 Rationale for Study Design

According to the guidelines on GVP Module V, VIII, and XVI, effectiveness of RMMs should be assessed (European Medicines Agency 2012a, 2012b, 2014). This will be achieved using a survey to prescribers (HCP) and patients or their carers to assess their awareness of the Hemlibra® educational program, knowledge of identified (TMAs and TEs) and potential risks associated with Hemlibra® use as described in the educational materials, and self-reported adherence to additional RMMs. To minimise selection bias, a comprehensive database of registered HCPs (IQVIA OneKey) will be used to randomly enrol HCPs meeting the inclusion/exclusion criteria. Patients or their carers will be recruited via *their* physicians.

8.2 SETTING

The survey will be conducted among office and hospital-based Hemlibra® prescribers in thirteen European countries.

Target countries have been selected for the conduct of the survey due to their representative nature of the European population. These countries from different parts of Europe have been chosen in such a way that countries with different sizes, cultures, and healthcare systems are represented.

In addition, countries were selected to capture the maximum number of eligible physicians and patients while minimising efforts in countries with too few haemophilia treatment centres to effectively reach prescribers (see Section 8.2.1).

8.2.1 Countries

It is planned to conduct the study in 13 European countries (UK, Italy, Germany, Spain, France, Belgium, Netherlands, Poland, Austria, Portugal, Czech Republic, Hungary, and Romania).

These countries were chosen to include over 80% of the haemophilia treatment centres from Haemophilia Central, a website developed as part of the European Haemophilia Network (EUHANET) project.

8.2.2 Study Population

The study population is HCPs who have prescribed Hemlibra® and patients with haemophilia A who have been treated with Hemlibra® or their carers, all of whom must meet the following inclusion/exclusion criteria:

Inclusion criteria

HCPs

- HCPs who prescribed Hemlibra® at least once outside the context of a clinical trial to patients with haemophilia A with FVIII inhibitors or patients with severe haemophilia A without FVIII inhibitors
- HCPs who are willing to participate in this survey

Patients/Carers

- Patients who received at least 4 doses of Hemlibra® within the last 6 months, including patients on ongoing therapy
- Patients who are willing to participate in this self-administered survey, or their carers (parent or legal guardian) if the patient is under the age of 18

Exclusion criteria

HCPs

- HCPs who may have conflicts of interest with the study (e.g., HCPs employed by Roche or IQVIA)

Patients/Carers

- Patients/Carers who may have conflicts of interest with the study (e.g., patients/carers employed by Roche or IQVIA)
- Patients who have participated in a Hemlibra® clinical trial
- Patients with non-severe (i.e., mild or moderate) haemophilia A without FVIII inhibitors

For details on identification of HCPs and patients, see Section 8.4.1.

8.2.3 Concomitant Medication and Treatment

No information on concomitant medication and treatment will be collected

8.2.4 Dosage, Administration, and Compliance

Not applicable

8.3 VARIABLES

The following variables are collected:

Prescriber (HCP) survey

- Variables related to HCP participation
  - Response rate
  - Refusal rate
- Variables related to HCP practice information:
  - Location (city/country)
  - HCP primary specialization
  - Years practicing as a physician
  - Practice setting (Haemophilia Comprehensive Care Centre, haemophilia treatment centre, hospital haematology department, other)
  - Past experience with Hemlibra® (overall number of patients, number of patients with inhibitors, and severe patients without inhibitors treated)
  - Participation as a Hemlibra® clinical trial investigator
  - Last time prescribing Hemlibra®
  - Makeup of patient population (adults or children)
- Variables related to HCPs' awareness of the Hemlibra® educational program
  - Receipt of each of the RM tools (Patient Alert Card, Patient/Carer Guide, Guide for Healthcare Professionals) (yes/no)
  - Reading of the Guide for Healthcare Professionals (yes/no)
- Variables related to the HCPs' knowledge of the risks associated with the use of Hemlibra®, as described in the educational materials:
  - Knowledge of guidelines on the use of bypassing agents in their patients receiving Hemlibra® prophylaxis, particularly for TMA and TE with concomitant aPCC use (true/false statements)
  - Knowledge of laboratory coagulation tests which have their reliability affected by Hemlibra® and associated recommendations (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
  - Knowledge of time period to follow dosing and laboratory testing guidelines (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
- Variables related to the HCPs' self-reported adherence to the educational measures by correct implementation of the additional RMMs:
  - Distribution of Patient Alert Cards and Patient/Carer Guides to patients receiving Hemlibra® prophylaxis (or their carers) (tick boxes listing frequency of distribution of RM tools to patients)

- Counselling of patients or their carers to carry the Patient Alert Card for 6 months after their last dose of Hemlibra (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
- Use of aPTT test results in patient who receive Hemlibra® (yes/no)
- Precautions followed when prescribing Hemlibra® (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
- Bypassing dosing guidance in their patients receiving Hemlibra® prophylaxis (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)

Patient/carer survey

- Variables related to the patients treated with Hemlibra®:
  - Completion by patient or carer
  - Patient age (years)
  - Time since last dose of Hemlibra® (tick boxes with ranges of treatment duration in months)
  - Diagnosis with FVIII inhibitors (yes/no)
    - Severity of disease (mild/moderate/severe)
  - Receiving at least 4 doses of Hemlibra® in the last 6 months (yes/no)
- Variables related to the patients' awareness of the Hemlibra® educational program, or the awareness of their carer if the patient is under the age of 18:
  - Receipt of Patient Alert Card and Patient/Carer Guide (tick boxes for receipt)
  - Discussion with HCPs of risks associated with the use of Hemlibra® (yes/no)
  - Reading of the received educational materials (yes/no)
- Variables related to the patients' knowledge about the risks of Hemlibra®, or the knowledge of their carer if the patient is under the age of 18:
  - Knowledge of risks associated with the use of Hemlibra® (tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
  - Knowledge that the Patient Alert Card should be carried at all times tick boxes with answers that are either consistent or inconsistent with the additional RMMs)
  - Knowledge that Hemlibra® use can affect laboratory tests on blood clotting (true/false)
  - Knowledge of aPCC dosing and risks of concomitant use with Hemlibra® therapy (true/false statements)
- Variables related to the patients' self-reported adherence to the educational measures by correct implementation of the additional RMMs, or the self-reported adherence of their carer if the patient is under the age of 18:
  - Showing the Patient Alert Card to health care professionals (yes/no)
  - For patients taking aPCC while taking Hemlibra®:
    - Taking a first dose of aPCC of <50U/kg
    - Contacting their HCP before increasing the dose of aPCC above 50U/kg (yes/no/not applicable)
    - Not taking >100U/kg/24 hours for 24 hours or more (yes/no)

8.4 DATA SOURCES

The study is a primary data collection conducted through:

- a HCP survey administered online, with an option for phone guidance
- a patient survey administered online, which must be completed by the patient's carer for patients under the age of 18 years

Because haemophilia A is a rare disease, affecting only about 1 in 5,000 males, the number of patients with haemophilia and the number of HCPs treating them is limited (Stonebraker et al 2010). The selected study countries include over 80% of haemophilia treatment centres identified by EUHANET on the Haemophilia Central website, and every reasonable effort will be made to contact as many HCPs and patients as possible to achieve a sample size of 40 HCP questionnaires and 70 patient questionnaires.

8.4.1 Identification of HCPs and Patients

HCPs will be identified from a combination of public information on haemophilia treatment centre locations listed on the Haemophilia Central website and proprietary IQVIA OneKey lists. OneKey is the most comprehensive worldwide database of healthcare professionals, is representative of the HCPs population in the selected countries, and has specialties, addresses and contact information for HCPs.

To create a recruitment list of HCPs treating patients with haemophilia, addresses of haematologists from OneKey will be cross-referenced with addresses of haemophilia treatment centres and Haemophilia Comprehensive Care Centres. All haematologists working in these haemophilia treatment centres will be considered the recruitment population, since all could have potentially prescribed Hemlibra®. A screening question in the HCP questionnaire will verify that the HCP has, in fact, prescribed Hemlibra® to patients outside clinical trials. If a study country has guidelines that restrict Hemlibra® to certain locations, such as in a Comprehensive Care Centre, recruitment will focus on those locations in that country.

HCPs will be invited to participate in the survey until at least 40 completed HCP questionnaires have been returned or the list is exhausted (see Section 8.4.2).

Patients or their carers will be recruited via *their* physicians and will remain anonymous.

8.4.2 Data Collection

Questionnaire

Both the HCP and the patient questionnaire will include multiple-choice and closed-ended questions as appropriate, to collect information on their awareness of the Hemlibra® educational program, knowledge of important identified risks (TMAs and TEs) and potential life-threatening bleeding risks associated with Hemlibra® use, and self-reported adherence to additional RMMs.

The questionnaires will be translated into the relevant local languages. Translation will be done using the forward and *backward* method of translation (i.e., from English into local language and then from local language into English). The HCP questionnaire will be tested by a sample of physicians for clarity, and the patient questionnaire will be tested by a sample of non-physicians to check the understandability of language.

Completion of the HCP and patient questionnaires is estimated to take about 15 and 10 minutes each, respectively.

Conduct of survey

The data collection period is planned for approximately *12* months. Data collection is expected to be conducted between Q1 and *Q4* 2020. The fieldwork start date may vary by country based on the date of local market launch and the date of any necessary EC decisions.

To ensure comprehension of the invitation and the survey, outreach will be conducted in the local country language. The survey and invitation as well as any reminders will be translated by native speakers of the respective language at IQVIA Primary Intelligence.

Prescribers (HCPs)

HCPs will be randomly contacted by emails or phone calls, when needed. Their recruitment will be done as follows:

- HCPs will be invited to participate in the survey via emails or phone calls. The survey background and objectives, the requirement to have prescribed Hemlibra® at least once prior to the study, the contact information for questions, and the proposed compensation will be explained to the HCPs at this step. IQVIA will ensure that the compensation is in line with relevant guidelines of each country and that it only constitutes a compensation for the actual effort and time that is needed to complete the questionnaire
- If they agree to participate in the survey, they will click on the link included in the email to access the questionnaire and the instructions for the online questionnaire's completion
    - HCPs can also choose to participate in the survey by phone in the local language. In this case, an appointment for a phone interview will be scheduled with them.
- Screening questions included at the start of the questionnaire include that HCPs must have prescribed Hemlibra® at least once prior to the study and are not employed by Roche or IQVIA
- Once HCPs have passed the screening questions of the questionnaire, they are moved through the questions one question at a time. For the web-based questionnaire, HCPs can only progress to the next question when the previous question was answered, and only wholly completed questionnaires can be

submitted. If a phone interview is requested, the interviewer will complete the online questionnaire with the HCP.

- If the questionnaire is not completed within one week, the HCPs will be sent a reminder by email one week after the link was sent to them
- If the study sample size is not achieved in the country, a second reminder by phone will be conducted 1.5 weeks after the link has been sent.
- If the questionnaire is still not fully completed, a third and final reminder will be sent to the HCPs by email approximately three weeks after the start of the questionnaire.

For each HCP of the sample, the number of contacts and the date and time when he/she completed the online questionnaire will be recorded. An HCP will be considered as unreachable if he/she has been contacted between 3 and 5 times without having received any answer.

The recruitment in each country will be stopped when the target is reached. If the HCP list has been exhausted in any particular country, the recruitment in this country will be prematurely ended and a strategy will be determined to adjust the sample size with associated weighting.

Patients

HCPs that agree to participate in the patient survey will be sent informational material (kits) for distribution to up to 18 of their patients. The kit will include an explanation of the study and a simplified guide for taking the online questionnaire.

A pre-printed random unique number on the kit is registered by the HCP on a tracking web site. Tracking kit numbers allows monitoring of the number of patient questionnaires coming from the same practice. No log would be kept at the physician level which would link the kit number and the patient's identity.

The responses from the patient survey will be closely monitored and if the sample size is not reached, a second wave of outreach will be performed. This additional period will allow for an increase in the number of patients prescribed Hemlibra® by HCPs participating in the HCP survey who have agreed to distribute kit to patients. Reminder notices and additional kits will be sent to HCPs who have been invited to participate but have not yet recruited any patients.

The physicians will be paid for the distribution of questionnaires to their patients. This incentive will be small and compensates the physician for their time to ask the patient to participate and hand over the patient kit.

8.4.3 Data Collected at Study Completion

Not applicable

8.5 STUDY SIZE

8.5.1 Study Size Calculation

The sample size determination is based on the following sample size formula based on the normal approximation to the binomial:

$$n = \frac{P \cdot (1 - P) \cdot \left(Z_{1-\alpha/2}\right)^2}{e^2},$$

where P is the expected proportion, e is one half the desired width of the confidence interval, and Z1–α/2 is the standard normal Z value corresponding to a cumulative probability of 1 – α/2 (e.g., if α = .05 then Z = 1.96).

The proportions of interest (p) here are the proportions mentioned under specific objectives above. As p is not known in advance, we consider it to be 50% (maximum uncertainty). Such a hypothesis yields the most conservative, i.e., the largest, sample size. For example, the required sample size would be 43 for precision levels of 15%. Table 2 provides precision of the estimate (width of 95% CI around the estimate) for a range of sample sizes.

Table 2 Precision of the Estimate for a Range of Sample Sizes

Sample Size	Statistical Precision (%)
43	±15
67	±12
80	±11
96	±10

Prescriber (HCP) survey

A target sample size of 40 completed HCP questionnaires is based on statistical and practical considerations. With a sample size around 40, the statistical precision will be approximately ±15%; the precision would increase with larger sample size. It is to be noted that the final survey sample size will depend on HCPs' willingness to participate in the survey. Regardless of the number of respondents, all completed responses received by the cut-off date will be included in the analysis.

Assuming that the response rate could be as low as 10%, at least 400 HCPs will be invited to participate in the survey in order to increase the number of HCPs passing the screening questions and the likelihood that at least 40 HCPs fill out the questionnaire This estimate is in line with the response rate reported for similar surveys in the literature (Agyemang et al. 2017).

Patient/Carer survey

A target sample size of 70 patient/carer questionnaires is based on the below practical considerations and assumptions. With a sample size of 70, the statistical precision will be approximately ±12% (see Table 2).

Assuming that 15-20% of the targeted 40 HCPs will agree to propose the survey to up to 18 of their patients, a maximum of 144 patients will receive the survey. If approximately 50% of those patients complete the questionnaire, a sample size of 70 patient/carer questionnaires will be reached. HCPs will be reminded to focus efforts on survey distribution to their patients with inhibitors in order to include 25-35 patients with inhibitors or their carers in the target sample size. If a low patient response rate is observed during the course of the study, a second request to HCPs for patient survey distribution will be done if necessary (see Section 8.4.2).

Although the defined objective is to reach the targeted sample size of 70 completed patient questionnaires, participation is dependent on the HCPs and the patients and their interest in participating in the survey as well as the volume of Hemlibra sold. Every reasonable effort will be made to reach the target patient sample size in this very limited study population.

8.5.2 Sampling Plan

Prescriber (HCP) survey

For each selected country, the sample survey will include HCPs identified from cross-referencing haemophilia treatment centre locations listed on the Haemophilia Central website and IQVIA OneKey lists (see Section 8.4.1).

A screening question will check whether the physician has prescribed Hemlibra® at least once, and therefore can be considered for the survey.

Ideally, the sample HCPs should be proportionally split between the selected countries based on the number of prescribing HCPs in each. However, due to the expected variance of the number of HCPs in targeted countries (reflecting differences in degree of treatment concentration) such a distribution is not always feasible.

A pragmatic split will therefore be implemented to allocate a sufficient size to the less represented strata of the sample and to adjust to the market uptake of Hemlibra® in the countries included. We will then weight back the results according to the real proportion of HCPs in geographic regions from OneKey lists to reduce potential skewness of the overall sample (see Section 8.5.3).

Patient/Carer survey

For each selected country, the sample patient/carer survey will be distributed by HCPs who have agreed to participate in the patient/carer survey.

8.5.3 Sample Adjustment

Prescriber (HCP) survey

Since the relative weight of each country and each speciality of HCPs, e.g. paediatric haematologist or haematologist, in the final sample may be different from its real proportion, the extrapolation of the raw survey results to the overall target population would not be relevant without adjustment. The survey results will be weighted to reflect the real proportion in order to allow the extension of the survey results to the overall target population. Both unweighted and weighted results will be presented in the report.

A weight variable will be applied to each statistical unit (i.e., the HCPs) during the results calculation in order to correct any over-or under-sampling that may have occurred for a region. This weight variable will indicate how many unit(s) of the population of interest an observation will count in a statistical procedure. Its value will change per geographic region. The weights will be normalised to obtain their sum equal to the sample size.

Patient/Carer survey

Of note, the sample distribution for patients is uncertain, since it depends on sales of Hemlibra®, the level of contribution of HCPs distributing surveys, the number of patients in the practice of participating HCPs, and the response rate of patients. In any case, the sample will be weighted based on the number of patients who received Hemlibra® in each of the represented geographical regions.

8.6 DATA MANAGEMENT

IQVIA will be responsible for data management of this study, including quality checking of the data.

Collected data will be entered and stored in a central database specific to the survey.

A study database will be created by merging the databases of each country together. The study database will be locked once validated.

8.6.1 Data Quality Assurance

IQVIA will be responsible for the data management of this study, including quality checking of the data. IQVIA will produce a Data Quality Review Plan that describes the quality checking to be performed on the data.

Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomized to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values
- Cross-check the consistency of data for related variables (if feasible).

If missing values exist, the number of variables with missing values will be indicated. Missing values will be excluded from the calculation of percentages.

Automatic checks for plausibility and consistency will be programmed into the questionnaire tool, which will prevent contradicting values from being entered. IQVIA will not query HCPs' answers to questions in the questionnaire.

Non-admissible values will be avoided by implementation of the appropriate controls in the questionnaire at the time of its completion by the HCPs. Any non-admissible values identified after database lock (if any) will be excluded from the analysis.

The marketing authorization holder will perform oversight of the data management of this study, including approval of IQVIA data management plans and specifications.

The QC team will comply with the Roche's procedures regarding archiving and record management.

8.6.2 Source Data Documentation

Not applicable

8.7 DATA ANALYSIS

The statistical analyses will be described and further detailed in the Statistical Analysis Plan (SAP). The described analysis below might be revised, and adjustments might occur. The final SAP version will include (empty) table shells to be populated for the final study report.

8.7.1 General Considerations

The statistical analysis will be conducted using the SAS software V9.4 or above on Windows™ (SAS Institute, North Carolina, USA).

All the analyses will be descriptive. The statistical results will be presented separately for HCPs and patients/carers, overall for all 13 countries and by region (see Table 3 as an example for HCPs). *Other criteria for grouping may also be used for results presentation e.g., Euro Health Consumer Index.* As some questions may have multiple choices, the proportion of HCPs/patients having provided each possible answer will be described.

Table 3 Mock Tables to Implement in the Statistical and Study Reports

Region/country	Speciality	Speciality	All (unweighted)	All (weighted)
Region 1	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Region 2	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Region X	(N=xx)	(N=xx)	(N=xx)	(N=xx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - unweighted results	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Overall - weighted results	(N=xx)	(N=xx)	(N=xx)	(N=xxx)
answer 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
answer 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Continuous variables will be presented by their number (of valid cases, of missing values [if applicable]), mean, standard deviation, and median, first quantile (Q1), third quantile (Q3), minimum and maximum.

Categorical variables will be presented as the total number and relative percentage per category. These will be the percentage per category.

In case of multiple-choice questions, the frequency of each option provided by the physicians will be reported in the statistical results.

Confidence intervals of 95% will be evaluated, when relevant.

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be expressed among HCPs and patients/carers who provided answers

to those questions (If missing data exists, it will not be counted as a denominator in proportions).

8.7.2 Planned Analyses

Depending on the sample size, the endpoint will be assessed overall, by region and among subgroups of patients/carers.

In a first step, calculations will be performed on raw data for the overall sample. No projection factor will be applied to generalize the results to the entire prescriber's universe. As a consequence, the line "Overall - unweighted results" will show only the results observed on the overall sample and will not reflect the countries' universe since this sample is not proportional to the size of the lists in each country.

If possible, in a second step, the results will be weighted according to the real proportion of HCPs and patients/carers in each country in order to accurately reflect the population that the survey seeks to measure.

8.7.3 Analysis of *Response* Rate

The response rates will be calculated. In particular, the following different cases will be distinguished:

- *Selected HCPs (S): HCPs who were selected to be contacted from IQVIA* ***OneKey*** *lists: S = U + RE*
- *Unreachable HCPs (U): HCPs who were selected to be contacted from IQVIA* ***OneKey*** *lists but were unreachable (e.g., due to invalid contact information)*
- *Reachable HCPs (RE): HCPs who were reachable and received the invitation to participate in the survey: RE = N + C + P + R + NE*
- *Non-respondent HCPs (N): HCPs who were reachable but did not respond to the invitation to participate in the survey*
- HCPs with completed questionnaires (C): HCPs who completed the entire questionnaire
- HCPs with partially-answered questionnaires (P): HCPs *who partially completed the questionnaire (provided answers to the questionnaire but never completed/submitted it)*
- HCPs who refused to participate (R): HCPs who explicitly indicated their refusal to participate
- *Non-eligible HCPs (NE): HCPs who were confirmed to be non-eligible to participate in the survey after reaching out to them (e.g., retired)*

The HCP participation in the survey will be examined *in particular* as follows:

- $Complete\ response\ rate = \frac{C}{RE-NE}$
- $Partial\ response\ rate = \frac{P}{RE-NE}$
- Response rate $= \frac{C+P}{RE-NE}$
- Refusal rate $= \frac{R}{RE-NE}$

The participation rates will be presented by region and by speciality.

8.7.4 Questionnaire Analysis

Analysable questionnaires are those completed and submitted by the participants on the web. If the questionnaire is just filled on the web but not submitted, the questionnaire will not be analysed and will be discarded.

Analysis will be done on questions common to all HCPs and patients/carers as well as on a limited number of questions presented to the subgroup of patients with concomitant use of aPCC and Hemlibra® (or their carers).

For each question, the number and percentage of participants correctly answering each question will be presented. Individual awareness, knowledge, and adherence values will be calculated as the percentage of correctly answered questions; values will range from 0 to 100% with 100% representing the percentage of all questions in the category being answered correctly.

Awareness questions

- HCP questionnaire: Q8 and Q9
- Patient/carer questionnaire: Q1 and Q2

Knowledge questions

- HCP questionnaire: Q10, Q11, and Q12
- Patient/carer questionnaire
    - All: Q3, Q4, Q5, and Q6

Adherence questions

- HCP questionnaire: Q13, Q14, Q15, Q16, and Q17
- Patient/carer questionnaire
    - All: Q11
    - Additional questions for patients (or their carers) taking aPCC and Hemlibra: Q8, Q9, and Q10

In a first step, calculations will be performed on raw data. No projection factor will be applied to generalize the results to the entire prescribers' universe. As a consequence, the line "Overall - unweighted results" will show only the results observed on the overall sample and will not reflect the geographies' universe since this sample is not proportional to the size of the lists in each geography.

If possible, in a second step, the results will be weighted according to the real proportion of HCPs or patients/carers in a geographical region in order to accurately reflect the population that the survey seeks to measure.

Possible *participation* bias will be assessed by comparing the distributions of available characteristics (e.g., geography, type of setting [e.g., haemophilia treatment centre or HCCC], and speciality, if applicable and feasible) between respondents and non-respondents.

Assessment of success

The proportions of correct and appropriate answers to selected questions asked in the questionnaire will be presented for HCPs or patients/carers who provided answers to those questions, as outlined below.

Successful outcomes for the effectiveness of risk minimisation measures in the aspects of awareness, knowledge, and adherence are defined a priori by the following target levels:

For HCPs

- Awareness: Proportion of HCPs aware of the Hemlibra® educational program (Q8 and Q9) – Success: ≥75%
- Knowledge: Proportion of HCPs with knowledge of the important identified risks and potential risks associated with Hemlibra treatment (Q10, Q11, and Q12) – Success ≥60%
- Adherence: Proportion of HCPs self-reporting adherence to the additional RMMs for Hemlibra (Q13, Q14, Q15, Q16, and Q17) – Success ≥75%

For patients/carers

- Awareness: Proportion of patients/carers aware of the of the Hemlibra® educational program (Q1 and Q2) – Success: ≥60%
- Knowledge: Proportion of patients/carers with knowledge of the important identified risks and potential risks associated with Hemlibra treatment (Q3, Q4, Q5, and Q6) – Success: ≥60%
- Adherence: Proportion of patients/carers self-reporting adherence to the additional RMMs for Hemlibra (Q11) – Success: ≥60%

- Proportion of patients taking aPCC and Hemlibra (or their carers) self-reporting adherence to the additional RMMs specific for use of aPCC and Hemlibra (Q8, Q9, and Q10) - Success: ≥60%

Overall success is defined as success on all three domains measures (awareness, knowledge and adherence) for both HCPs and patients/carers.

Exploratory analysis of HCPs with higher success rates will also be performed and the percentage of HCPs who answered 80% and 90% of the questions correctly in each of domain will be calculated.

A sensitivity analysis will be performed to assess and compare the results of HCPs who were investigators in Hemlibra clinical studies (i.e., HAVEN) with the ones from HCPs who have prescribed Hemlibra exclusively in routine clinical practice.

Profile of HCPs with incorrect answers

The profile of HCPs with incorrect answers to the questions related to the three success factors will be described using all available and relevant HCPs characteristics collected in the survey (e.g., geography, speciality, duration of practice, practice setting) and past experience with Hemlibra® (number of patients prescribed).

Profile of patients with incorrect answers

The profile of patients with incorrect answers to the questions related to the three success factors will be described using all available and relevant patient characteristics collected in the survey (e.g. geography, age, diagnosis with inhibitors).

Note that other additional analyses will be performed. These include the comparison of the knowledge and adherence to additional RMMs of HCPs and patients that are aware of the additional RMMs as opposed to those who are not aware of the RMMs.

Analyses will be defined in more detail in the SAP and final report.

Note that the selection of these thresholds for success is subjective (7 May 2015 PRAC Rapporteur PASS Protocol Assessment Report; Procedure no.: EMEA/H/C/000387/MEA 087.2) and not based on a priori knowledge, experience, or established scientific criteria in the education or risk communication or evaluation literature. Therefore, the results will be contextualized considering other available information.

8.7.5 Handling of Missing Data

The online questionnaires require responses before proceeding through the form, and missing data are expected to be few and distributed at random. Since there is no applicable method unanimously accepted, there will be no replacement or imputation of missing data (Sterne et al. 2009).

8.8 QUALITY CONTROL

8.8.1 Study Documentation

Data will be collected using a questionnaire administered online for both HCPs and patients/carers, and HCPs will also be given an option of a phone interview as an alternative.

Testing of questionnaire

For the online questionnaires, data will be collected using an electronic data capture (EDC) system developed following a full validation process. The programmed questionnaire will be tested and validated in accordance with IQVIA Standard Operating Procedures (SOPs), which cover validation for all clinical and risk management-related applications. The internet-based repository will be used to store survey data and other relevant program information. Questions are programmed to ensure that they are asked in the appropriate sequence. Skip patterns are clearly indicated. Respondents cannot go back to a question once the question has been answered and they cannot skip ahead. Response options presented in a list are randomized to minimise positional bias. Programming will be reviewed by Quality Control and simulated users (User Testing) prior to implementation.

Collected data will be entered and stored in a database specific to the survey and the country. A study database will be created by merging databases of each country. HCP identifying information will be stored separately from study data.

Data will be checked in terms of consistency before data analysis:

- Removal of duplicates (if required)
- Data labelling and data formatting
- Range and consistency checks for each variable to identify potential non-admissible values
- Cross-check the consistency of data for related variables (if feasible)

The study database will be locked once validated.

Approaches for language testing of the questionnaires

The HCP online questionnaire will be translated and tested in an initial release to two to three HCPs in several countries for its comprehensibility, consistency and the appropriateness of medical terms. HCPs comments will be implemented in the final version.

Similarly, the patient/carer online questionnaire will be tested with a sample of non-physicians, providing the educational materials for review before their completion of the questionnaire.

The translated versions of the questionnaire from English into local language will be done using the forward and *backward* method (from English into local language and then from local language into English) to ensure an accurate translation.

Approaches for validating the results

The quality control for validating the results will be conducted at five levels:

1. Every effort will be undertaken to collect complete and valid data
2. At the study database level, final data quality checks will be applied to count the number of missing values and estimate the associated relative percentage.
3. At the statistical analysis level: all data management and statistical analysis programs developed and used in the analysis will be documented. All versions generated will be dated, kept with accompanying documentation and archived. The original database will be stored. A derived database will be created for the new versions of the data in order to include recoding and computing of new variables, especially stratification of continuous variables, combination of modalities for categorical variables, calculation of composite indicators, etc.
4. At the results level, a data review will be done to ensure data integrity. A statistical analysis report including all the results will be provided for review and discussion. The final statistical report will take into account the reviewer's comments.
5. At the study level, all aspects of the study will be conducted according to the SOPs of IQVIA Real World Evidence Solutions. The study documents have been approved by people competent in medical and safety areas of IQVIA. According to the SOPs, an independent review of the study results and report will be conducted by a person who was not in charge of their preparation.

8.8.2 Site Audits and Inspections

Not applicable.

8.8.3 Safeguards, Security and Traceability of Contacts

Operators of the call centres specialized in health surveys will be assigned to the project and trained on the survey methodology prior to fieldwork. The email contacts and phone calls will be traced using management software.

Participating HCPs/patients/carers will access the website (https:// secured site) via a secure link. This link is unique to each HCP/patient/carer.

The answers provided will be collected in an anonymous way, and only aggregated data presented as a synthesis will be transmitted to the MAH.

Data will be recorded in a central database and tracked using an audit trail. The system will enable retrieving all introduced data at any time and will include security elements to

prevent anyone other than authorized staff from accessing data. Each user will have a specific profile which will limit his/her use of the database. A copy of the database and the application files will be made outside the server housing the web-based study. These copies for security purposes will be periodically made and stored outside this server.

8.8.4 Retention of Records

The study documentation will be stored in the study master file.

The data from the online questionnaires and the phone interviews will be stored on the study database for 5 years.

Data storage will be in line with national data protection requirements for each of the countries where the study will be conducted.

All documentation pertaining to the study, including electronic records will be retained for a minimum of 5 years after the end of the study.

8.9 LIMITATIONS OF THE RESEARCH METHOD

Bias

The potential for selection bias of physicians participating in a survey is an inherent bias/limitation to any study based on volunteer participation. For instance, it is possible that HCPs willing to participate in the study are those with the highest awareness of the risks associated with Hemlibra®. In order to quantify any selection bias, the distribution of each stratification criterion of physicians (country, speciality, and the other available characteristics present in the screening log) will be compared between participants and non-participants.

Additionally, non-response bias may also be introduced into the study if targeted HCPs have activated filters in their mailbox that block spam and unsolicited emails. Having multiple email addresses could also affect responsiveness, especially if the one used for sending the invitation is not the primary address. HCPs who do not check their email frequently might not receive the invitation during the recruitment period. These are among the reasons why the HCPs will also be contacted by phone.

Moreover, online surveys may promote information bias that may result from social desirability, which refers to the tendency of physicians to give socially desirable/expected responses instead of choosing those reflecting their current knowledge or behaviour, e.g. physicians can copy-paste or refer to information gathered online instead of giving their own opinions (Wyatt 2000).

Social desirability can affect the validity of survey research findings, but the use of pre-populated items in the questionnaire could/tends to reduce this bias (Nederhof 1985).

Theoretically, the social desirability bias may also arise when the patients are recruited by the same HCP who has participated in the survey. There is also a potential for a HCP who participated in the survey to increase the awareness of his or her patients about the topic covered in the survey. However, due to the anonymity of the survey, the competitive recruitment (the HCP will not be certain if a patient questionnaire will ultimately be considered in the study), and the fact that the results of the patient survey will not be analysed per centre but as separate samples, this limitation is less likely to happen. As a result, we do not consider it necessary to distinguish between HCPs who participate in the survey from those who recruit patients.

The access to the online questionnaire interface will be limited to the invited participants. Each participant will receive a unique link (URL) to the questionnaire and will only be allowed to participate once.

This survey includes products that are prescribed to patients under 18 years of age. In such cases, the questionnaire will be filled by the parent or the guardian, which may impact responses to questions related to awareness and knowledge of Hemlibra® risks.

Finally, the patient recruitment model, which is done exclusively through HCPs, can introduce a potential bias if the HCPs select patients in a non-random manner.

Limits inherent to surveys

In such surveys, the generalisation and external validity of the results is restricted to HCPs who have an active email address and willing (and able) to answer a questionnaire online. These physicians may not be fully representative of the whole targeted population (Wyatt 2000).

In terms of the patient survey, the use of the online questionnaire format limits participants to patients with internet access.

Generalisation of the survey results to the overall target population with adjustment

The most important limitation for the generalization of the results are the sample size which could yield a confidence interval which is very wide. Although all reasonable efforts will be undertaken to achieve the required sample size, if the final sample is below 30, the usual statistical tests will be of limited validity and the generalization of the sample will be jeopardized.

The raw survey results can only be generalized to the overall target population, except if a sample adjustment is applied. For more transparency and accuracy, both unweighted (i.e., raw data) and weighted results will be presented.

8.10 OTHER ASPECTS

Strengths of the research methods

1. The information contained in the OneKey list of each country is updated continuously with proactive updates. Quality controls are performed on OneKey content on a regular basis. OneKey is the most comprehensive list of HCPs in the world with very high coverage in most countries.
2. The sampling of HCPs follows a randomized method which guarantees the representativeness of the contacted population in order to limit selection bias due to voluntary participation. Batches of HCPs will be contacted up to five times before moving forward to other HCPs in the lists.
3. The questionnaire includes general questions followed by specific ones in order to limit a learning process during the survey. As the physicians may understand the right answer in subsequent questions, it would not be possible to go back in the questionnaire and edit answers in former questions.
4. The questionnaire is tested for its clarity. It is also checked whether there are questions which would suggest a specific answer for any reason for example social desirability. The translation of the questionnaire is tested before implementation.

9. PROTECTION OF HUMAN SUBJECTS

The survey is non-interventional and totally anonymous to the study sponsor. Data collected will remain absolutely confidential and only aggregated data will be analysed and communicated in a report. The study will be conducted in agreement with the regulation (EU) 2016/679 of the European Parliament on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation, GDPR).

9.1 INFORMATION ON SURVEY PARTICIPANTS AND INFORMED CONSENT

IQVIA will ensure that the national and European data protection and ethical requirements are met for the patients and physicians.

9.2 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

The study will comply with national and European Union requirements for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

9.3 INFORMED CONSENT

HCPs participating in the survey will be informed about the targets of the investigation, the nature of the transmitted data, the intended use of data, recipients of these data, and their right of access and rectification to their personal data, as well as their right of objection to use their data or to IQVIA keeping their data. They must agree with the terms via a checkbox in the questionnaire before any information is stored.

Patients participating in the study will be informed about the purpose of the survey, and the storage of their data, and they must agree with the terms via a checkbox in the questionnaire before any information is stored.

9.4 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

The non-interventional study will be submitted for approval to Clinical Research Ethics Committee or Independent Review Board as per local applicable requirements.

9.5 FINANCIAL DISCLOSURE

HCPs will be offered a compensation for the time spent participating in this survey (that they may refuse). For HCPs involved in the HCP survey, the estimated time to complete the questionnaire is 15 minutes. In addition, the physician will receive a small incentive for asking the patient if he/she wants to participate and handling over the patient kit.

The amount of this compensation will be determined according to the European Pharmaceutical Marketing Research Association (EphMRA) recommendations and the Association of Opinion and Behaviour in health field research companies (ASOCS) charter, which states: “When it is necessary to compensate a HCP in return to the time spent during an interview or a group meeting, the compensation must not exceed the fees commonly taken by the HCP for his/her advice or consultation and must be proportional to the time provided. The compensations should be clearly stated prior to the HCP’s participation in the survey. They must be declared to the tax authorities in accordance with applicable laws”.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

This study is a survey to evaluate the effectiveness of educational materials implemented as additional RMMs. This survey does not involve data collection on clinical endpoints for individual patients.

HCP and patient/carer questionnaires contain a minimal number of open questions (i.e., free text questions) and will not be used for collecting adverse events.

Although adverse event information is not being actively solicited via this protocol, physicians/patients/carers are reminded to report any adverse reactions (for which they

suspect a causal role of a medicinal product) that come to their attention to the concerned competent authorities via the national spontaneous reporting system.

In addition, physicians are reminded the following should also be reported if occurring during exposure to Hemlibra, even in the absence of adverse events:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products
- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a subject is not exposed to Hemlibra, but the physician/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

In the event that a study participant reports a safety event associated with a Roche product, IQVIA will forward any information on adverse events (AE; serious and non-serious) that involve Roche products to the Roche Pharmacovigilance department. This will be done within one business day for serious AE or within 30 days for non-serious AE.

11. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, Roche is dedicated to openly providing information on the study to HCPs and to the public, both at scientific congresses and in peer-reviewed journals. Roche will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the marketing authorization holder prior to submission for publication or presentation. This allows the marketing authorization holder to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication

of the study in which contribution of marketing authorization holder personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate marketing authorization holder personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the marketing authorization holder, except where agreed otherwise.

The final study report will be communicated to the EMA after validation by Roche.
An abstract of the results will be uploaded to the EU-PAS register.

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Appendix 1 ENCePP Checklist

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: HEMLIBRA SURVEY TO PRESCRIBERS AND PATIENTS/CARERS TO EVALUATE AWARENESS, KNOWLEDGE AND COMPLIANCE TO ADDITIONAL RISK MINIMISATION MEASURES

Study reference number: BO40853

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5
1.1.2 End of data collection[2]	☒	☐	☐	5
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS register	☒	☐	☐	5
1.1.6 Final report of study results.	☒	☐	☐	5

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
2.1.2 The objective(s) of the study?	☒	☐	☐	7.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	8.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	8.1
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	8.2.1
4.2.4 Disease/indication?	☒	☐	☐	8.2.2
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.5.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.7
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	8.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	8.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4.2
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	8.7.1, 8.7.2
10.2 Are descriptive analyses included?	☒	☐	☐	8.7.1, 8.7.2
10.3 Are stratified analyses included?	☒	☐	☐	8.7.1, 8.7.2
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.5
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	8.5.1

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.8.4
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6.1
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	8.6.1

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	8.9
12.1.2 Information bias?	☒	☐	☐	8.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	8.5

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

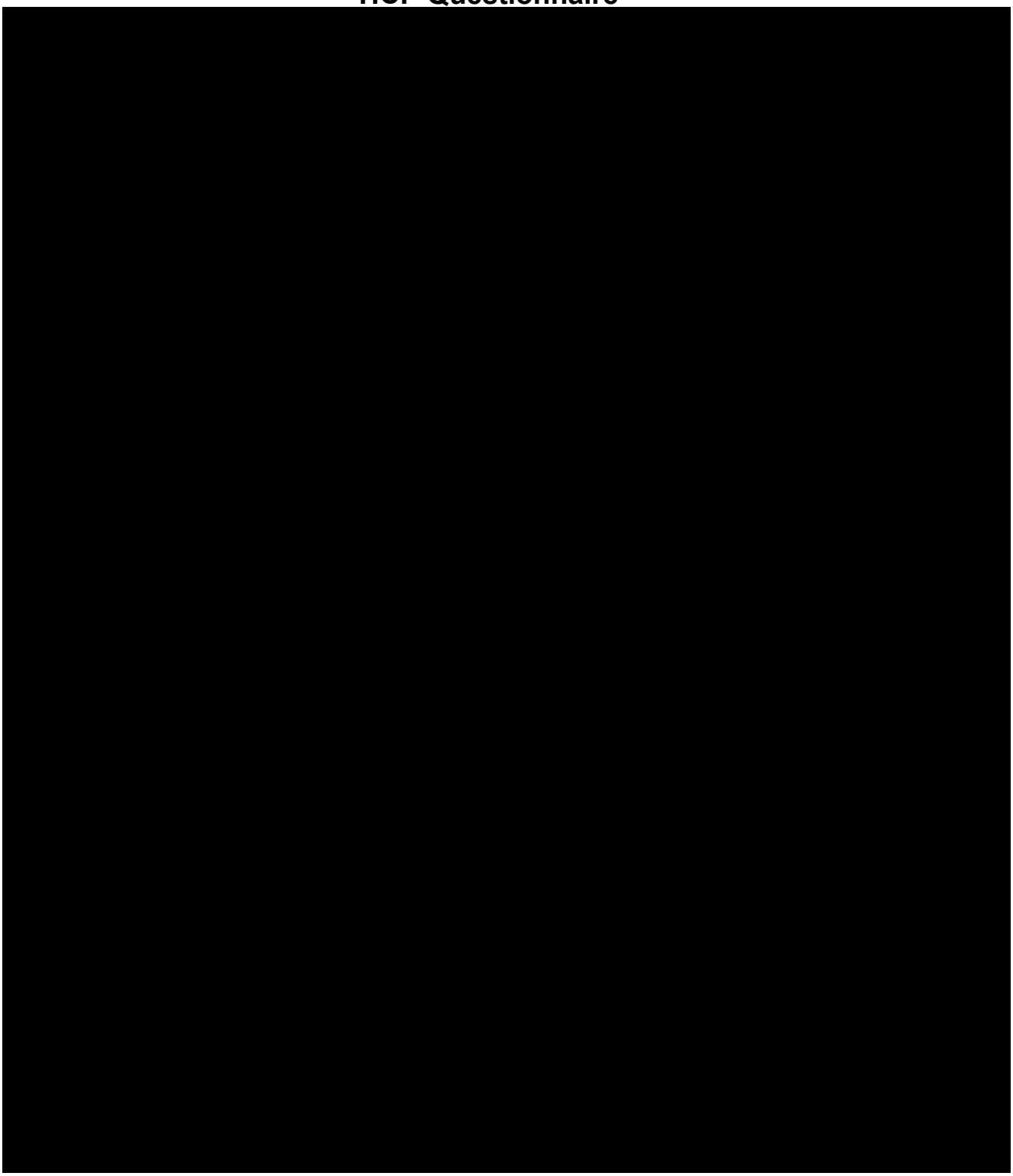
Comments:

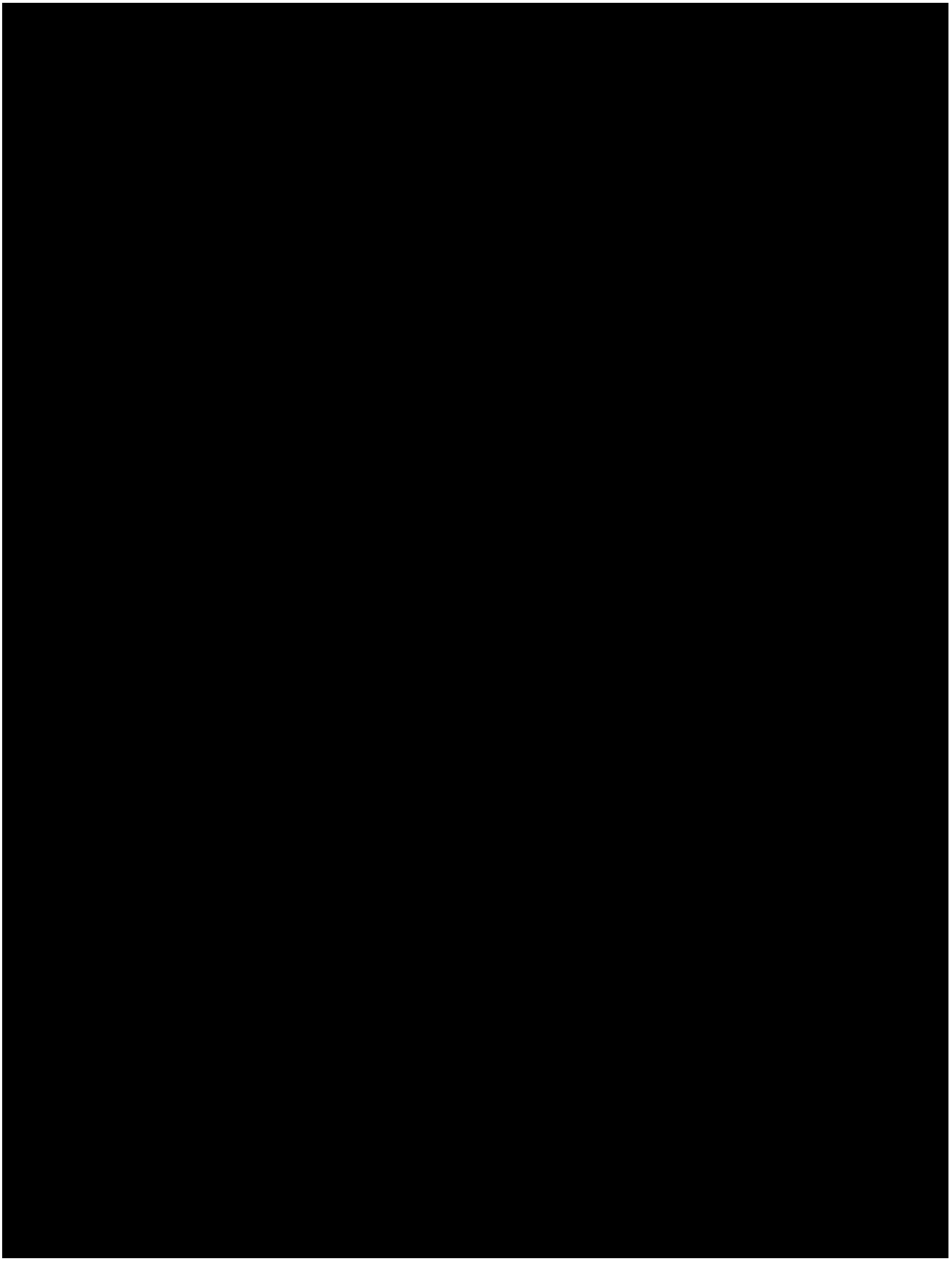
Name of the main author of the protocol:	[redacted]
Date: dd/month/year	22/03/2019
	[redacted] on behalf of [redacted]
Signature:	[redacted]

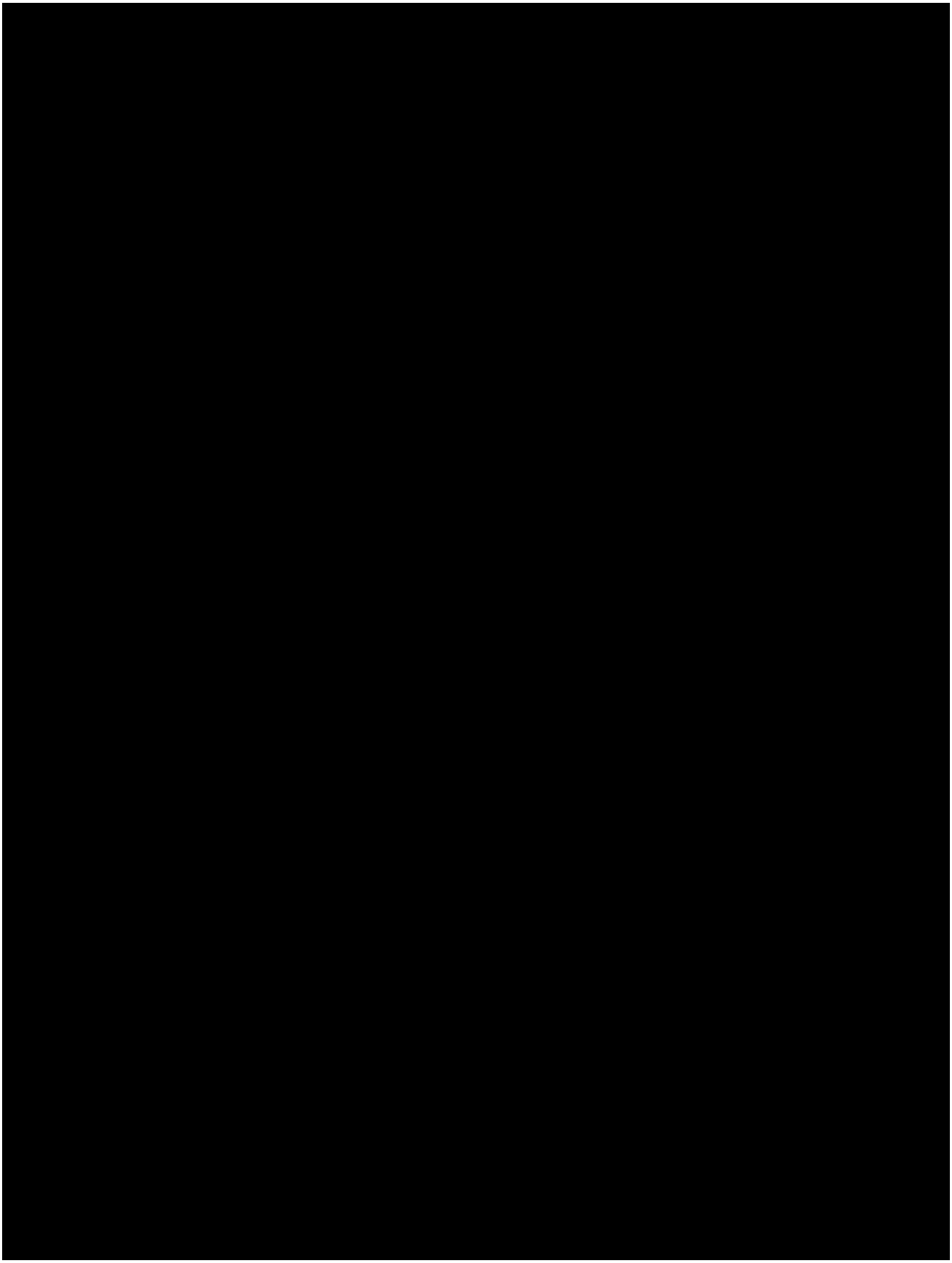
Appendix 2 HCP Questionnaire

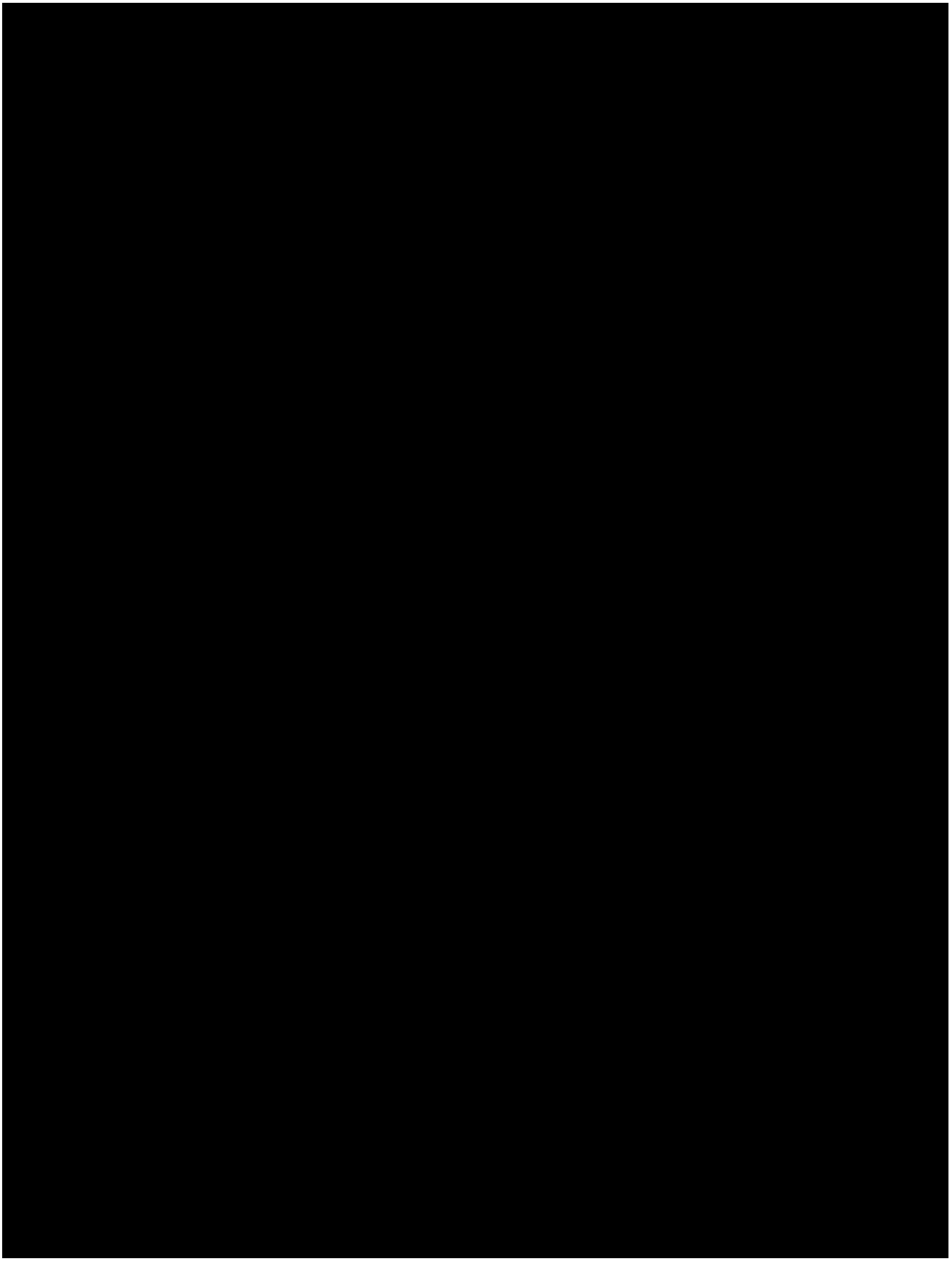
Evaluation of the effectiveness of additional risk minimisation measures for Hemlibra in the European Union

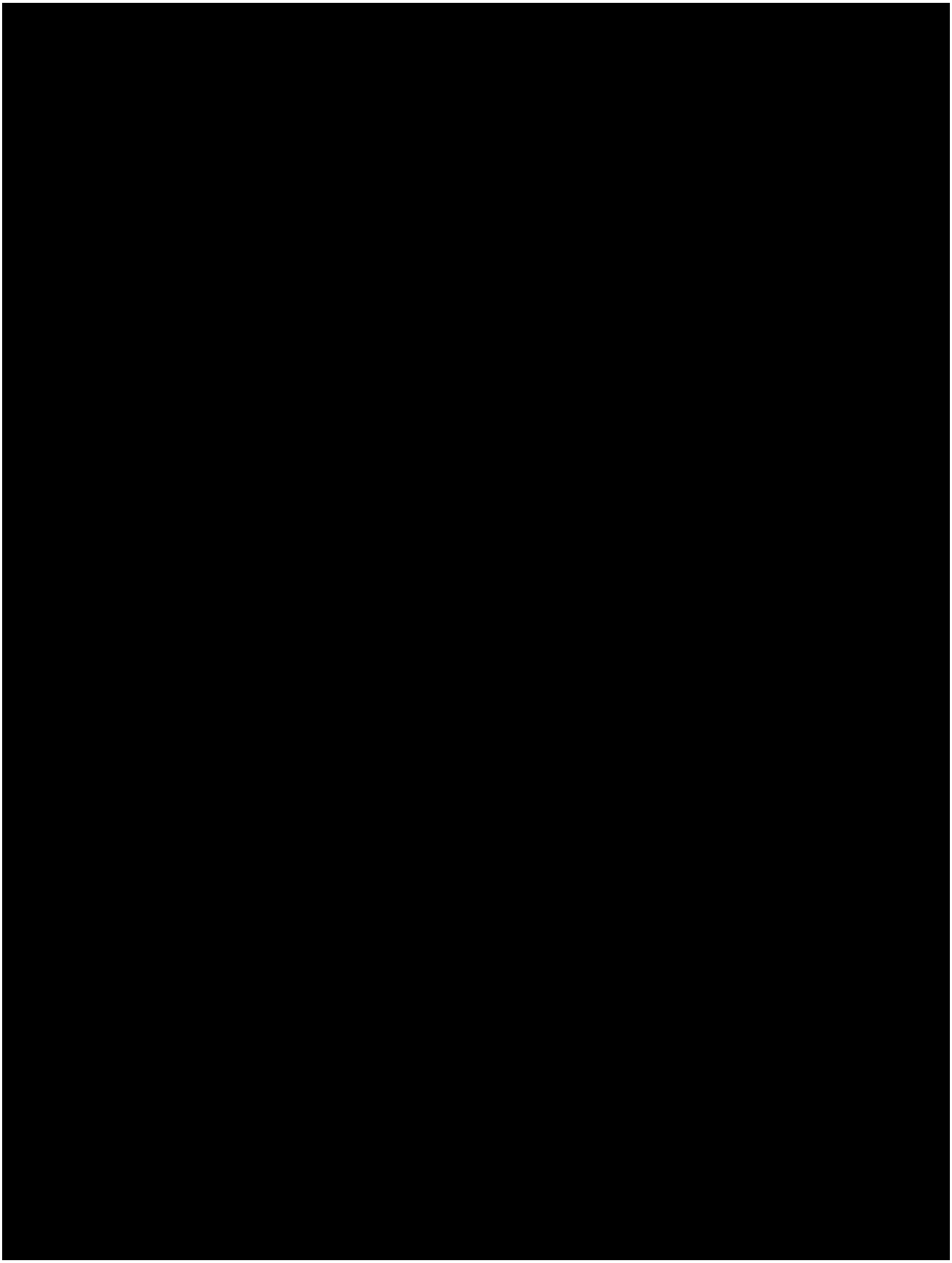
HCP Questionnaire

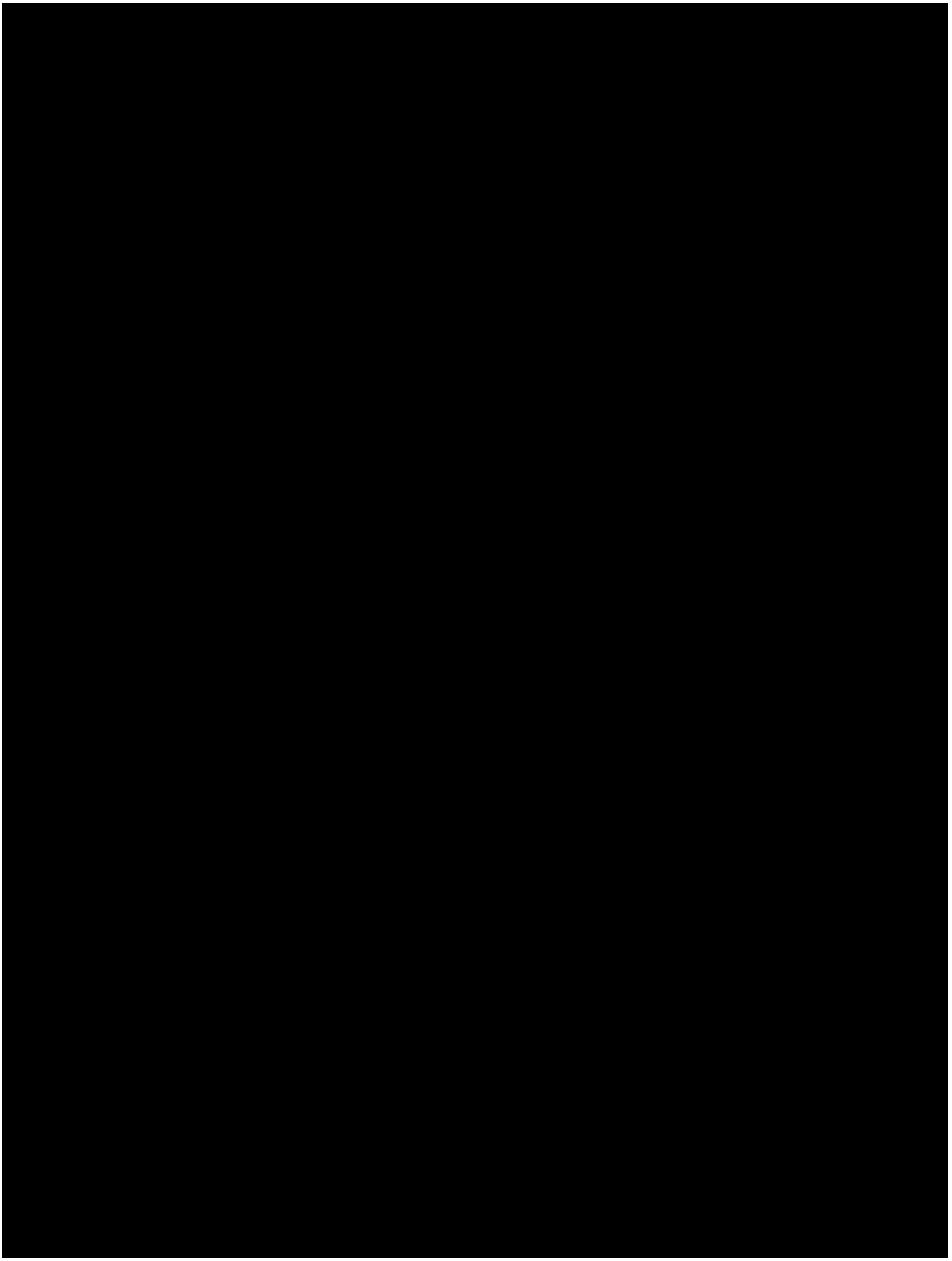


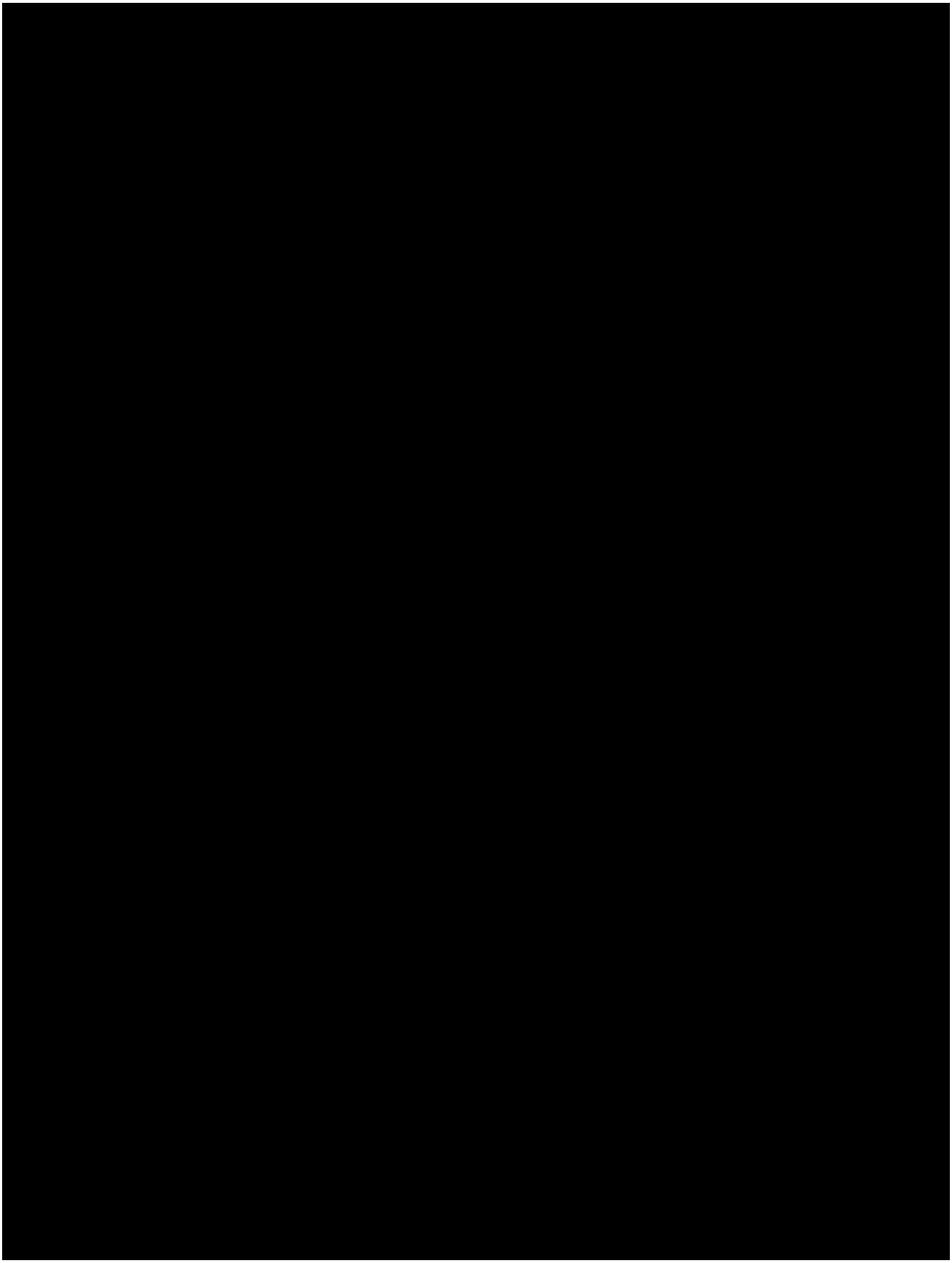


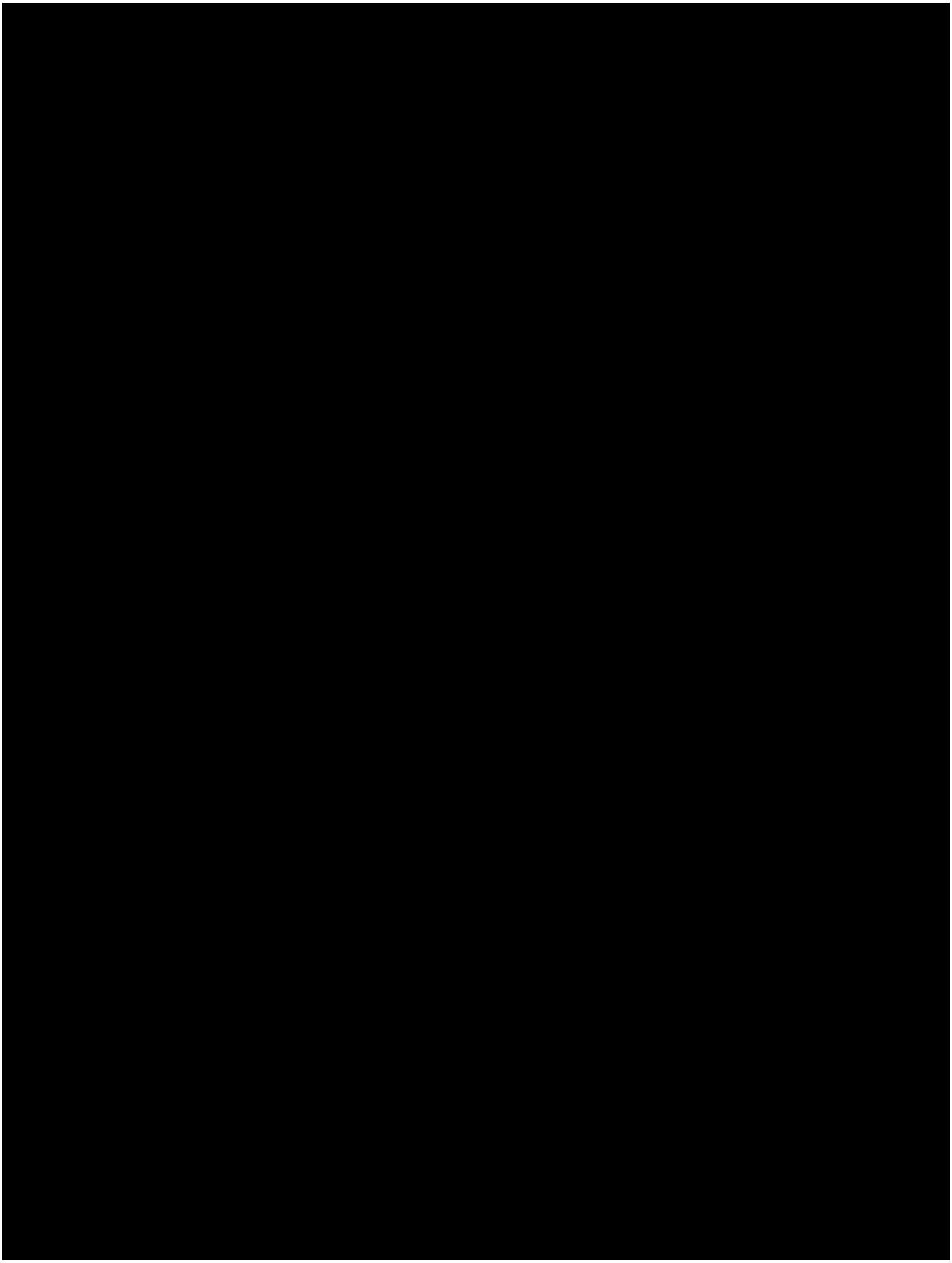


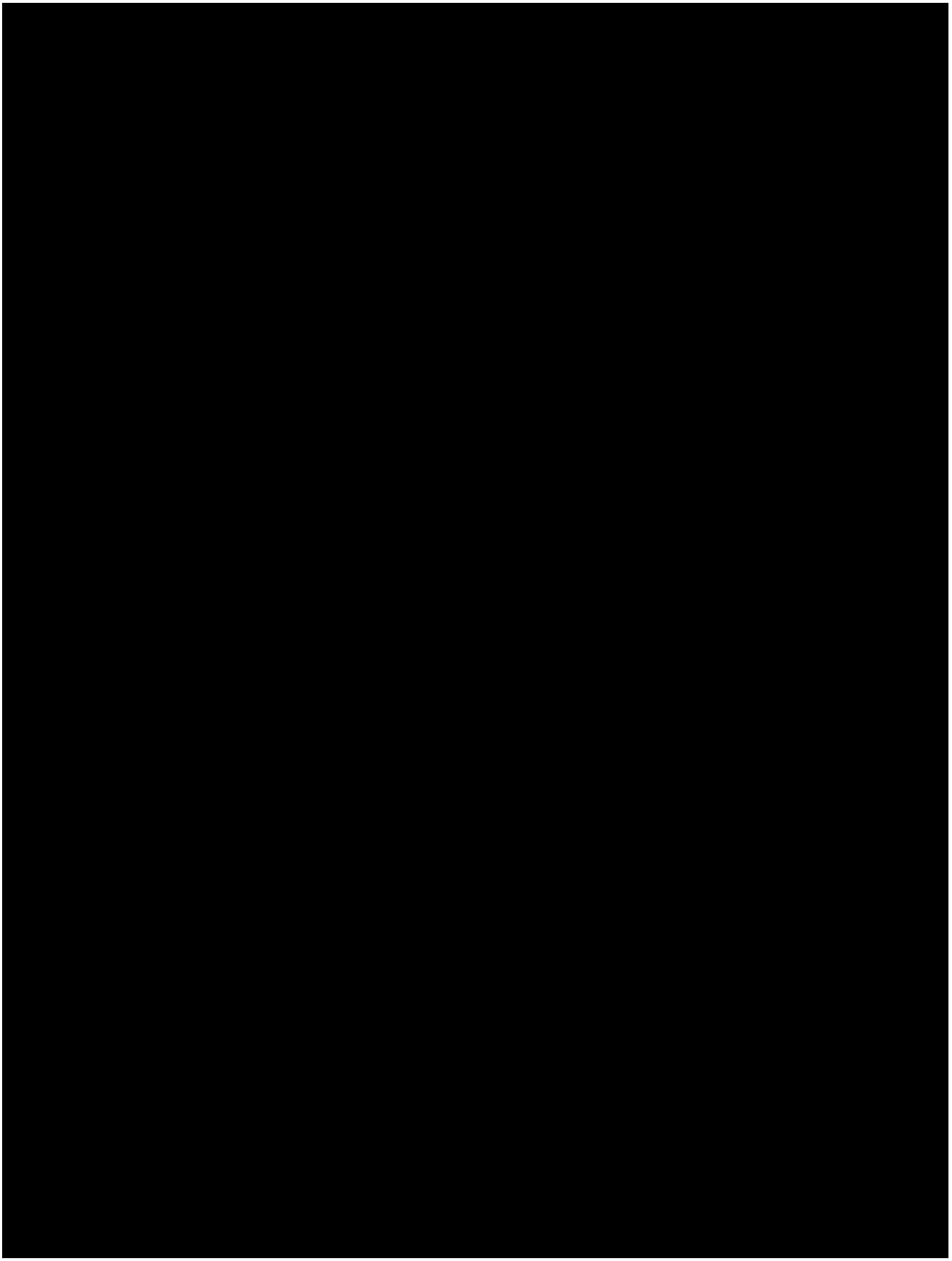


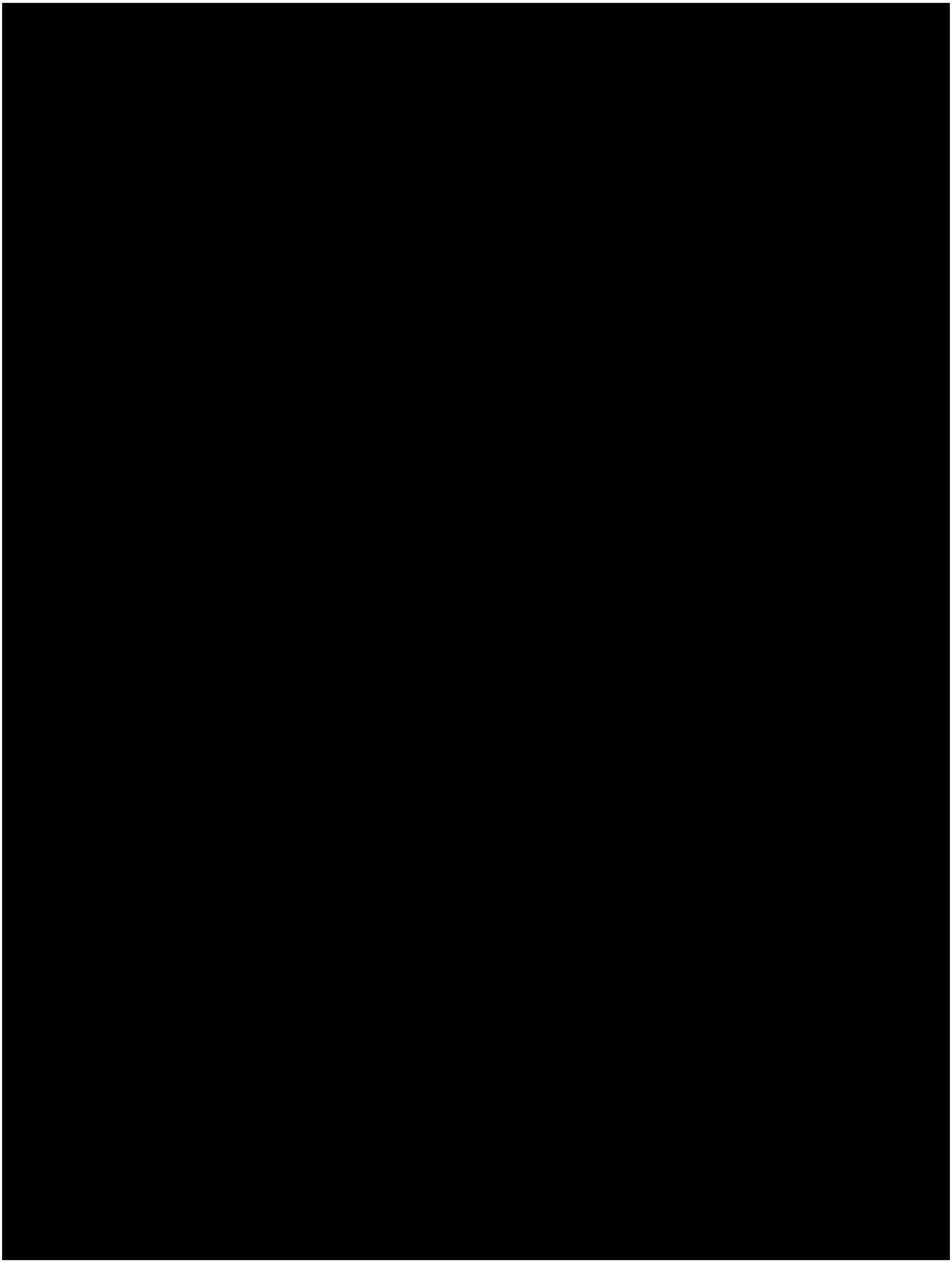


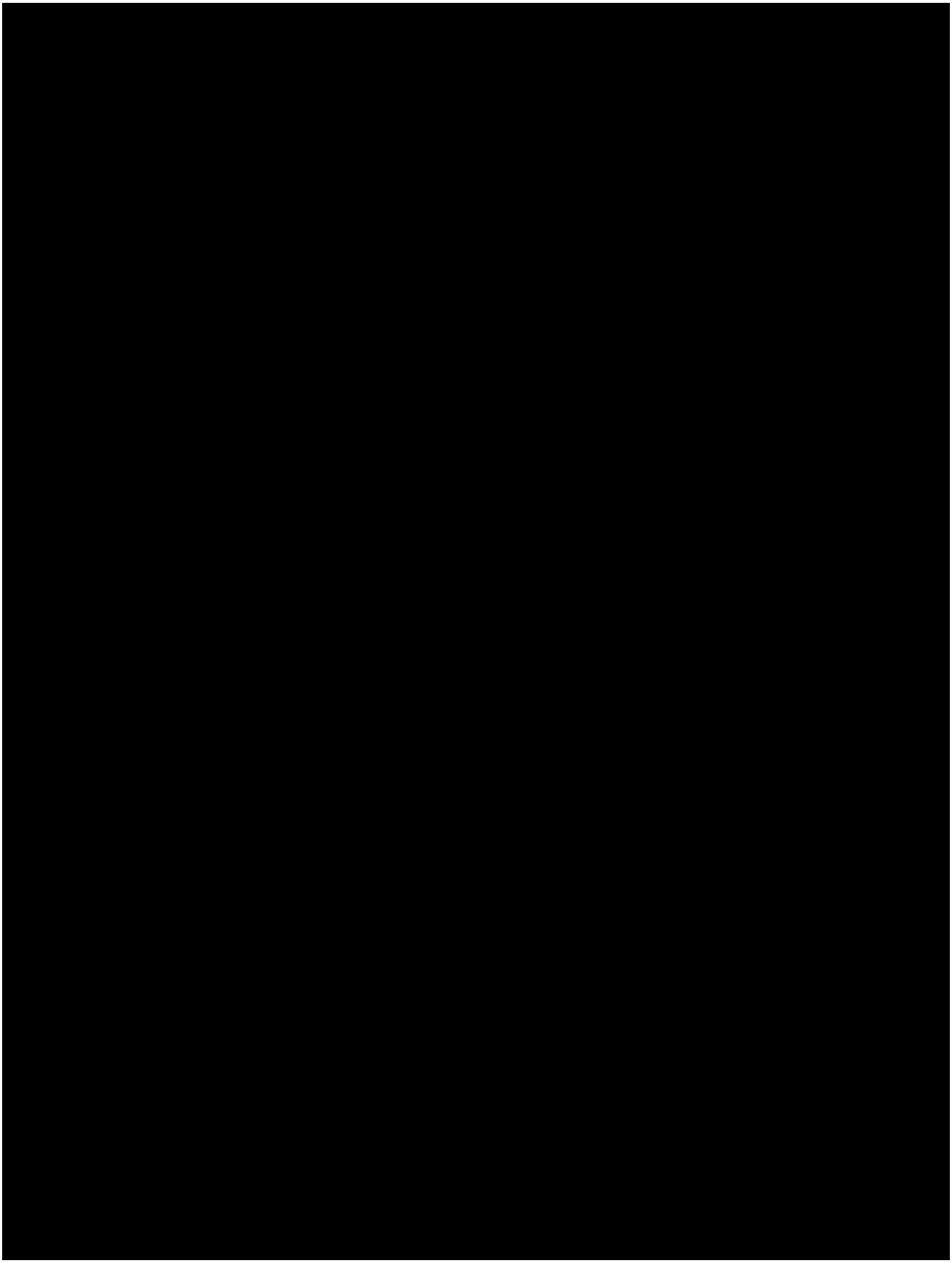








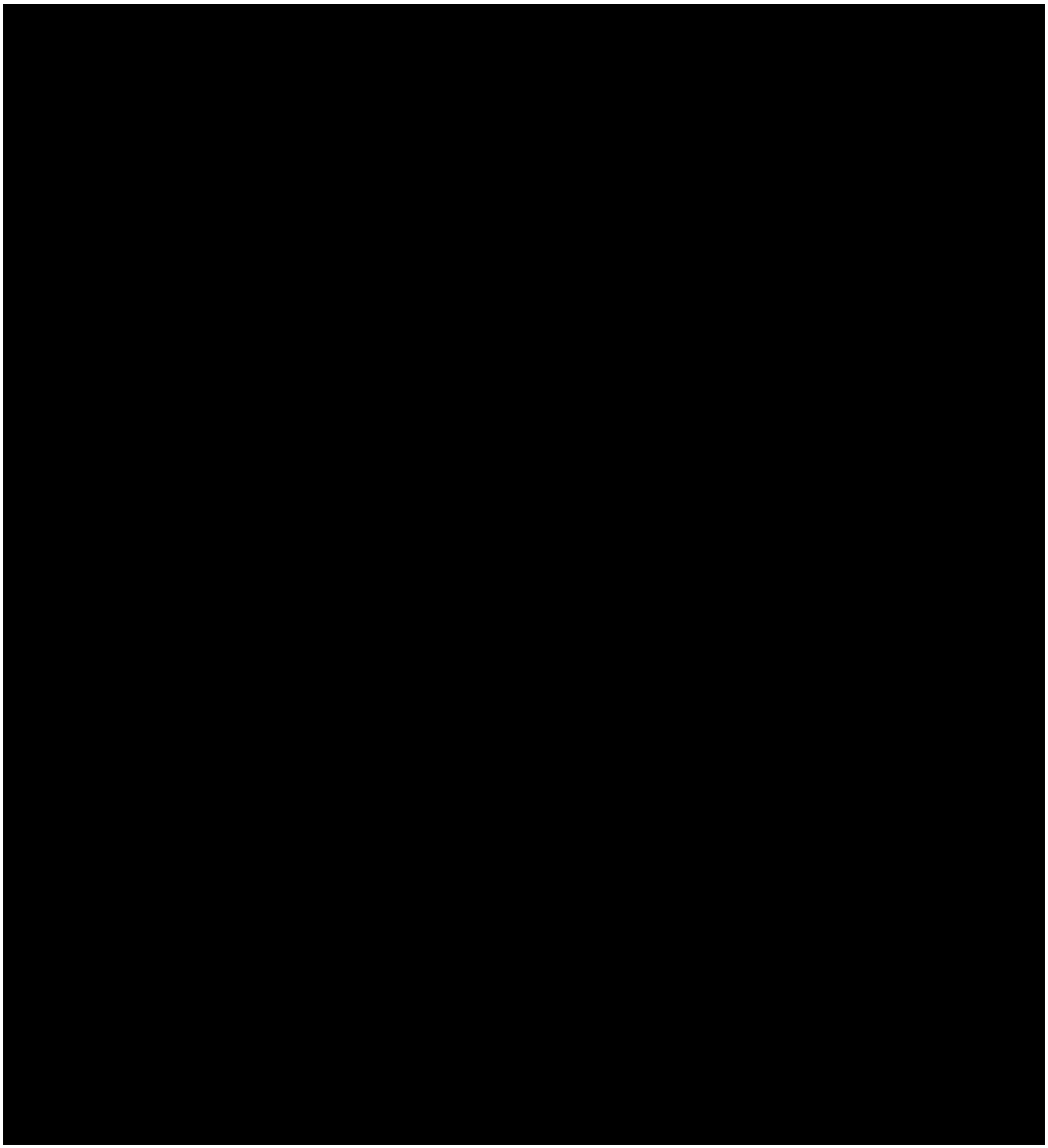


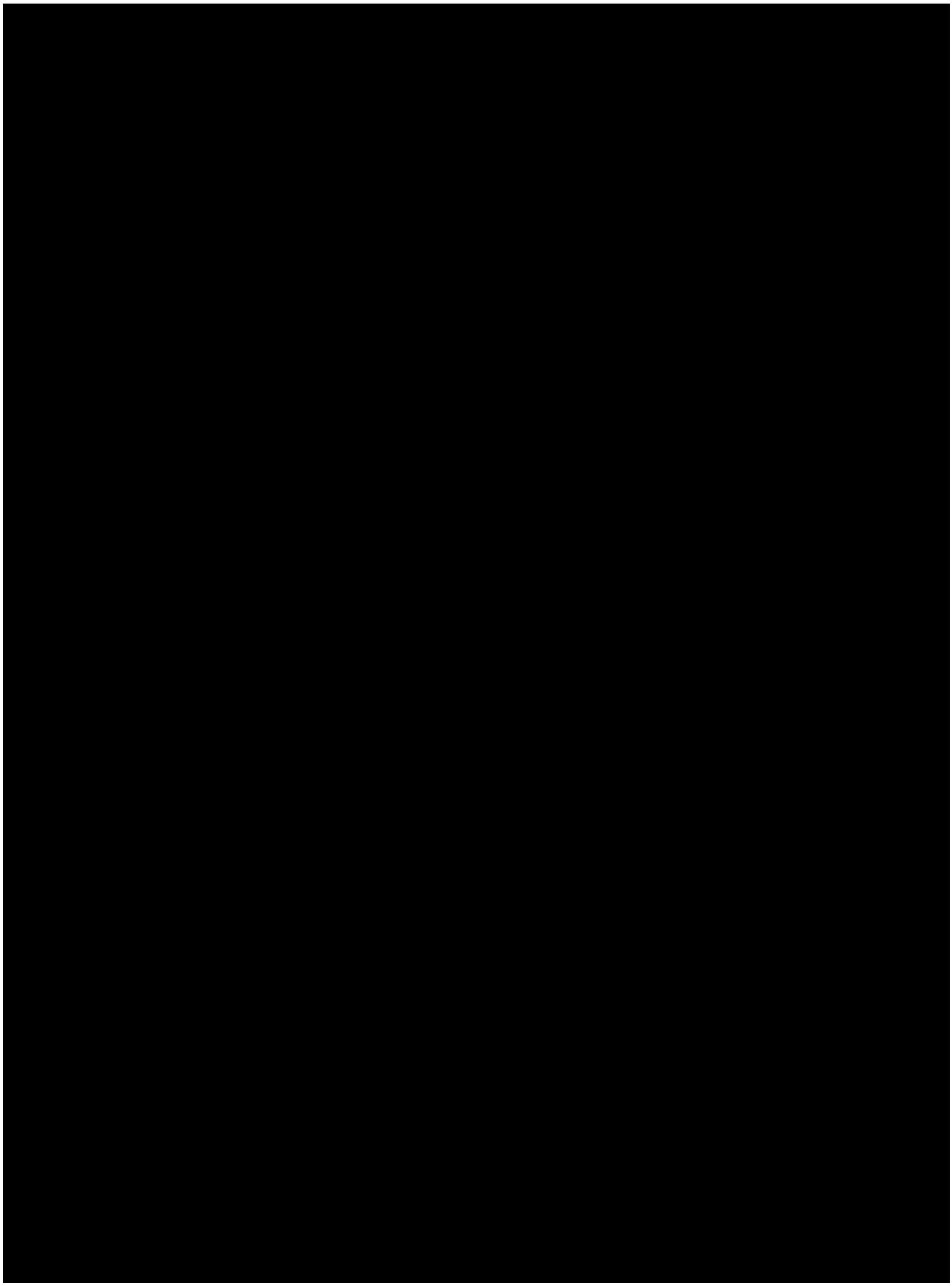


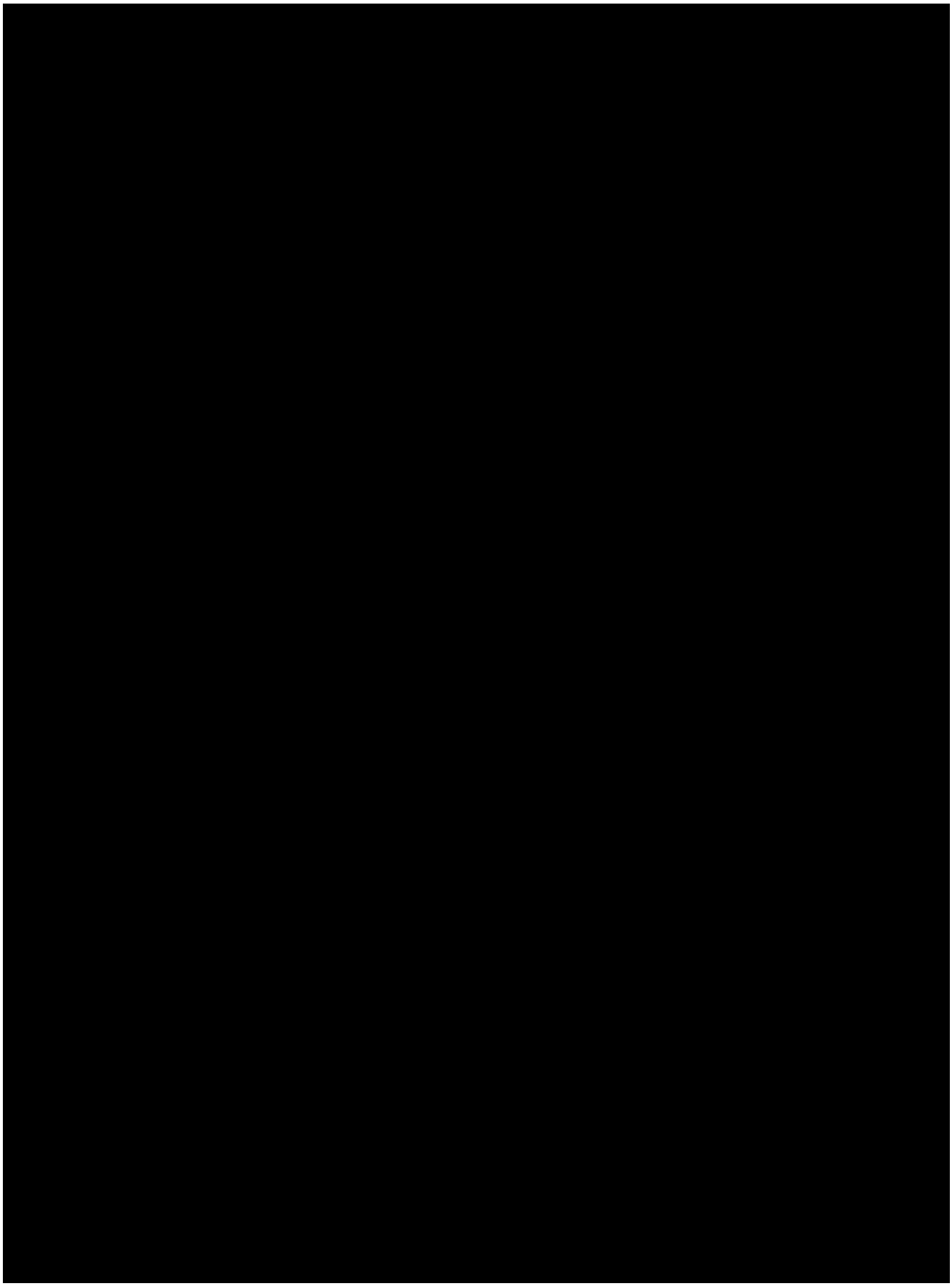
Appendix 3 Patient Questionnaire

Evaluation of the effectiveness of additional risk minimisation measures for Hemlibra in the European Union

Patient Questionnaire







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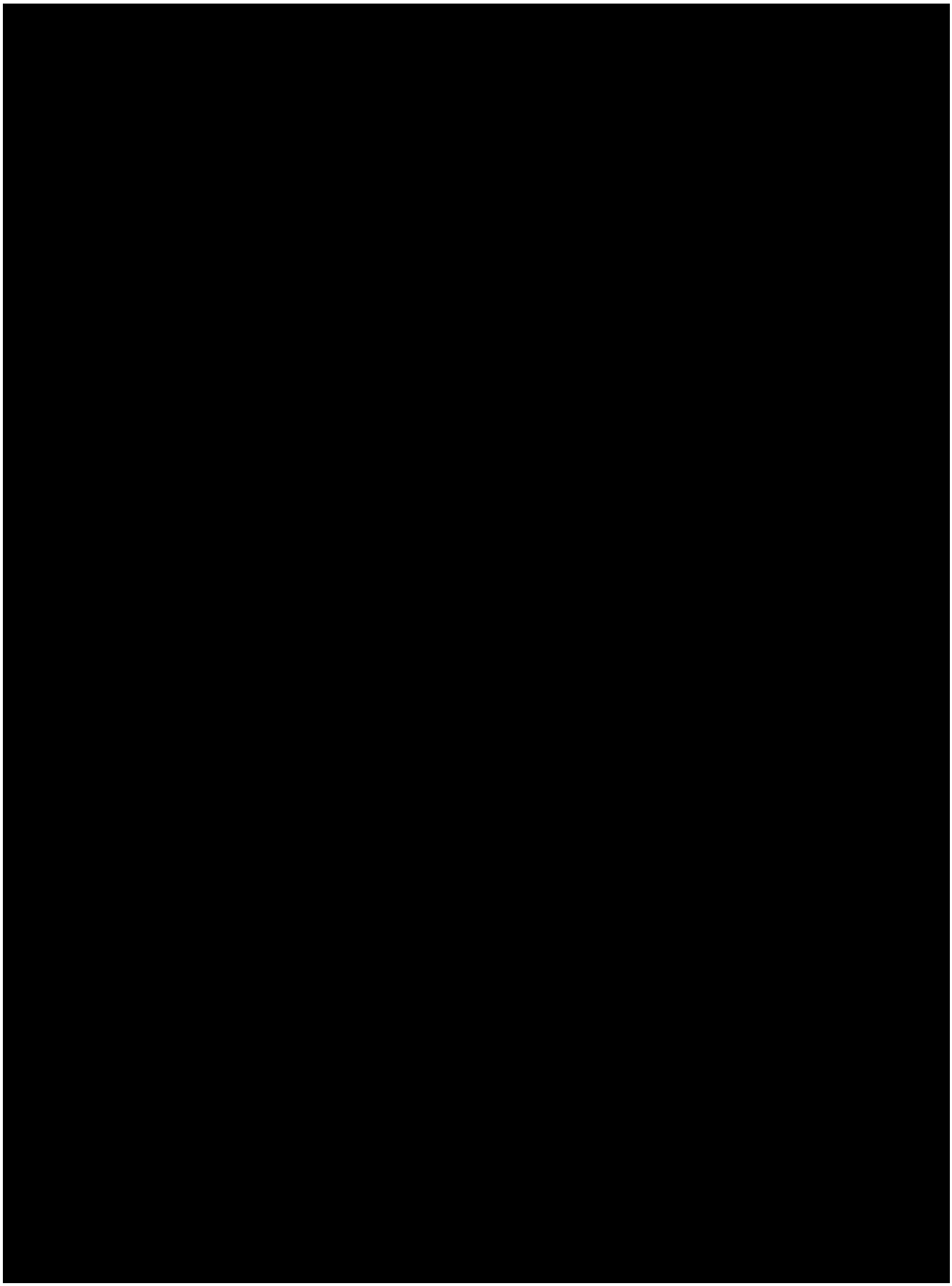
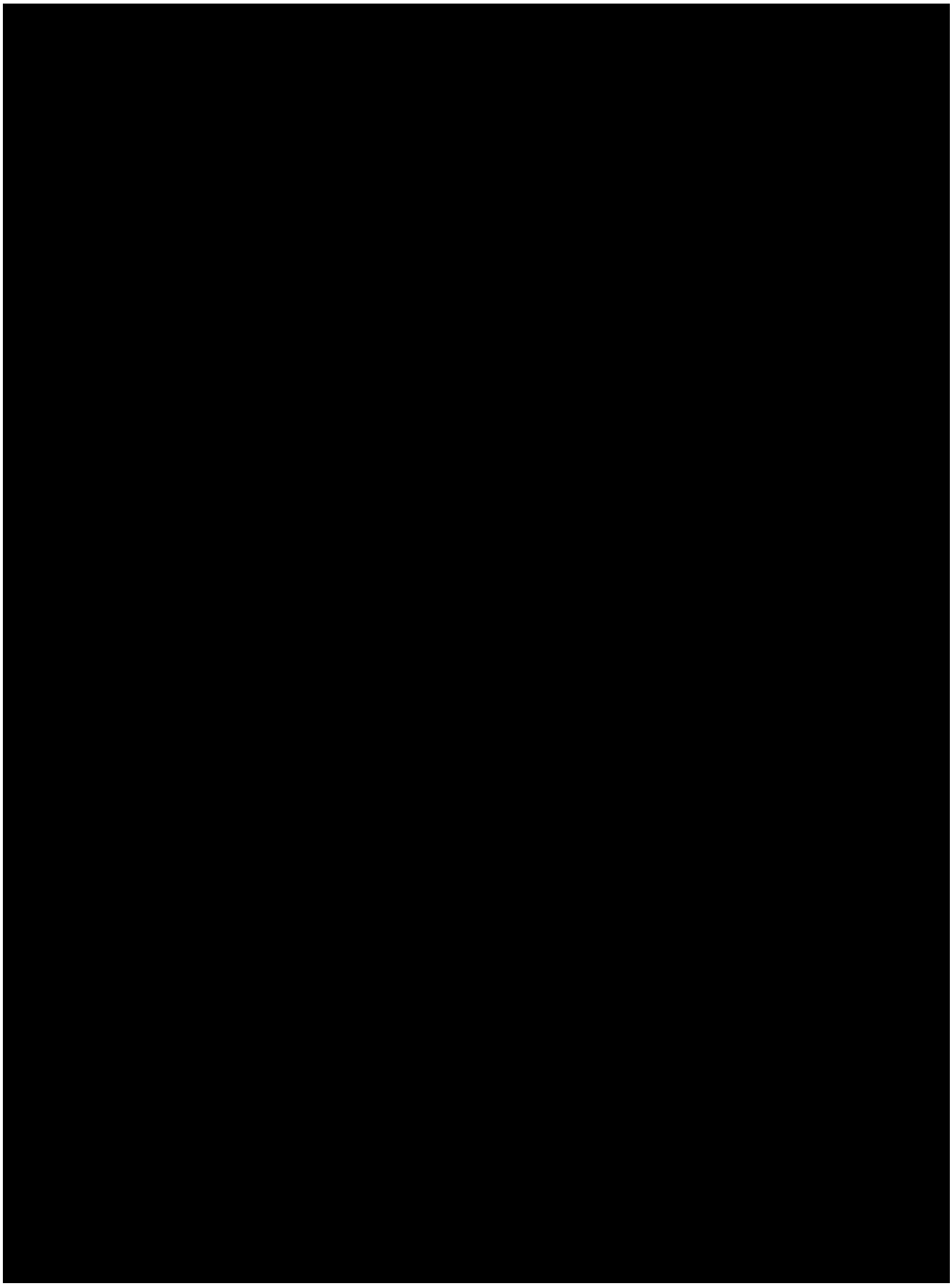
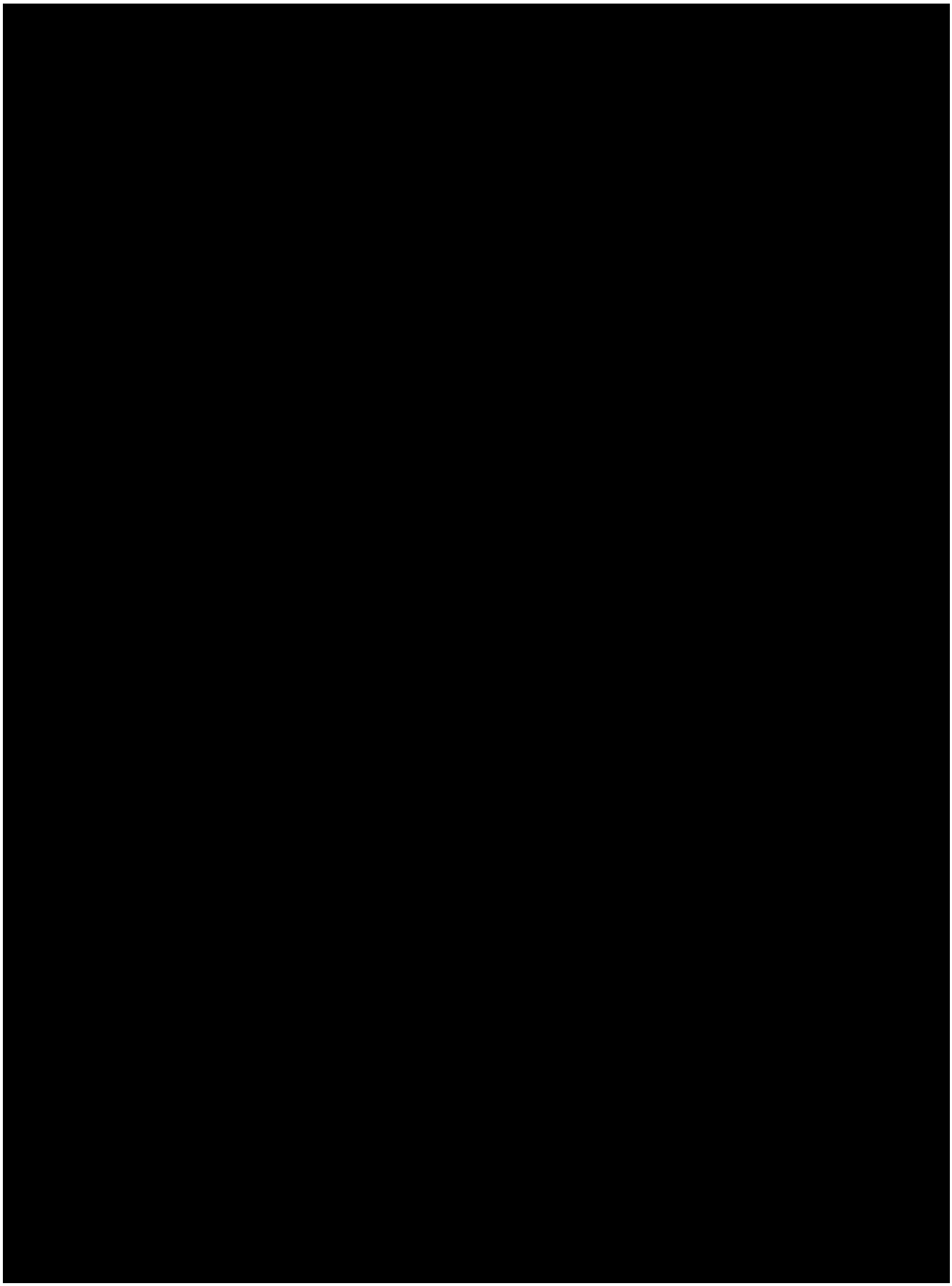
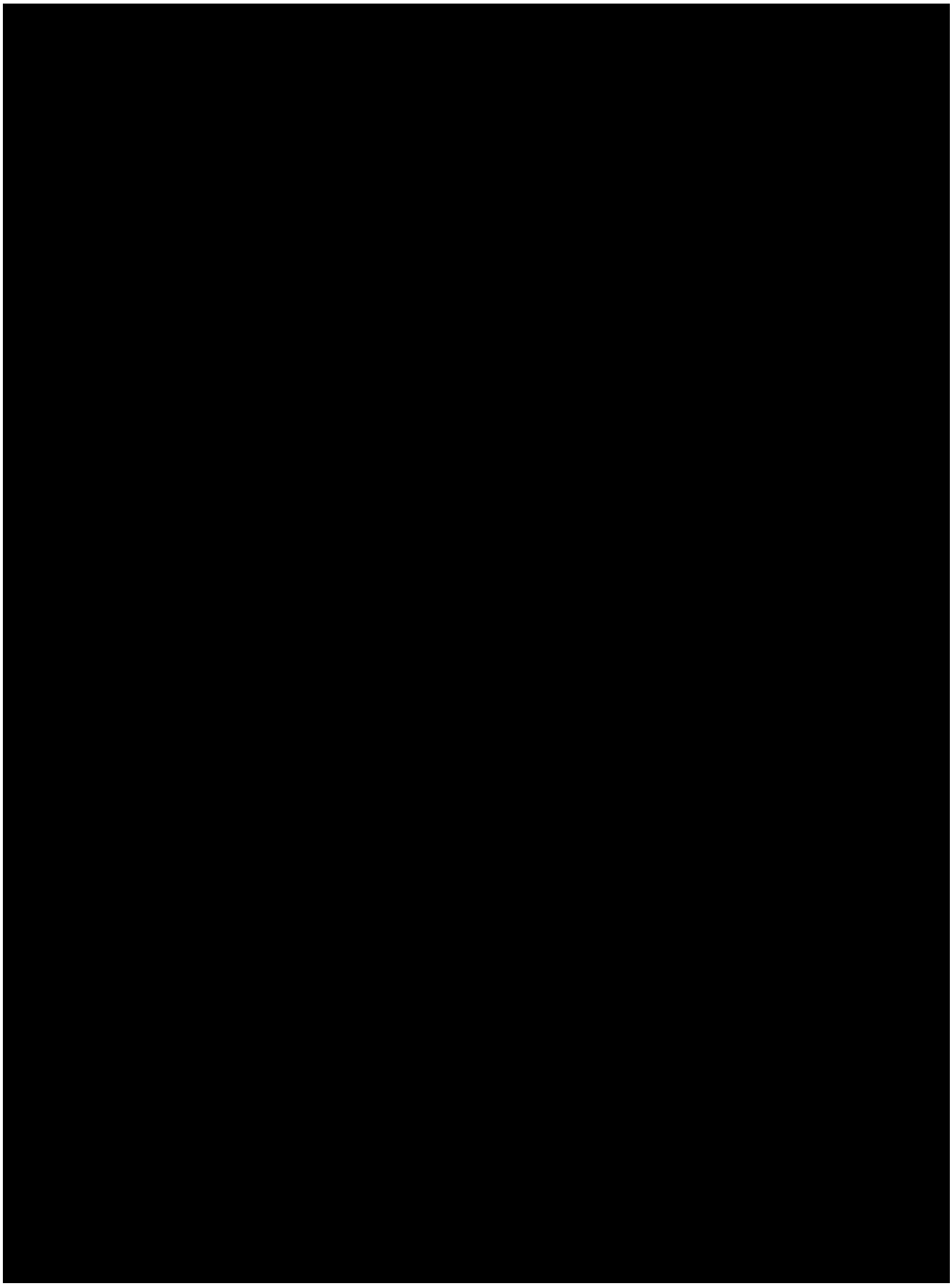
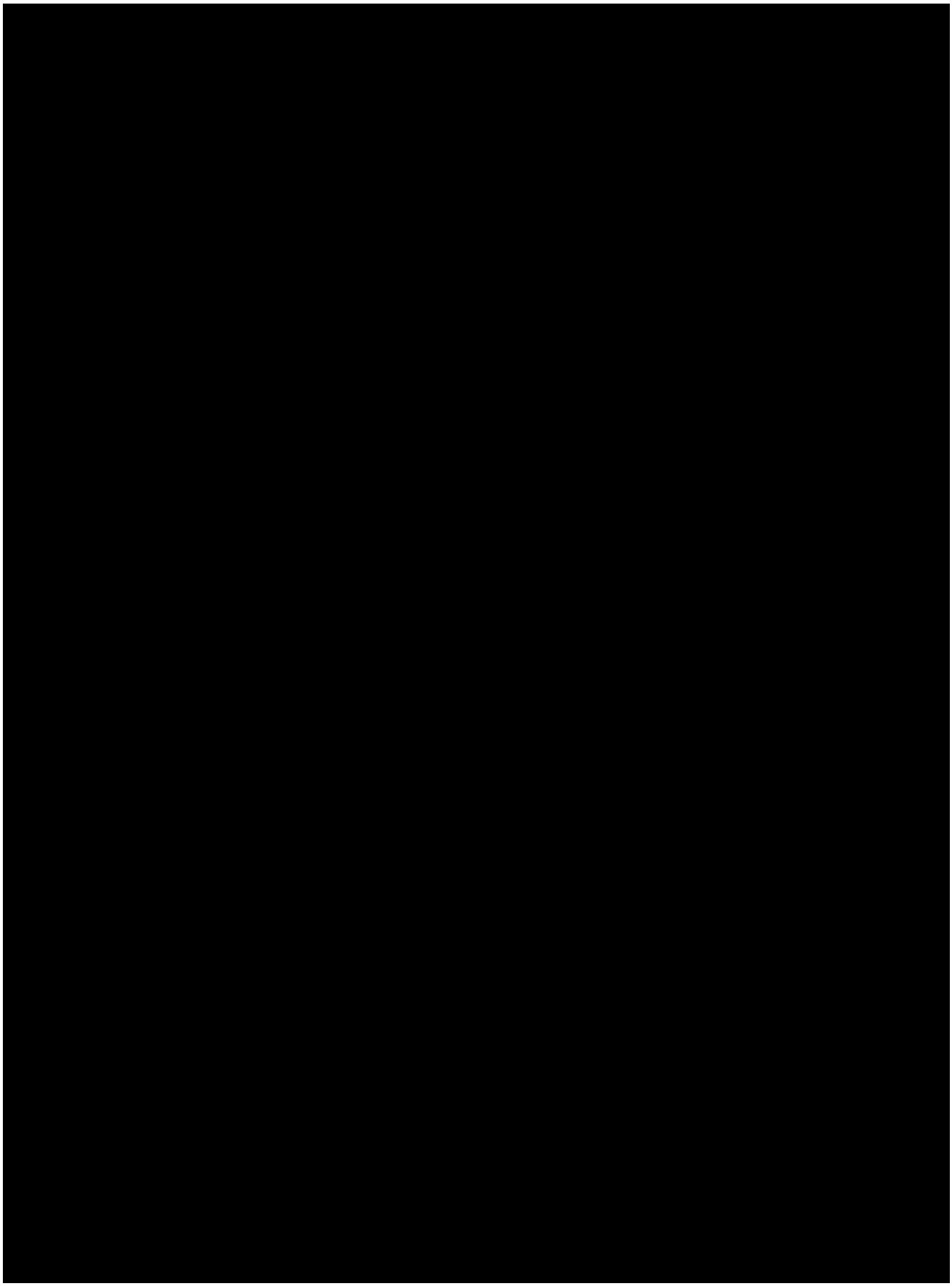
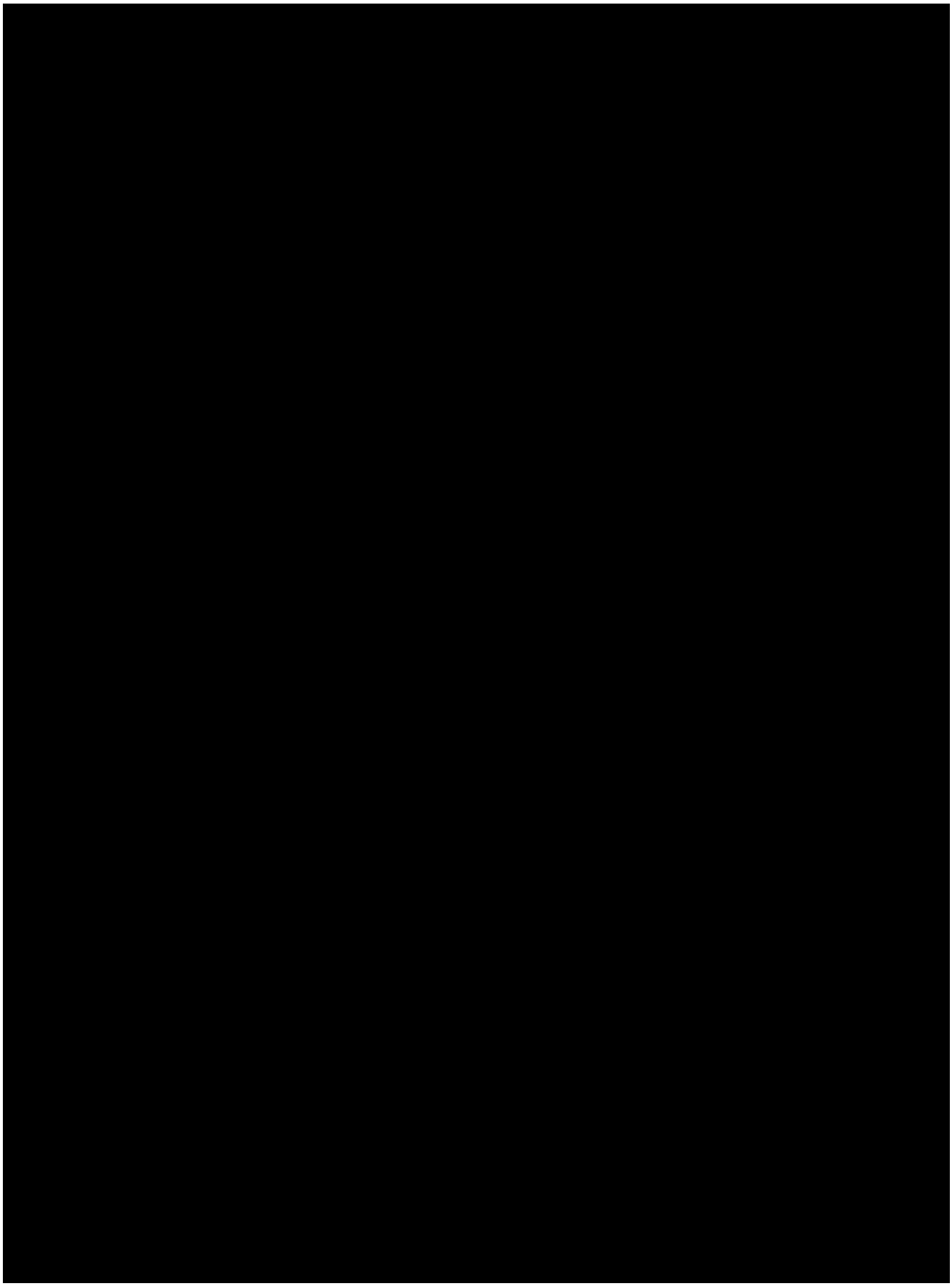


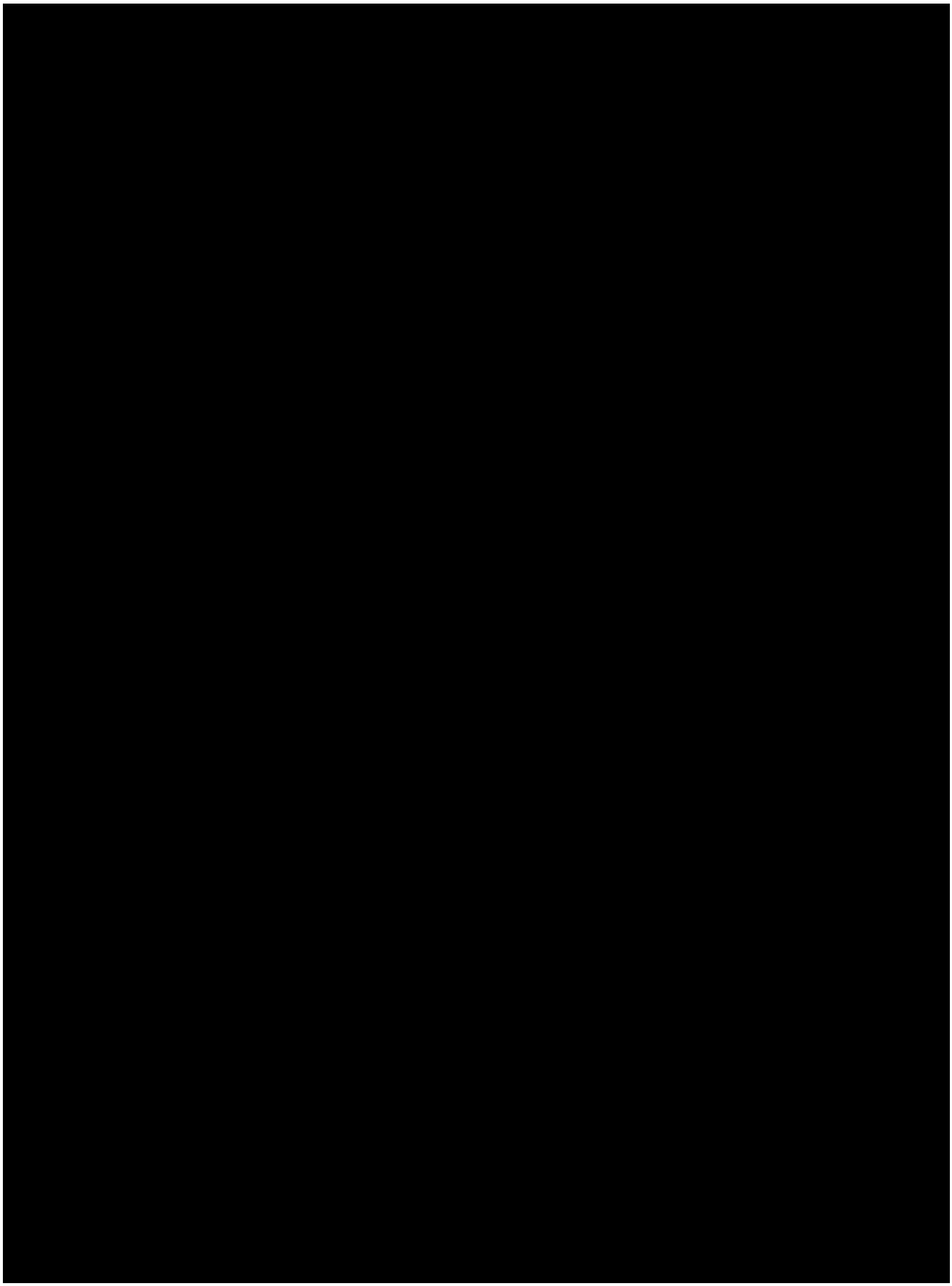


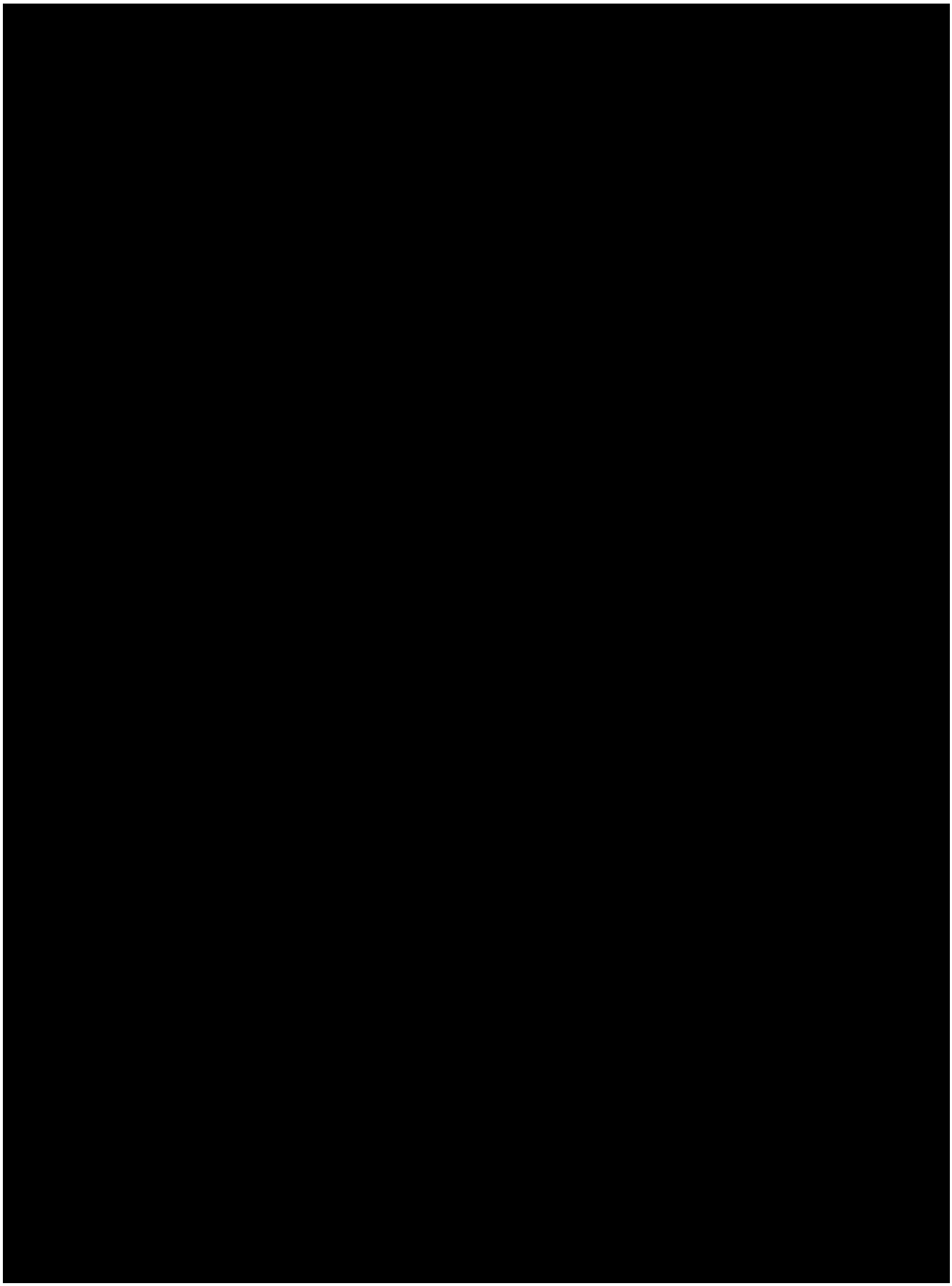








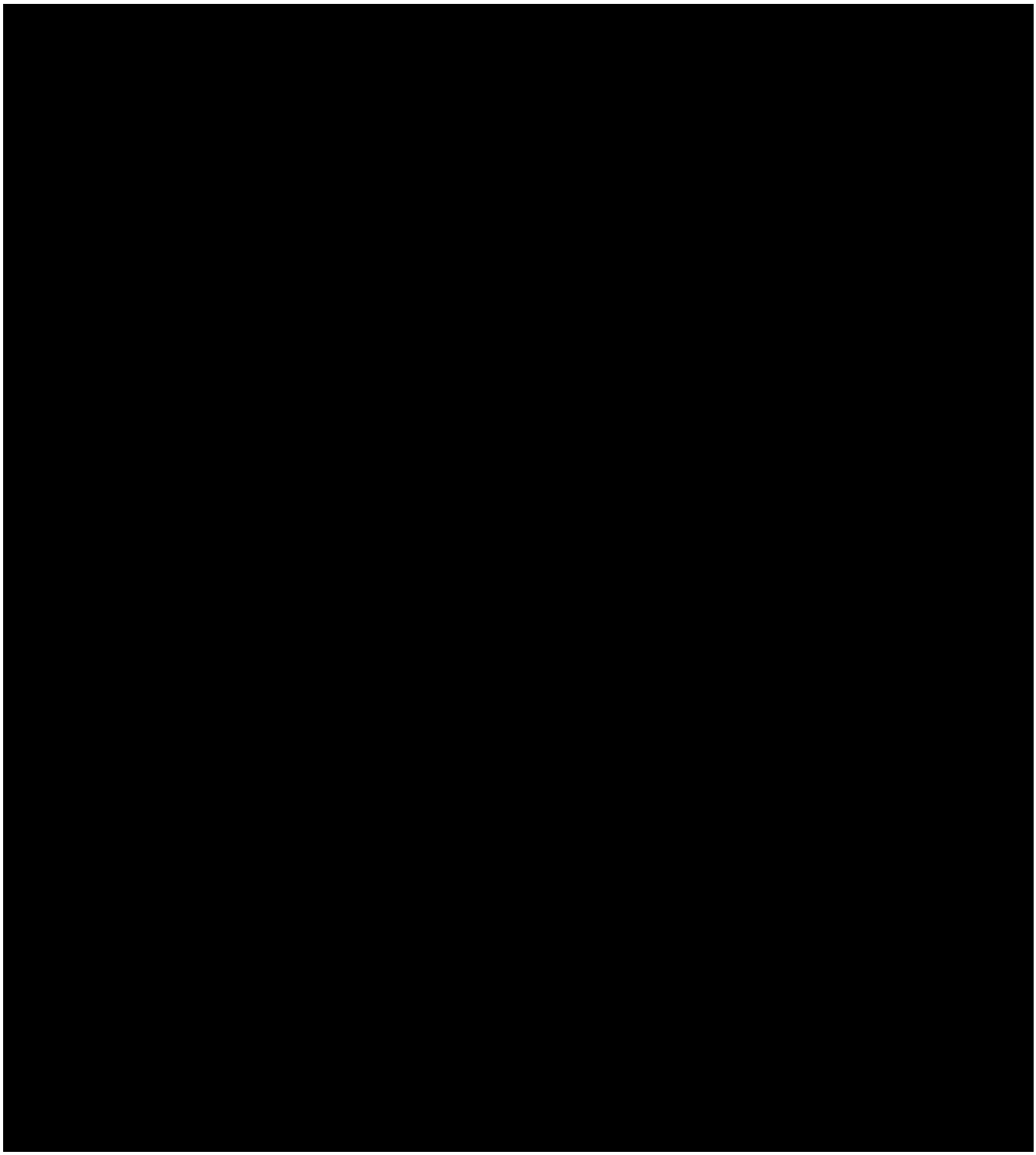


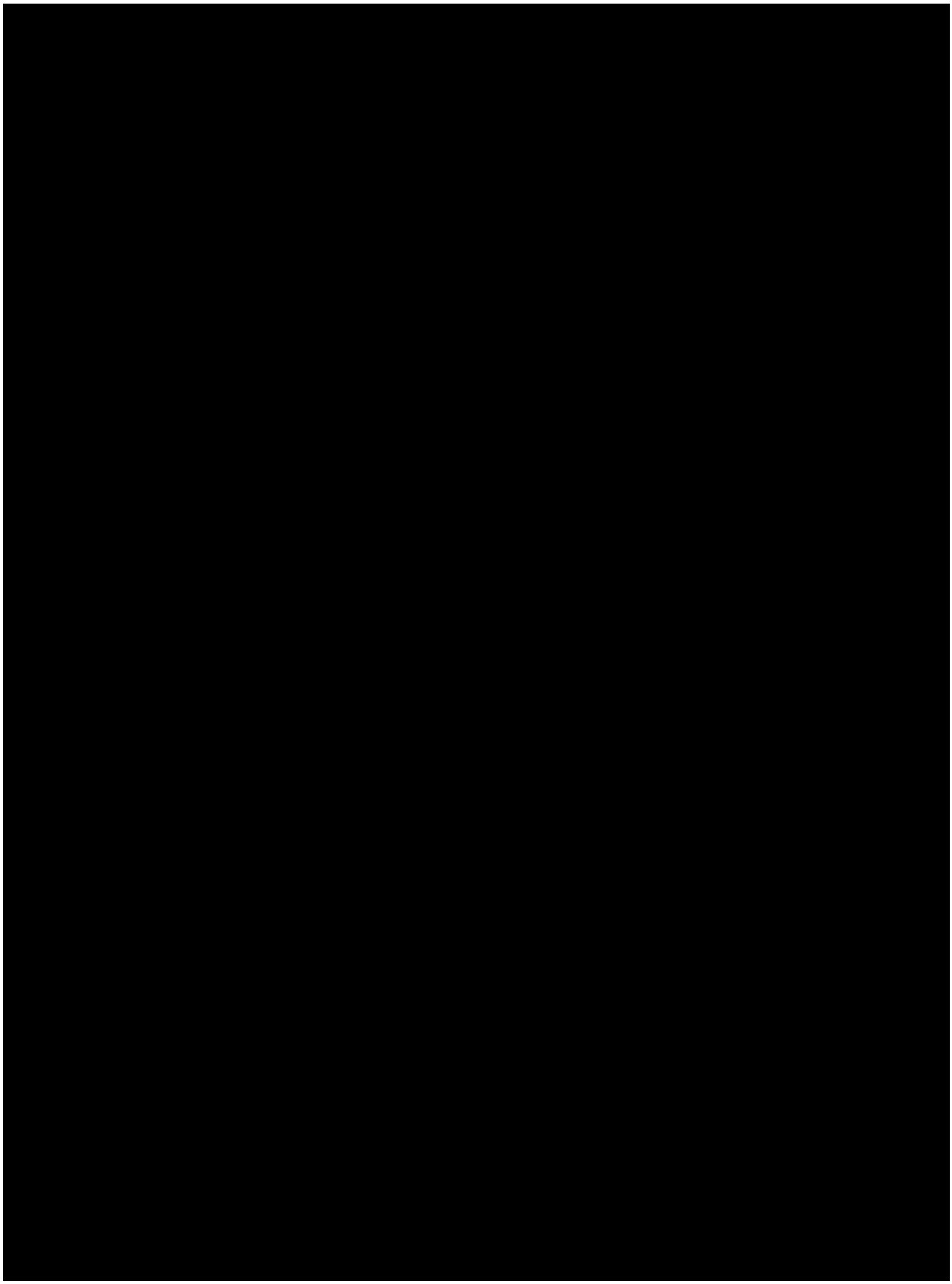


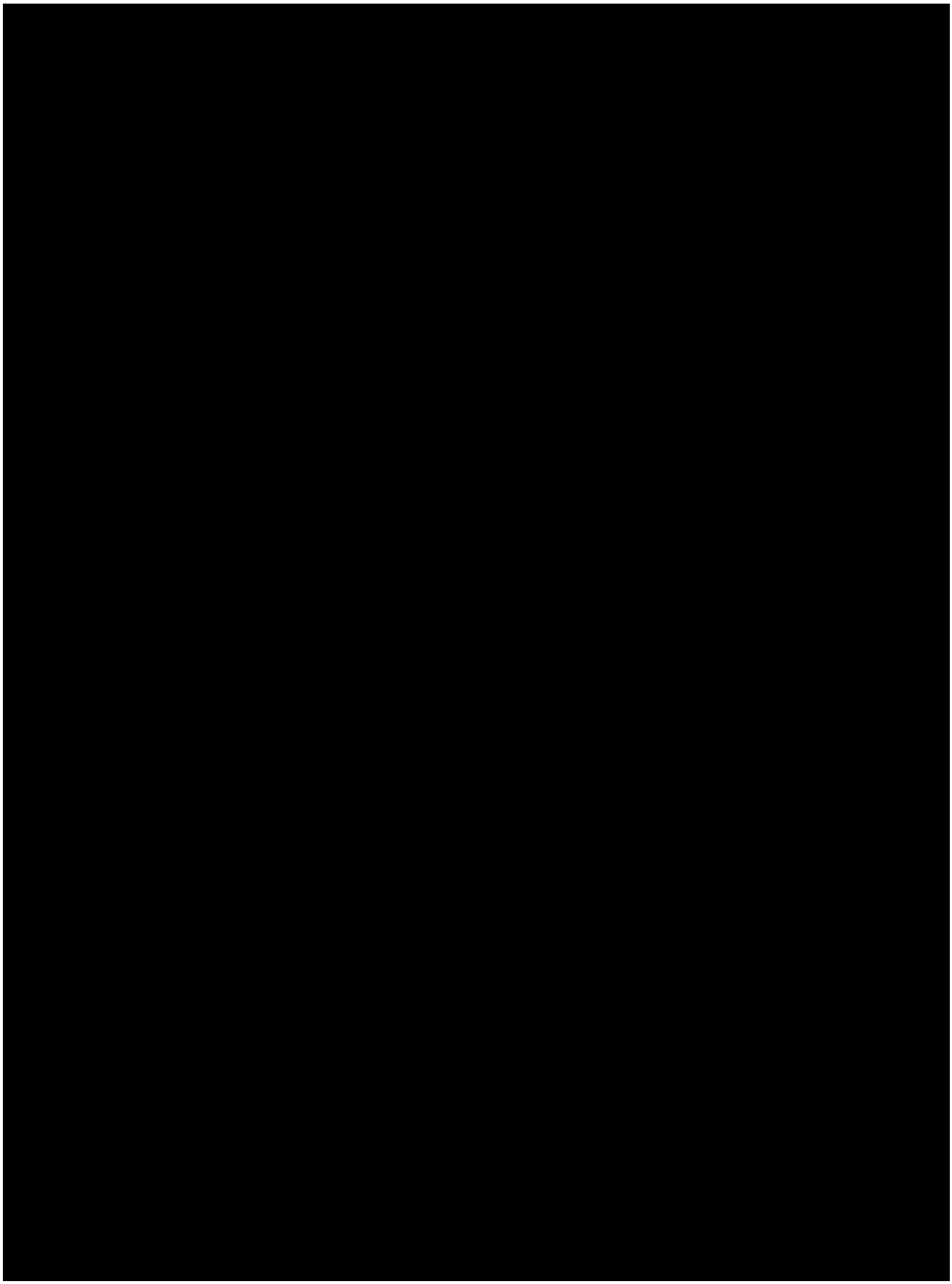
Appendix 4 Carer Questionnaire

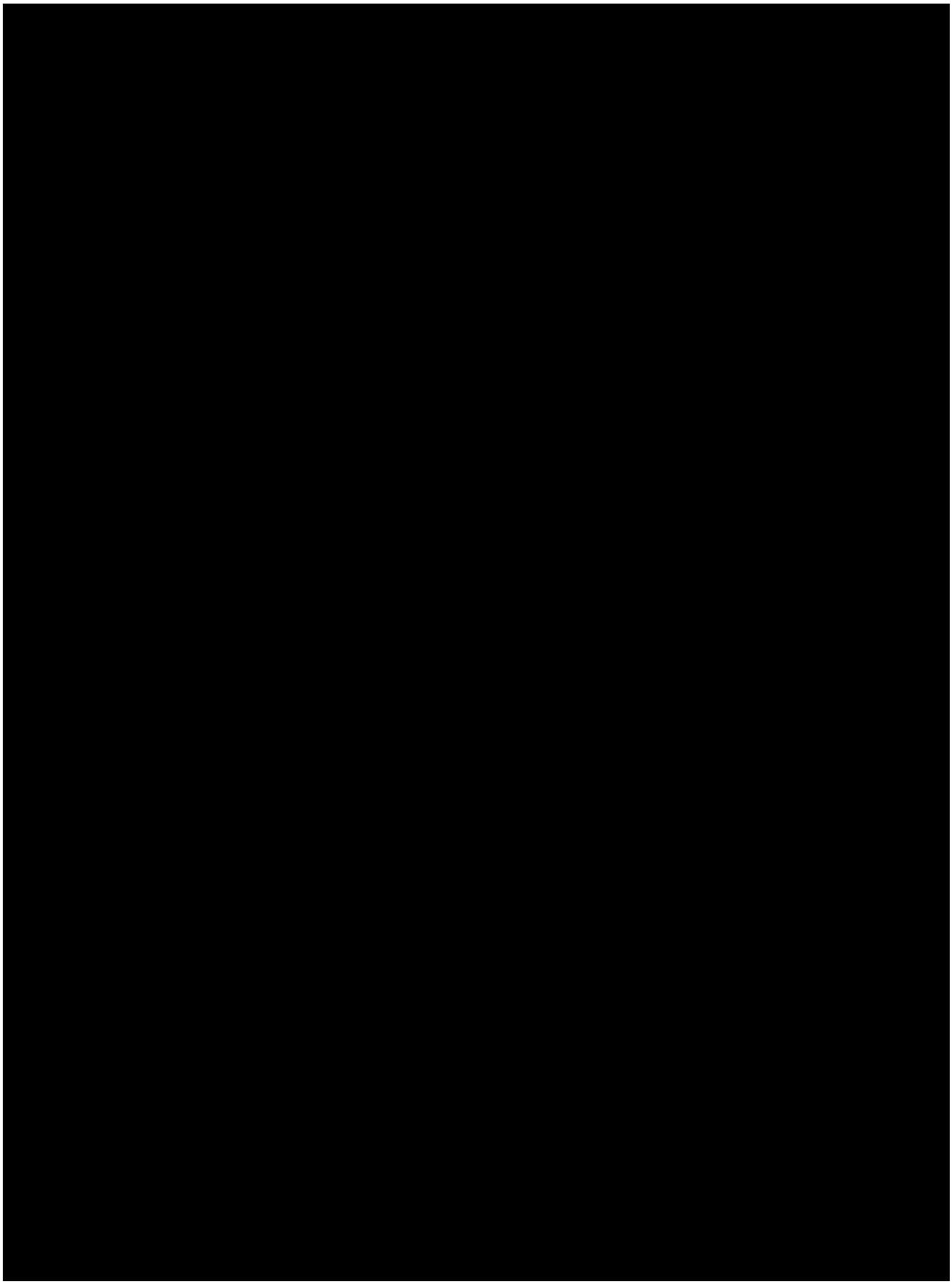
Evaluation of the effectiveness of additional risk minimisation measures for Hemlibra in the European Union

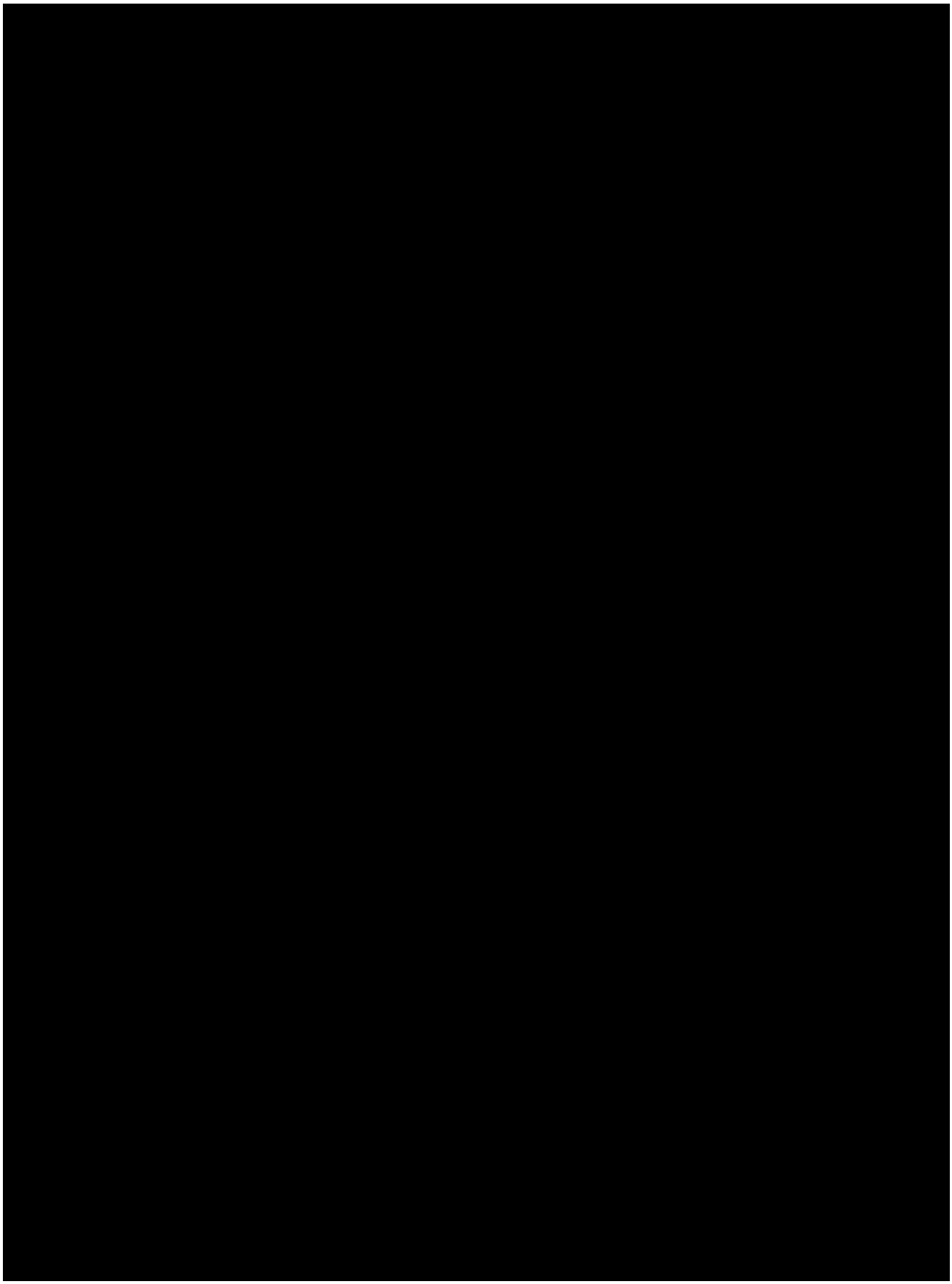
Carer Questionnaire











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