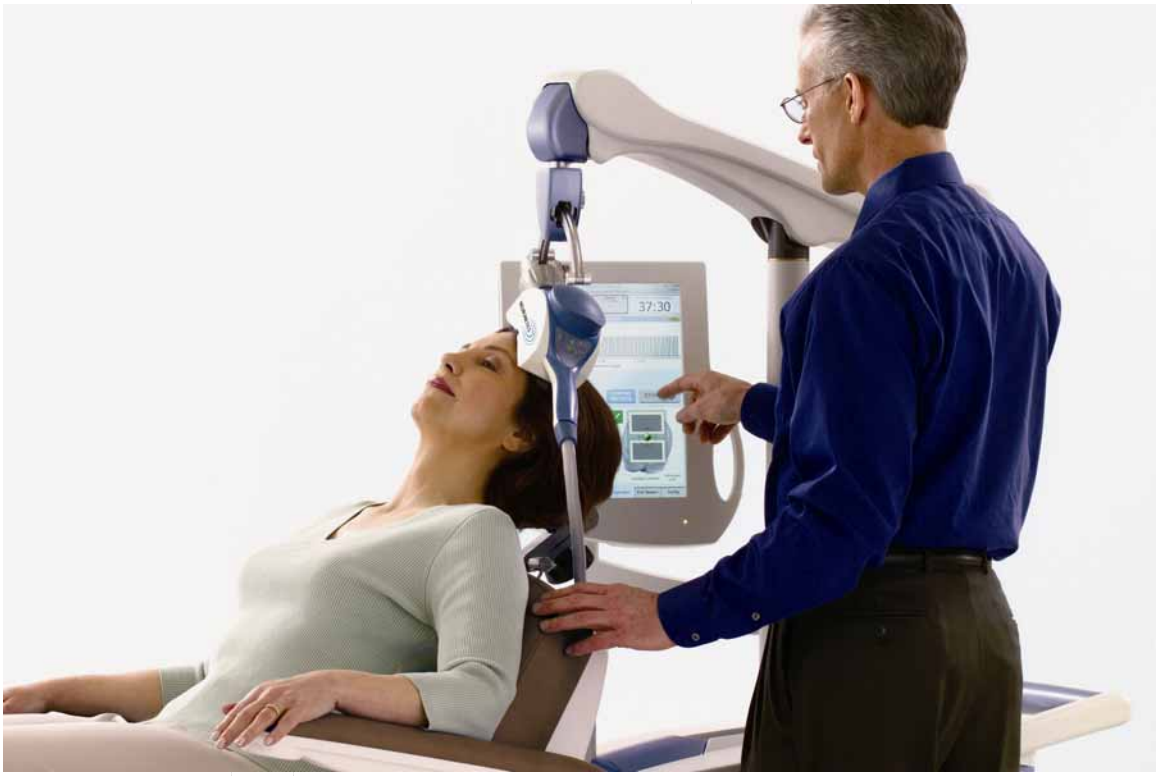
Neuronetics NeuroStar TMS System™ User Manual



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CONFIDENTIAL

Preface

This manual provides operating instructions and guidelines for the use of the Neuronetics® NeuroStar TMS System.

> Federal (U.S.A.) law restricts this device to sale by or on the order of a physician.

User Requirements and Training

The Neuronetics NeuroStar TMS System is used by prescription only under the supervision of a physician. The instructions in this manual assume that the user has been trained in the proper use of the Neuronetics® NeuroStar TMS System and that he or she has the required medical education and experience to operate the device safely and effectively. If you need training, please contact Neuronetics.

Intended Use and Indication

The NeuroStar TMS System is indicated for the treatment of major depressive disorder.

Patent and Trademark Information

Equipment and software that comprise the NeuroStar TMS System are covered by the following U.S patents: 6,255,815, 6,161,757, 5,725,471, 6,132,361, 6,086,525, 6,425,852, 6,491,620, with other patents pending.

Neuronetics® and MT Assist® are registered trademarks of Neuronetics, Inc.

Contact Information

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Alternatively, you can send your questions to the following E-mail address: techsupport@neuronetics.com.

The Neuronetics Web site address is http://www.neuronetics.com

To purchase supplies, accessories, or additional NeuroStar TMS Systems, call Neuronetics at 610-640-4202.

How to Use This Manual

- SECTION 1, INTRODUCTION, contains cautions, warnings, and important clinical information for all users. It also provides a high-level description of the NeuroStar TMS System itself. ***All users need to read and be familiar with this section***.
- SECTION 2, NEUROSTAR TMS SYSTEM CONTROLS, describes and illustrates the NeuroStar TMS System parts with which you will have regular interaction. The terms and part names in this section are used in describing the procedures in Section 3 and Section 4. ***All users need to read and be familiar with this section.***
- SECTION 3, DAILY TREATMENT ROOM PREPARATION, lists the steps to ensure that the NeuroStar TMS System is ready to provide treatment and that you have the required supplies on hand. ***All users need to read and be familiar with this section.***
- SECTION 4, CLINICIAN'S INSTRUCTIONS, provides detailed step-by-step instructions for using the NeuroStar TMS System to treat patients. It covers patient screening, treatment planning, patient positioning, motor threshold location, motor threshold level determination, and treatment steps. ***All users need to read and be familiar with this section***.
- SECTION 5, SYSTEM ADMINISTRATOR INSTRUCTIONS, provides step-by-step instructions for managing the system data. It also includes a technical explanation of the system's operating principles. ***Only system administrators and technical personnel will need to use this section.***
- SECTION 6, SYSTEM MAINTENANCE INSTRUCTIONS, provides instructions for maintaining the system, including basic maintenance, diagnostics and troubleshooting.
- SECTION 7, USING PDMS, provides step-by-step instructions for operating the Practice Data Management System.
- APPENDICES contain supplemental information that is useful in operating the system.

Table of Contents

1. Introduction

The NeuroStar TMS System (see Figure 1-1) is a computerized electromechanical instrument that produces and delivers brief duration rapidly alternating, or pulsed, magnetic fields to induce electrical currents directed at localized regions of the cortex.

Figure 1-1. Neuronetics NeuroStar TMS System

The NeuroStar TMS System is a non-invasive tool for the stimulation of cortical neurons and is intended for the treatment of major depressive disorder (MDD).

The NeuroStar TMS System is used for patient treatment by prescription only and must be operated by a licensed medical professional. It can be used in both inpatient and outpatient settings including physician's offices and clinics, psychiatric hospitals, and general medical/surgical hospitals with psychiatric units.

The NeuroStar TMS System is offered in the following configurations:

- Mobile Console standalone configuration (Mobile Console, therapy coil, head support unit, and treatment chair)
- Mobile Console standalone configuration with Practice Data Management System (PDMS)
- Multiple Mobile Consoles/PDMS configuration to address the needs of facilities with large patient populations.

1.1. Technical Overview

The mechanism by which the NeuroStar TMS System has its intended effect derives fundamentally from Faraday's Law, which asserts that a time-varying magnetic field produces an electrical current in an adjacent conductive substance. In transcranial magnetic stimulation, the conductive substance is the brain, in particular the region of the cortex that lies beneath the NeuroStar TMS System coil.

The electric current induced in this region of the cortex travels in a path orthogonal to the direction of the alternating magnetic field with the point of maximum field strength and greatest current located directly beneath the center of the coil. The induced current is tangential to the scalp at the cortical surface, and diminishes in magnitude with increasing depth. In the targeted area of the motor cortex, where field strength achieves the stimulation threshold, neuronal depolarization occurs. The peak magnetic field strength achieved with each pulse in the cortex is approximately 0.5 Tesla.

Activation of adjacent cortical neurons occurs predominantly by trans-synaptic pathways. Human functional neuroimaging studies have shown that indirect change in brain functional activity also occurs at cortical sites distant from the direct area of magnetic stimulation presumably due to the known extensive neural circuits among cortical brain regions.

The resulting neuronal depolarization and changes in brain functional activity achieved with TMS are associated with various physiological changes in the brain that are associated with symptomatic relief of depression.

Treatment should not exceed the recommended stimulation parameters as listed in Appendix A – 1998 NINDS Consensus Guidelines.

1.2 Indications

The Neuronetics NeuroStar TMS System is indicated for the treatment of major depressive disorder (MDD).

The efficacy of the NeuroStar TMS System for MDD was established in a nine-week randomized, sham-controlled clinical trial in outpatients who met DSM-IV diagnostic criteria for MDD.

A major depressive episode as defined in the DSM-IV implies a prominent and relatively persistent (nearly every day for at least two weeks) depressed or dysphoric mood that represents a change from previous functioning, and includes at least five of the following nine symptoms, one of which is either of the first two symptoms:

- Depressed mood
- Markedly diminished interest or pleasure in usual activities
- Significant change in weight and/or appetite

- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Increased fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Slowed thinking or impaired concentration
- Recurrent thoughts of death or suicidal ideation or a suicide attempt.

The maintenance of an acute clinical response to the NeuroStar TMS System in patients with MDD was demonstrated in a 24-week uncontrolled clinical trial.

For a description of the clinical trials and their results, see Appendix B.

1.3 Contra-indications	When used as directed, the NeuroStar TMS System is safe and effective. Treatment with the NeuroStar TMS System of areas of the human body other than the patient's cranium (head and scalp) is contraindicated. The NeuroStar TMS System is contraindicated for use for some patients, as identified in the sections below. These patients should not be treated with the system or will need to take special precautions before treatment with the NeuroStar TMS System. To ensure safe treatment, all patients must be screened for contraindications.

Implanted Electronic Devices and/or Conductive Objects	The NeuroStar™ TMS System treatment coil produces very strong pulsed magnetic fields which can affect certain implanted devices or objects. The magnetic field strength diminishes quickly with increasing distance from the coil. At ~30cm from the face of the treatment coil, the peak magnetic field is less than 5 Gauss which is the recommended static magnetic field exclusion level for many electronic devices. Metallic Objects in or near the Head The NeuroStar TMS System is ***contraindicated*** for use for patients having conductive, ferromagnetic, or other magnetic-sensitive metals in the head or within 30cm of the treatment coil. Failure to follow this restriction could result in serious injury or death. Implants Controlled by Physiological Signals The NeuroStar TMS System is ***contraindicated*** for use for patients who have an implanted device that is activated or controlled in any way by physiologic signals, even if the device is located outside the 30cm distance. This includes pacemakers, implantable cardioverter defibrillators (ICD's) and vagus nerve stimulators (VNS). The device is also contraindicated for patients using wearable cardioverter defibrillators (WCD) , even if the device is removed, due to the potentially unstable cardiac condition of such patients. Failure to follow this restriction could result in serious injury or death. Implants Not Controlled by Physiological Signals Patients may have other implanted devices or metallic objects located in areas outside the 30cm distance from the coil during TMS Therapy if such devices are not controlled by physiologic signals. Examples include: sutures and implanted insulin pumps. However, great care must be taken by the NeuroStar TMS System operator to ensure that the treatment coil is never placed within 30cm of these implants, otherwise serious injury could result. Wearable or Removable Devices If patients have removable devices or objects that may be affected by the magnetic field, the device(s) should be removed from the patient area before treatment (e.g. earrings, hearing aids, eyeglasses, cell phones, MP3 players, etc.) to prevent possible injury or damage to the device. This also includes wearable monitors and bone growth stimulators. Metallic Object and Implant Checklist Prior to treatment, each patient should be checked against the items listed in Table 1-1, which summarizes compatibility requirements for devices and conductive objects in the vicinity of

	the NeuroStar™ TMS System treatment coil. This list is for guidance in screening a patient for magnetic field compatibility; it is non-inclusive, so prudent judgment must be applied for cases not listed including contacting the device manufacturer if compatibility is uncertain. The items in Table 1-1 MUST be reviewed for each patient prior to treatment with the NeuroStar™ TMS System. The colors in the table have the following meanings: • Red indicates contraindication. • Yellow indicates that the treatment coil must be kept at a safe distance (i.e. >30cm) from the device or object. • Blue indicates devices that should be removed from the patient area.

Device or Object	Action Required by NeuroStar Operator Before Treatment			Possible Interaction with NeuroStar Magnetic Field			Potential Consequences of Operator Inaction
	TMS treatment is contraindicated	Keep treatment coil >30cm from device/object	Remove device from patient area	Device/Object becomes disabled	Device/Object may dislodge or move	Device/Object may overheat	
Magnetically activated dental implants	X			X			Patient injury
Aneurysm clips or coils	X				X		Serious patient injury or death
Cochlear, otologic implants	X			X		X	Patient injury
CSF Shunt	X				X	X	Patient injury
Ferromagnetic ocular implants	X				X	X	Patient injury
Pellets, bullets, fragments < 30cm from coil	X				X	X	Patient injury, irritation
Facial tattoos with metallic ink	X				X	X	Patient injury, irritation
EEG electrodes	X					X	Patient injury
DBS electrodes	X			X	X	X	Patient Injury or death
Metallic devices implanted in the head	X			X	X	X	Patient Injury or death
Cardiac Pacemakers, ICD's	X			X			Affected therapy; patient injury
Vagus Nerve Stimulator	X			X			Affected therapy; patient injury
Wearable cardioverter defibrillator (WCD)	X			X			Affected therapy; patient injury
Wearable infusion pumps		X		X			Affected therapy; patient injury
Implanted insulin pump		X		X			Affected therapy; patient injury
Stents, filters, heart valves		X			X	X	Patient Injury or death
Magnetically programmable shunt valves		X		X		X	Affected therapy; patient injury
Cervical fixation devices		X				X	Patient injury
Staples, sutures		X			X		Patient injury
Radioactive seeds		X				X	Affected therapy; patient injury
VeriChip microtransponder		X		X	X	X	Inconvenience
Wearable physiologic monitors (e.g. Holter)			X	X			Inconvenience
Bone growth stimulators			X	X			Inconvenience
Portable glucose monitors			X	X			Inconvenience
Hearing aids			X	X			Inconvenience
Eyeglasses			X	X			Inconvenience
Cell phones/PDA's			X	X			Inconvenience
Headphones/MP3 players			X	X			Inconvenience

Table 1-1. Partial List of Devices and Objects that may be affected by the NeuroStar™ Magnetic Field

1.4 Warnings	To ensure the safe operation of the NeuroStar TMS System, you must consider the following warnings before proceeding to treatment.

Risk of Seizure	No seizures have been reported with the use of the NeuroStar TMS System in over 6000 patient treatments. However, caution should be used when the NeuroStar TMS System is used in patients who have a history of, or potential alteration in seizure threshold. Be alert for signs of an imminent seizure and terminate the treatment session if those signs appear. If a seizure threshold altering medication was taken, the motor threshold determination should be repeated prior to the next treatment session. Patients with risk of seizure include those with: • History of seizure or epilepsy, • History of stroke, head injury, severe headaches, or unexplained seizures, • Presence of other neurologic disease that may be associated with an altered seizure threshold, or • Concurrent medication use as such as tricyclic antidepressants, neuroleptic agents or other drugs that lower the seizure threshold.

Worsening Depression or Suicidality	Patients with MDD may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are being treated with an antidepressant, and this risk may persist until significant remission of symptoms occurs. Patients undergoing treatment for MDD should be observed closely for clinical worsening and suicidality. If worsening of symptoms continues, consideration should be given to changing the therapeutic regimen, including possible discontinuation of treatment with the NeuroStar TMS System.

Effects on Medical Devices Containing Electronics or Ferromagnetic Material	The NeuroStar TMS System should be used only as directed and should not be placed on or near other body locations due to its possible effects on devices implanted or located in those areas and that may be affected by the magnetic field. Effects of the magnetic field may include the movement, heating, or dysfunction of objects and devices that contain ferromagnetic materials (see 1.3 Contraindications). ***The NeuroStar™ treatment coil must be kept more than 30cm from all electronic devices to prevent malfunction or damage to the device. Additionally, certain implanted electronic medical devices that process physiological signals, such as pacemakers, may be more sensitive to the TMS magnetic field and could malfunction resulting in patient injury or death. Patients, physicians and others implanted with such devices should not be treated or in the vicinity of the NeuroStar™ treatment coil when it is pulsing.***

1.5 Clinical Precautions

This section lists information pertaining to the safe operation of the NeuroStar TMS System.

Treatment Parameters

In order to reduce the potential risk of seizure, observe the published 1998 National Institute of Neurological Disorders and Stroke (NINDS) Workshop report guidelines (Appendix A in this manual). Treatment outside of these guidelines is not recommended.

Hearing Protection

The patient must always wear earplugs or similar hearing protection devices with a rating of 30db of noise reduction when being treated with the NeuroStar TMS System. When used with appropriate hearing protection, the NeuroStar TMS System has had no demonstrated effect on hearing or auditory threshold. Hearing protection is also advised for the clinical operator if he or she is frequently located within 6 feet (2 meters) of the coil for an extended period during patient treatment.

Long-Term Effects

Treatment with the NeuroStar TMS System was safely tolerated in patients for periods up to 12 continuous weeks, and no negative effects of treatment were reported during a 24-week follow-up observation period. Experimental and observational evidence indicates that exposure to the magnetic fields produced by the NeuroStar TMS coil does not present any significant risk of causing acute or long-term adverse effects.

1.6 Procedure Warnings and Cautions

This section lists the warnings and precautions associated with the operation of the NeuroStar TMS system.

Risk of explosion. Do NOT use the NeuroStar TMS System in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide.

Risk of electrical shock. Do NOT use the NeuroStar TMS System in or near water or other liquids, or place liquids on or near the mobile console or any of the cables or coil.

Risk of electrical shock. Do NOT open the panels of the NeuroStar TMS System mobile console. There are no user-serviceable parts in the system. If the system malfunctions, call Neuronetics for assistance at (610) 640-4202.

Risk of electrical shock. Always turn the coil power switch to "STANDBY" before you attempt to remove or connect a coil cable to the mobile console.

Do NOT place the NeuroStar TMS System near other medical equipment during operation. Malfunction of the other equipment could result in injury or death.

Do NOT allow unsupervised children near an operating NeuroStar TMS System. Serious injury could result.

A 20-minute interval between patient treatment sessions is required to guarantee that the coil operates within temperature specifications. If the therapy coil becomes uncomfortably warm to the touch, immediately discontinue use of the stimulator. Failure to observe the 20-minute interval between treatment sessions could result in coil overheating and patient burns.

Discontinue treatment with the NeuroStar TMS System for any patient who has a continued significant adverse reaction or discomfort during or immediately after use. (Temporary mild discomfort at the site of stimulation is normal during and/or shortly after treatment.)

Operate the NeuroStar TMS System only with parts and components provided and/or recommended by Neuronetics, Inc. The performance of the NeuroStar TMS System cannot be guaranteed if other parts or components are used.

Do not place computer discs, audio recording tapes, credit cards, hotel room keys, or electronic automotive ignition keys on or near

the coil while operating. The NeuroStar TMS System produces time varying magnetic fields that may affect the integrity of data stored on these types of magnetic media if placed near an operating coil.

Do not use the NeuroStar TMS System on patients who cannot communicate levels of comfort or discomfort with the selected treatment settings.

Operation of the NeuroStar TMS System requires special precautions regarding electromagnetic compatibility (EMC) and needs to be installed and put into service according to the following EMC information:

- Portable and mobile radio frequency communications equipment can affect the operation of the NeuroStar TMS System.
- Use of a power cord other than the one provided with may result in increased emissions or decreased EMC immunity of the NeuroStar TMS System.
- Do not use the NeuroStar TMS System adjacent to or stacked with other equipment. If adjacent or stacked use is necessary, you must observe the NeuroStar TMS System to verify that it is operating normally.

For more information on the NeuroStar TMS System's electromagnetic compatibility, see Appendix F.

1.7 Emergency Procedures

If you should encounter a patient emergency situation that requires immediate cessation of treatment, take the following steps immediately:

1. Stop the treatment.
2. Press the brake release button on the coil and pull the coil away from the patient.
3. Manage the patient's condition and/or call for help.

In the event of an emergency building evacuation during a treatment session, press the PAUSE button on the screen then press the brake release button on the coil and move the coil away from the patient. Assist the patient in getting up from the treatment chair.

1.8 Special Patient Populations

- The safety of TMS during pregnancy has not been established. Therefore, women of childbearing age should be questioned regarding the possibility of pregnancy prior to receiving treatment.
- The safety of the use of the NeuroStar TMS System in anyone younger than 18 years of age or older than 70 years of age has not been established.

1.9 Adverse Experiences

There were no deaths or seizures reported in Neuronetics studies 44-01101, 44-01102, or 44-01103.

The most frequently reported events were headache and application site pain. Headache was equally represented in both active and sham TMS groups. Application site pain was more frequently represented in the active TMS group. Both headache and application site pain lessened with time over the TMS treatment course.

Additional Clinical Safety Testing: Cognitive Function and Auditory Threshold

There was no evidence of clinically significant cognitive function testing change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics NeuroStar TMS System

There was no evidence of clinically significant auditory threshold change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics NeuroStar TMS System (with use of earplugs during TMS treatment).

The following table presents a summary of MedDRA preferred term adverse events occurring with an incidence on active TMS of $\geq$ 2% and greater than the incidence on sham TMS.

Body System Preferred Term	Sham (N=158) N (%)	Active (N=165) N (%)
Ear and labyrinth disorders		
- Ear pain	1 (0.6)	4 (2.4)
- Tinnitus	2 (1.3)	7 (4.2)
Eye disorders		
- Eye pain	3 (1.9)	10 (6.1)
- Lacrimation increased	1 (0.6)	7 (4.2)
- Visual disturbance	2 (1.3)	4 (2.4)
Gastrointestinal disorders		
- Diarrhea	6 (3.8)	8 (4.8)
- Nausea	10 (6.3)	17 (10.3)

Body System Preferred Term	Sham (N=158) N (%)	Active (N=165) N (%)
- Toothache	1 (0.6)	12 (7.3)
- Vomiting	3 (1.9)	7 (4.2)
General disorders and site administration conditions		
- Application site discomfort	2 (1.3)	18 (10.9)
- Application site pain	6 (3.8)	59 (35.8)
- Facial pain	5 (3.2)	11 (6.7)
- Pain	3 (1.9)	7 (4.2)
- Pyrexia	1 (0.6)	4 (2.4)
Injury, poisoning and procedural complications		
- - Overdose (Extra pulses due to procedural error)	0	4 (2.4)
Musculoskeletal and connective tissue disorders		
- Arthralgia	5 (3.2)	10 (6.1)
- Muscle twitching	5 (3.2)	34 (20.6)
- Musculoskeletal stiffness	4 (2.5)	5 (3.0)
- Neck pain	4 (2.5)	8 (4.8)
Nervous system disorders		
- Dyskinesia	2 (1.3)	5 (3.0)
- Headache	87 (55.1)	96 (58.2)
- Hypoaesthesia	2 (1.3)	5 (3.0)
- Paraesthesia	4 (2.5)	6 (3.6)
- Tension headache	2 (1.3)	4 (2.4)
Psychiatric disorders		
- Agitation	3 (1.9)	4 (2.4)
- Anxiety	18 (11.4)	19 (11.5)
Reproductive system and breast disorders		
- Dysmenorrhoea	2 (1.3)	5 (3.0)
Respiratory, thoracic and mediastinal disorders		

Body System Preferred Term	Sham (N=158) N (%)	Active (N=165) N (%)
- Cough	2 (1.3)	4 (2.4)
- Dyspnoea	1 (0.6)	6 (3.6)
Skin and subcutaneous tissue disorders		
- Pain of skin	1 (0.6)	14 (8.5)

1.10 Minimal Operator Training

The NeuroStar TMS System is used by prescription only under the supervision of a licensed physician. The system can only be operated by licensed medical professionals who have medical training and who assist as part of the staff and who are operating under the direction of a physician. The user of the NeuroStar TMS System must be trained on its operation, and must have knowledge of the operational environment.

NeuroStar TMS System operators must complete Neuronetics-provided training before using the system.

1.11 General System Description

The NeuroStar TMS System consists of the following major components.

Equipment and Software

- Mobile Console (includes processor module, power module, mast, gantry, halo, and display arm)
- System Software 1.0
- Therapy coil
- Head Support Unit (includes coil positioning guide)
- Treatment Chair
- Cushion Set (to enhance the comfort and positioning of the patient in the required posture for the duration of the treatment session)

Options

- Practice Data Management System (PDMS) 1.0
- PDMS Package (includes PDMS 1.0, a configured computer, and the wireless interface)
- Positioning pad set

Supplies (for each treatment session)

- Head cushion liner
- Head side pad liner
- Earplugs
- SenStar™

1.12 Connection to Other Equipment

Additional equipment connected to medical electrical equipment must comply with the respective IEC or ISO standards (e.g. IEC 60950 for data processing equipment). Furthermore, all configurations shall comply with the requirements for medical electrical systems (IEC 60601-1-1 or clause 16 of the 3Ed. of IEC 60601-1, respectively). Anybody connecting additional equipment to medical electrical equipment configures a medical system and is therefore responsible that the system complies with the requirements for medical electrical systems. Local laws may take priority over the above mentioned requirements. If in doubt, consult your local representative or the technical service department.

1.13 HIPAA Compliance

The NeuroStar TMS System fully complies with Federal HIPAA regulations. Patient data is securely stored. Access to the system is controlled by user name/password combinations. Passwords entry is unreadable on the display screen. Patient identification information is kept confidential and is accessible only to authorized system users. The system maintains patient records through unique identifiers.

The optional PDMS operates on a separate system, and the data that is transferred is protected by a wireless encryption program to protect the confidentiality of patient data.

2. NeuroStar TMS System Controls

This section provides a guide to the individual NeuroStar TMS System components and controls and explains the basic terminology used in this manual.

2.1 NeuroStar TMS System Overview

The NeuroStar TMS System consists of a combination of hardware, software, and consumable supplies. It is delivered in either a basic configuration or with optional features. Operation of the system requires the use of disposable supplies.

Major hardware components are illustrated in Figure 2-1.

2.2 Standard Configuration

The basic configuration includes the following components:

- **Mobile Console** – An enclosed module that forms NeuroStar TMS System's wheeled base and integrates various subsystems into a single package. It houses or supports the processor module, the power module, the gantry, the display arm, the mast, and the display.
- **System Software 1.0** – A proprietary application that provides the NeuroStar TMS System graphical user interface (GUI) and incorporates work flow management to guide the system user through a TMS procedure, and also supervises and controls various subsystems.
- **Coil** – An enclosed electromagnet that is mounted to the coil gantry which supports its weight as it is placed against the patient's head. The coil generates and applies a pulsed magnetic field to tissue immediately beneath the coil in response to commands from the processor and power modules.
- **Treatment Chair –** An operator controlled, adjustable chair that positions the patient comfortably at a desirable height and angle for TMS treatment and provides lumbar support. It includes a separate attachment for the chair that provides adjustable head support and includes a guidance apparatus to aid in positioning the coil on the patient's head.
- **Head Support Unit –** An electro-mechanical device that consists of several parts that are designed to provide maximum patient comfort and reliable coil position measurement of the patient's MT location and TMS treatment location.

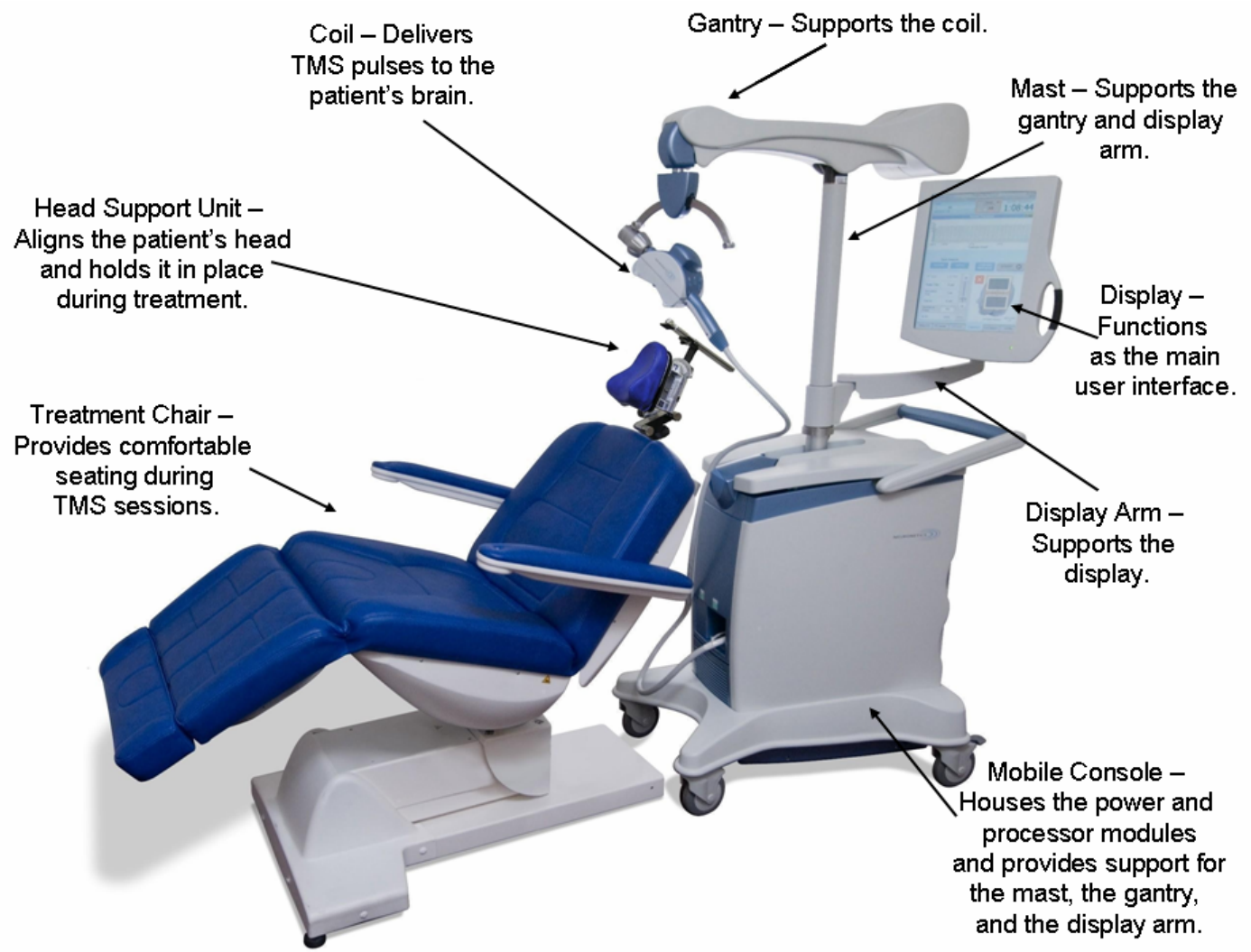


Figure 2-1. . NeuroStar TMS System Main Hardware Component

Mobile Console

The Mobile Console is the central workstation for a TMS procedure using the NeuroStar TMS System and is the main control center for all NeuroStar TMS System subsystems. The Mobile Console houses the Power Module, the Processor Module, the Gantry Assembly, Mast, and the Display Arm Assembly. The Mobile Console has an enclosed frame with rear doors for service. This unit provides interfaces for input power, coil power, and networking. Containment in this enclosure keeps these connections out of the reach of the user and out of the patient's view.

As illustrated in Figure 2-2, the Mobile Console is mounted on medical grade locking wheels with sufficient radius to clear elevator thresholds and other small irregularities in floor surfaces. It also has a handle that the user grips when positioning for treatment or moving it to a new location. The rear of the mobile console includes a drawer for storage.

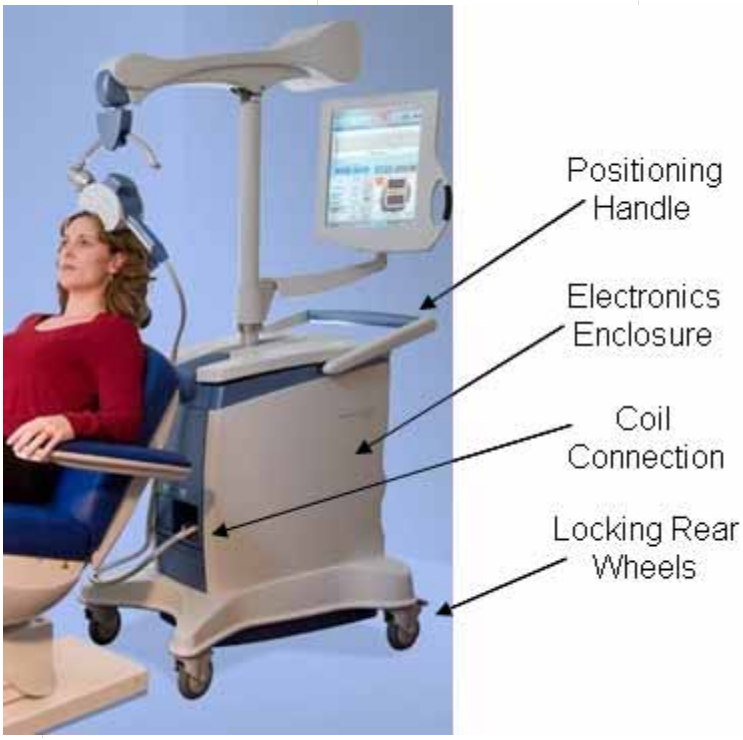


Figure 2-2. NeuroStar TMS System Mobile Console (Side View)

Display

As illustrated in Figure 2-3, the display has touch-activated images of alphanumeric keys and buttons for user interaction with the system, and displays graphic representations of system activity, messages, and alarms.

Figure 2-3. Display with Touch Screen

The display is capable of presenting graphics, text displays, and touch controls and provides graphics system resolution of 1024 x 768 with a 15” display. It is readable from 10 feet away in ambient light up to 6,000 foot candles.

The position of the display is adjustable for comfortable viewing by the user during various stages of the workflow. It swings both sides to accommodate both left and right side patient treatments (right side use is for research use only). The display’s mounting is rigid enough such that during normal touch screen operation, the display does not move.

The display has a viewing angle of at least 150° from side to side. It has two degrees of freedom:

- Rotation around the vertical axis (320°)
- Rotation about the horizontal axis (± 30° from vertical).

The display presents graphical user interface screens as described in Section 4 of this user manual.

The green LED on the lower corner of the display indicates that the display is getting power. If you shut down the system, as described in Section 4.4 of this manual, but leave the power switch in the ON position, the green LED will flash on and off at three second intervals until the power switch is moved to the OFF position.

Gantry

The gantry consists of a lateral translation table within the Mobile Console, a vertical mast, a balance arm, and a halo assembly that connects to the coil as shown in Figure 2-4.

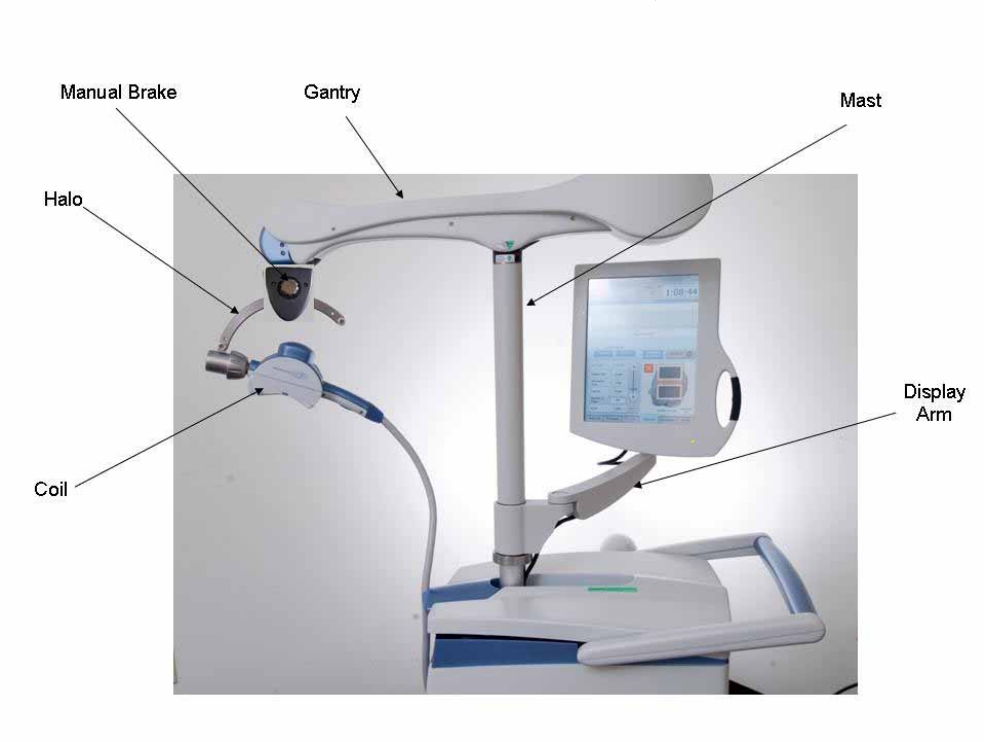


Figure 2-4. Gantry: Showing the Coil, Halo, Mast, Display Arm

The gantry supports the weight of the coil and allows free movement for easy placement on the patient's head. It incorporates electro-mechanical brakes that automatically lock four degrees of motion when the push-button switch on the coil is released, or when commanded under software control. The brakes are designed to lock upon loss of power or when the Mobile Console is not powered.

There are three degrees of freedom in the mechanism that immediately connects to the coil (the "wrist") of the support arm. There is a manual brake to stop motion of the halo ring and a manual brake to adjust coil axial rotation resistance. To facilitate exchanging the coil for service or for research applications (e.g., swapping active and sham coils), the user can mechanically disconnect the coil from

the halo using the release pin in the Halo Clamp Housing. (See Section 5.4. in this manual.)

The display arm moves separately from the gantry along a horizontal plane, enabling the user to adjust the position of the display.

Coil

The coil generates a magnetic field that penetrates the skull and reaches the patient's cortex when the coil is placed against the patient's head. This pulsed field is controlled by the NeuroStar TMS System power module and system software in response to user settings.

During treatment, a single-use SenStar™ is attached to the face of the coil and provides the contact surface with the patient's head. The coil mechanically attaches to the halo, as illustrated in Figure 2-5. Coil buttons for brake release, pulsing, and MT level adjustment are located just above the coil handle. For convenience a second brake release button is located under the handle.

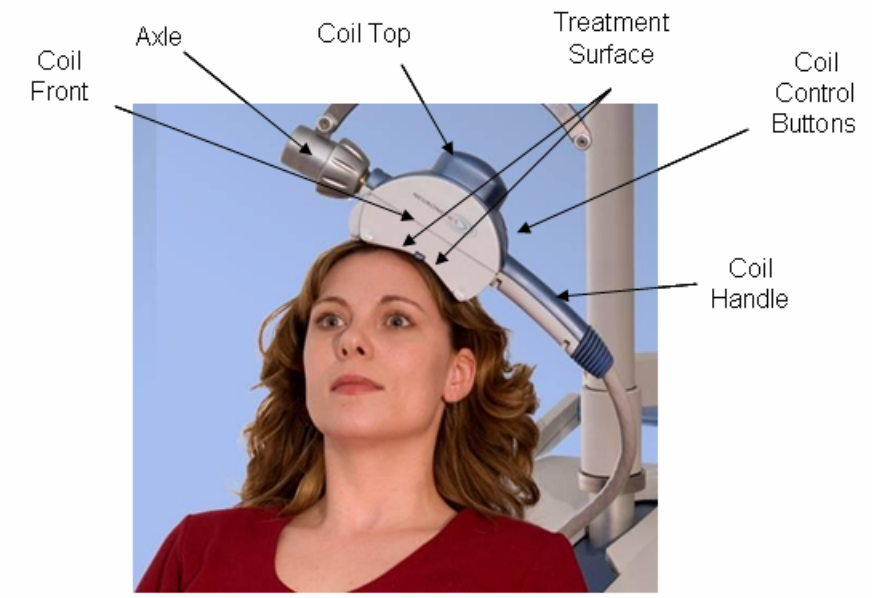


Figure 2-5. Coil Parts

During coil positioning, the user typically grasps the handle with one hand and the coil top with the other before pressing one of the brake release buttons. Holding the coil in this manner gives the user more flexibility and control over placement while the brakes are released.

System Software 1.0

The NeuroStar TMS System Software 1.0 controls all internal system functions, monitors system status to ensure safe operation and provides the user with a graphical means to manage the course of TMS treatment. Three important user features of the system software are:

- Graphical User Interface (GUI) – This is the user's primary, graphical touch screen interface with the system.

Interactive buttons, fields, and images are displayed that enable the user to direct and interact with system functions, such as entering data, starting and stopping treatment, and running diagnostics.

- MT Assist® - This feature facilitates motor threshold determination by calculating a predicted MT value based on a series of observations of muscle twitches in response to coil pulses, as reported by the user.
- Diagnostics – The embedded diagnostic software consists of an automated set of instructions that test and verify the operation of system components

Treatment Chair

The treatment chair is an electromechanical device on which the patient is seated during treatment with the NeuroStar TMS System. The chair resembles the type of chair used in dental treatment environments and is commercially available for use in other environments. It was selected for use with the NeuroStar TMS System because it meets the treatment regimen requirements for comfort, safety, and efficacy.

The treatment chair includes a wired pushbutton control unit that adjusts the chair height, the patient's reclining position, and the patient's leg support. It also includes a substantial base for overall stability and a built-in adjustable lumbar support cushion for patient comfort. The seat tilt feature helps lift the patient's seat to avoid patient slouching. The chair is wide enough to accommodate a range of patient sizes.

Head Support Unit

The Head Support Unit consists of several parts that are designed to provide maximum patient comfort and reliable coil position measurement of the patient's motor threshold (MT) location. The individual parts are identified in Figure 2-6.

Figure 2-6. Head Support Unit with Patient Alignment Parts

- **Head Support –** An electro-mechanical attachment mounted on the patient chair that provides comfortable support for the patient's head during treatment sessions. It can be set at different heights, angles, and distances to accommodate a range of patient positions in response to patient physical characteristics. Specifically, it has degrees of freedom that enable the user to adjust the head support in the anterior-posterior as well as the inferior-superior directions for patient comfort.
- **Side Pad and Bracket** – A moveable cushion that is mounted on a bracket designed to be set up on either the left or right side of the patient's head. The user can move the side pad toward or away from the side of the patient's head until a comfortable position has been established.
- **Superior Oblique Angle (SOA) Guide** - An angle indicator located behind the head support cushion associated with a pivot arm that supports the AP Guide. The pivot arm allows the AP Guide to be rotated through a range of superior oblique angles +/- 90° from the mid-sagittal position.
- **Anterior/Posterior (AP) Guide** - A straight flat scale that aids the clinician in accurately positioning the coil. The AP guide moves parallel to the patient's AP axis and provides a calibrated index of its position.
- **Lateral Canthus (LC) Guide** - A flat scale oriented in the patient's superior/inferior direction and located behind the head support cushion. This scale is used to indicate a reference position for aligning the patient's head to the Head

Support Unit for repeatable positioning from session to session.

- **Coil Angle Indicator** - A flat curved scale that is attached to the end of the AP guide. It enables the user to record the position of the coil up to 20° to the left or right of the center location.

Cushion Set

This is a set of cushions that can help enhance the comfort and positioning of the patient in the required posture for the duration of the treatment session.

2.3 Options

The following options are available.

Practice Data Management System (PDMS) 1.0

The optional Practice Data Management System (PDMS) is a software package that runs on an external PC with a wireless connection capability to one or more mobile consoles. This package is useful for tracking and documenting patient treatments and outcomes. It is also useful to users of multiple NeuroStar TMS Systems who need a centralized management apparatus.

PDMS Package

The optional PDMS package includes the PDMS 1.0 software and a personal computer that is equipped with a wireless connection that provides communication with one or more NeuroStar TMS System mobile consoles.

2.4 Supplies

Operating the NeuroStar TMS System requires the use of the following supplies:

- SenStars™
- Head Cushion Liners
- Side Pads
- Side Pad Liners
- Earplugs.

Your system was delivered with a starter kit containing the following quantities:

- SenStars™ (50)
- Head Cushion Liners (100)
- Side Pads (3)
- Side Pad Liners (50).

SenStar™

As illustrated in Figure 2-7 and Figure 2-8, the SenStar™ is a one-time use disposable component that serves four primary purposes:

- It includes a contact sensing element that detects when the coil is properly positioned against the patient's head.
- It detects the level of the magnetic field being applied by the coil.
- It reduces the magnetic field at the patient's scalp (without affecting the deeper therapeutic field in the cortex) to aid in patient comfort during treatment.
- It provides a clean hygienic surface for each treatment session.

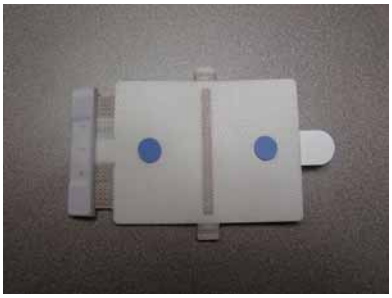


Figure 2-7. SenStar™ - Patient Contact Surface

Figure 2-8. SenStar™ - Coil Contact Surface

Head Cushion Liner

The Head Cushion Liner is a thin, tissue-like disposable cover that is placed on the Head Cushion as a hygienic barrier for each patient session.

Side Pad

The head support system offers the patient further comfort through the use of a side pad that could be set up both on left or right side of the patient's head. The side pad is a replaceable foam pad that is mounted on the side pad bracket. During treatment, the side pad is covered by a disposable side pad liner.

Side Pad Liner

The side pad liner is a thin, tissue-like disposable cover that is placed on the side pad as a hygiene barrier for each patient session.

Ear Plugs

The ear plugs are commercial grade noise reduction supplies made of malleable foam for custom fit in the ear canal. When properly inserted, they can provide up to 30db noise reduction.

3 Daily Treatment Room Preparation

This section provides steps for you to take at the beginning of each day to prepare the treatment room for TMS sessions.

3.1 Completing the Checklist

At the start of each treatment day, complete the following checklist.

Action	Checked
1. There are no cracks in or damage to the coil housing, the gantry and mast covers, or to the mobile console covers.	
2. There is no visible damage to the power cable.	
3. The power cable is plugged into the wall socket.	
4. The coil cable is connected to the mobile console.	
5. When the power switch is turned to ON, you can hear the mobile console internal fan running.	
6. The touch screen displays the system boot-up process and the Welcome screen.	
7. The system processor check, the power module check, and the treatment coil check pass.	
8. The touch screen responds when you touch the **CONTINUE** button.	
9. Pressing and holding the brake release button on the coil enables you to move and reposition the coil, gantry, and mast.	
10. Releasing the brake release button on the coil locks the coil, gantry, and mast in place.	

If you encounter a problem with any item in this checklist, use the troubleshooting table in section 5.4 of this manual to identify the cause and possible remedy.

3.2 Preparing the Treatment Room

Prepare the equipment as follows:

- Move the mobile console away from the back of the chair.
- Position the coil up and out of the way and the display arm in the park position.
- Position the side pad bracket in the vertical position.
- Position the SOA guide 90 degrees to patient's right (park position).
- Position the A/P guide all the way back (park position).
- Position the coil angle indicator at the 0 position.
- Remove the Coil Retainer from the AP Guide.
- Position the chair in its upright position with the leg support in its vertical position and the chair at its lowest height.
- Position the head support in line with the back of the chair.

To prevent the system from overheating, do NOT block the fan vent or position the fan vent against a wall or other obstacle. Also, make sure that the room temperature is lower than 86° F.

The mobile console power cord presents a tripping hazard. Ensure that the power cord is safely out of your working area and out of the patient's path.

3.3 Attaching the SenStar™ to the Coil

You must attach a new SenStar™ to the face of the coil for each patient session.

The SenStar™ comes into direct contact with the patient's scalp. Handle the SenStar™ carefully. Keep it away from contaminants or other substances. If the patient reports skin irritation where the SenStar™ contacts the patient's scalp, replace the SenStar™.

SenStars™ are one-time use, disposable supplies. A SenStar™ is new until you have attached it to an operating coil. After you have initiated an MT location task or a treatment session, the SenStar™ cannot be reused. However, the same SenStar™ can be used for both MT location and treatment when MT location and treatment are performed during the same session. If you have inadvertently

installed a used SenStar™, the system prompts you to install a new unused SenStar™ when you log into the system.

1. Position the coil as illustrated in Figure 3-1.

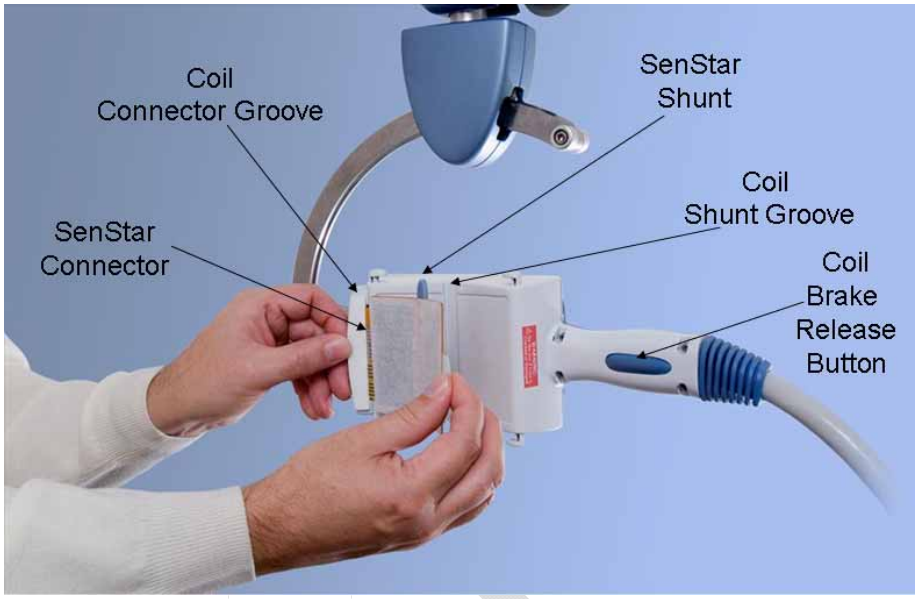


Figure 3-1. Installing the SenStar™

2. Press the SenStar™ connector into the coil connector groove.
3. Press the SenStar™ shunt into the coil shunt groove.

3.4 Starting Up and Logging In

The steps in this section enable you to do the following:

- Start the system
- Log in as an authorized user.
- Run the pulse test to verify that the system is properly set up for treatment.

To complete these steps, you must first properly install a SenStar™, as described in Section 3.3 of this manual.

Step 1: Start the System.

1. Move the ON/OFF switch on the back of the mobile console to the ON position.
2. When the Microsoft® Windows™ self-diagnostics routine has finished, double-touch the NeuroStar TMS System icon on the desktop. In response, the system automatically runs the self-diagnostics application and displays the diagnostic routine's progress on the touch screen.
3. If all diagnostics tests pass, the power-on diagnostics screen prominently displays the following message for 5 seconds: All start-up tests passed. The system is functional. (See Figure 3-2.)

When the self-diagnostics routine has finished, the system activates the brake release button on the back of the coil. Press the brake release button and move the coil out of the way before attempting to wheel the mobile console into the treatment position.

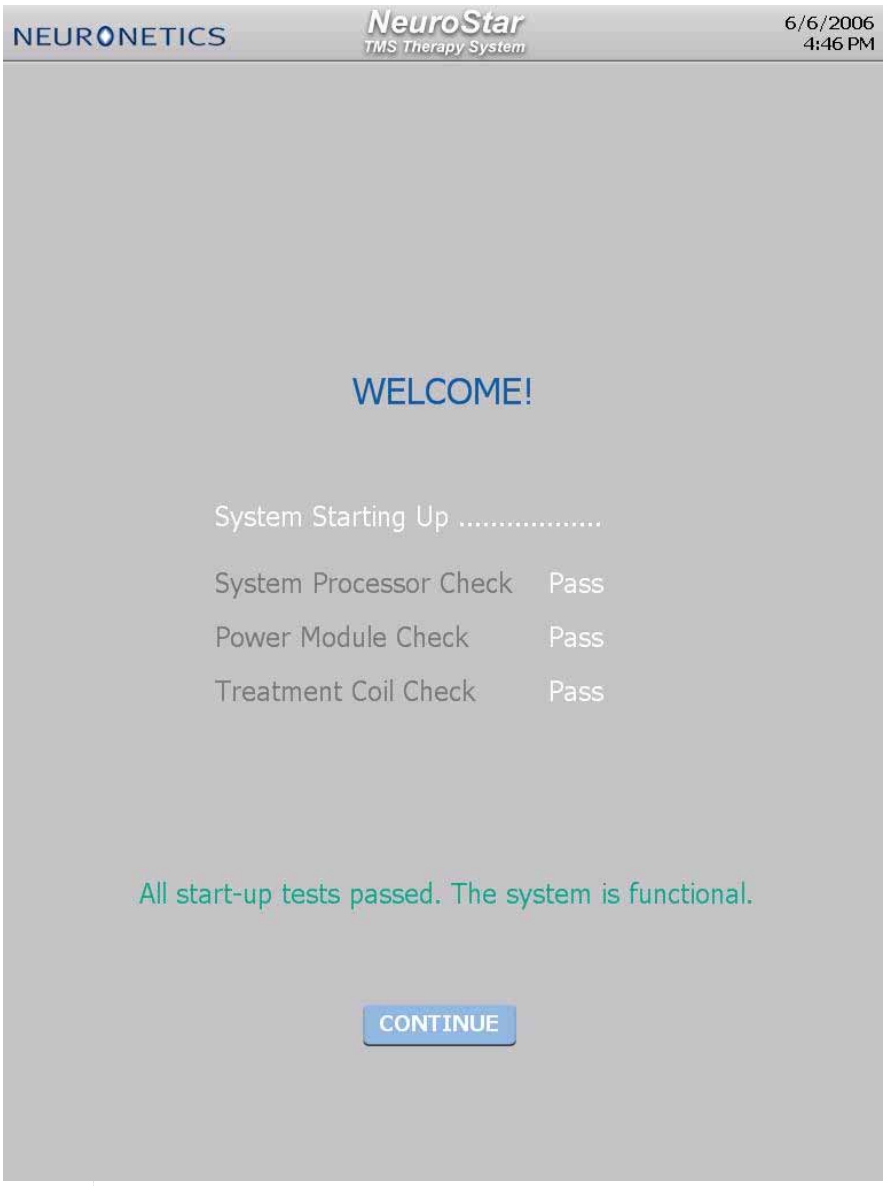


Figure 3-2. System Self-Test Screen

After 5 seconds, the system displays the user login screen. (If you touch the **CONTINUE** button before 5 seconds have elapsed, the system advances you to the login screen.) The User ID field displays the user ID of the previous user.

If any diagnostics test fails, the power-on diagnostics screen prominently displays the Neuronetics System Help telephone number. Call that telephone number before attempting to use the system.

Press and hold the brake release button on the coil and move the gantry up and out of the way.

Release the coil brake release button.

Normally, you should do Steps #5 and #6 before you shut the system down at the end of the day. However, if this was not done by the last user, you must do it.

Step 2: Log In.

The NeuroStar TMS System provides two levels of user privileges:

- User, and
- Administrator.

Individuals who have administrator privileges have all the privileges of a user plus the ability to add new users to the system. (See section 5.1.)

1. Use the on-screen keyboard to enter your assigned user ID and password and touch the **LOGIN** button on the screen as illustrated in Figure 3-3.

Figure 3-3. Login Screen

2. When a valid user ID and password combination has been entered, the system displays the SenStar™ Detection Screen (Figure 3-4). If you have not attached a SenStar™, or if the SenStar™ has already been used, the system prompts you to attach a new SenStar™ and disables the **TEST PULSE** button until you have done this.

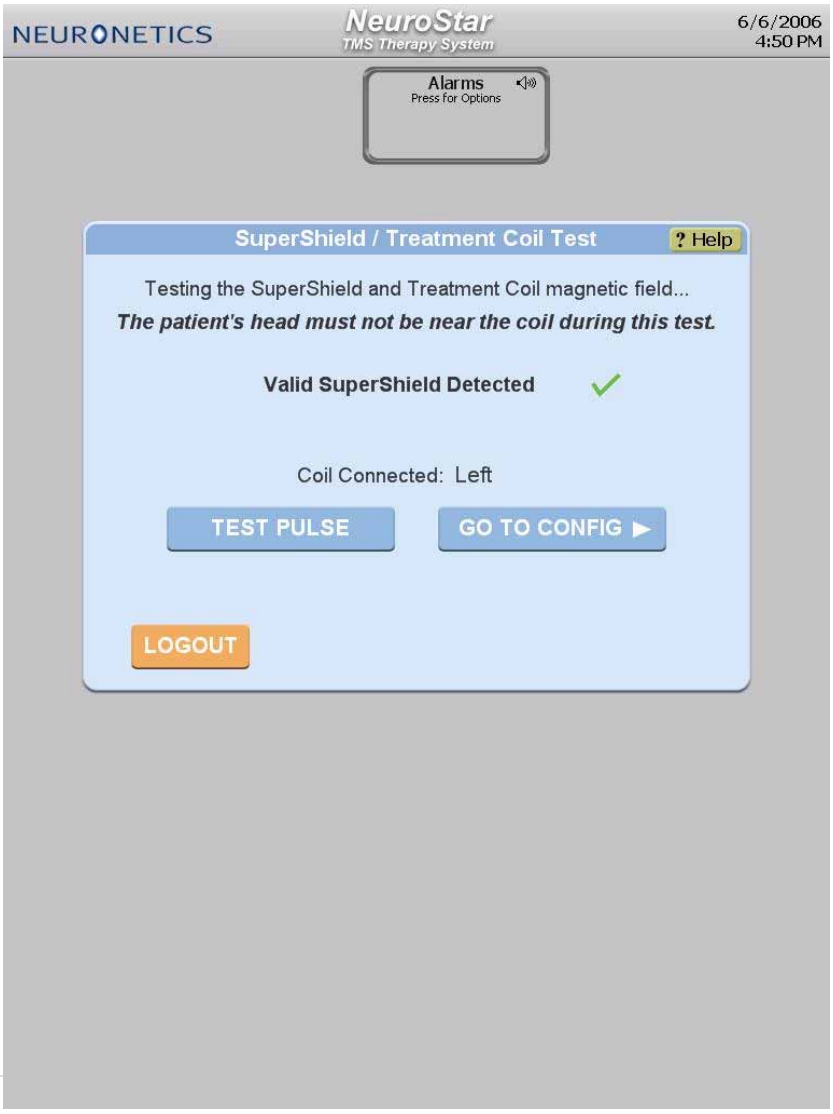


Figure 3-4. SenStar™ Detection Screen

When a new SenStar™ has been detected, the system enables the **TEST PULSE** button on the touch screen. If there is no contact detected on the SenStar™, the system generates an audible success tone.

Step 3: Run the Pulse Test

Before using the system, you must perform the pulse test. In this test, the system generates two pulse sets.

If the system fails to detect the levels of these pulses, it displays a failure message and prevents you from performing treatments or MT searches.

If the test is successful, the system enables the **CONTINUE** button.

Keep the coil away from the patient's head during this test!

1. Touch the **TEST PULSE** button on the touch screen. In response, the system displays a progress screen, as illustrated in Figure 3-5.

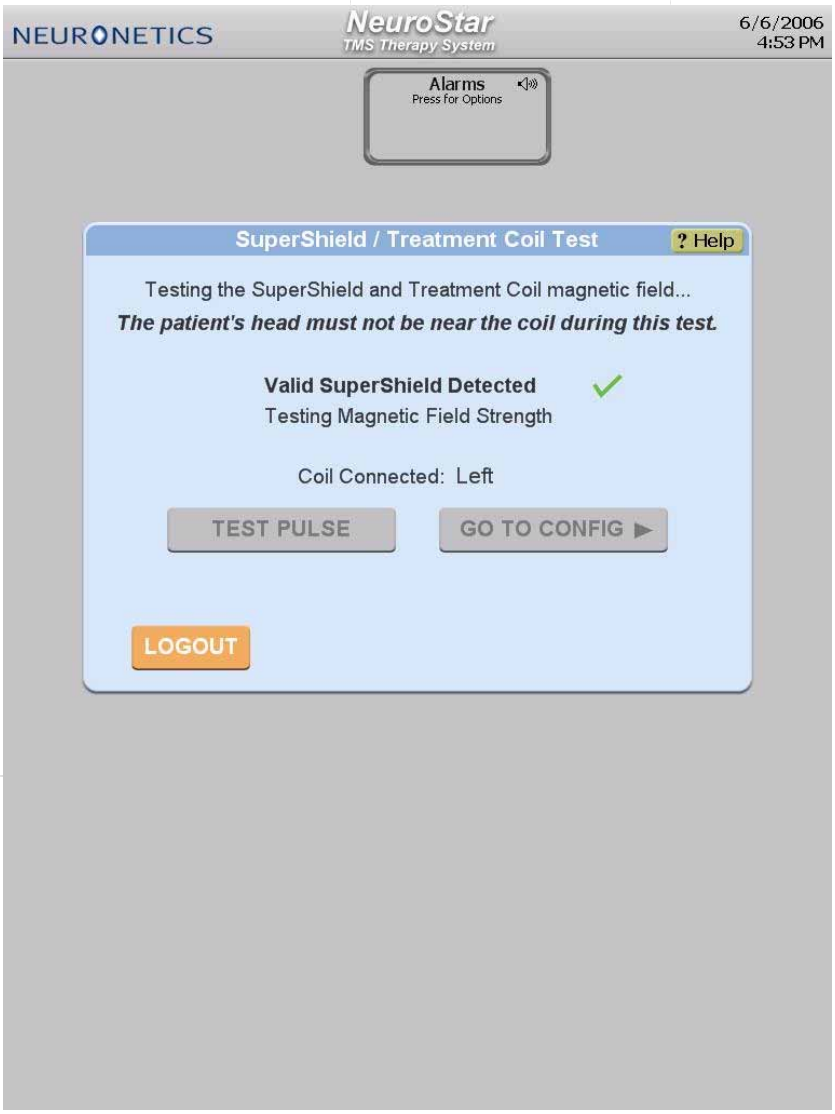


Figure 3-5. Test Pulse Progress Screen

You can also use the pulse button on the coil to initiate the pulse test, as illustrated in Figure 3-6.

Figure 3-6. Coil Pulse Button

2. When the test is finished, the system displays the verification screen, as illustrated in Figure 3-7.

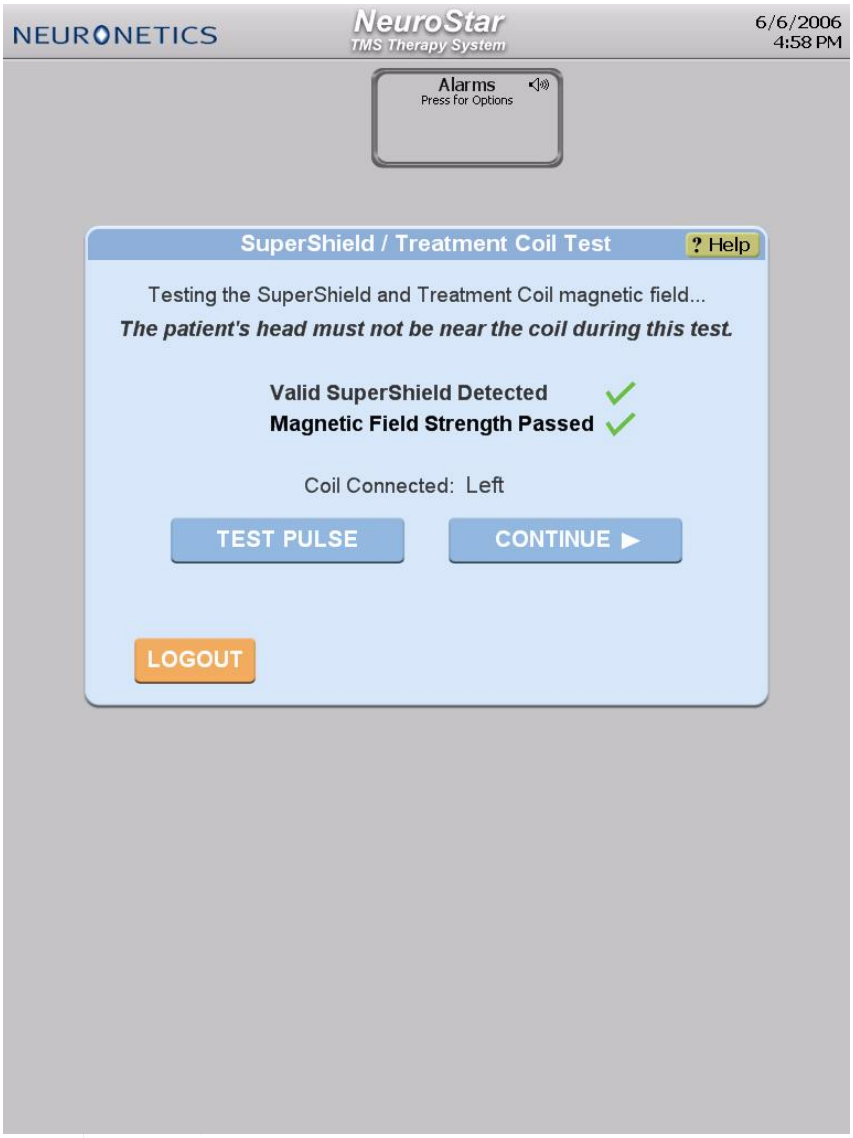


Figure 3-7. Test Pulse Completion Screen

3. Touch the **CONTINUE** button to display the Select Patient screen, as illustrated in Figure 3-8.

   If the test fails, make sure that the SenStar™ is properly mounted on the coil and retry the test. If after a few tries the pulse test continues to fail, try a different SenStar™. If failures continue with a different SenStar™, call Neuronetics for service.

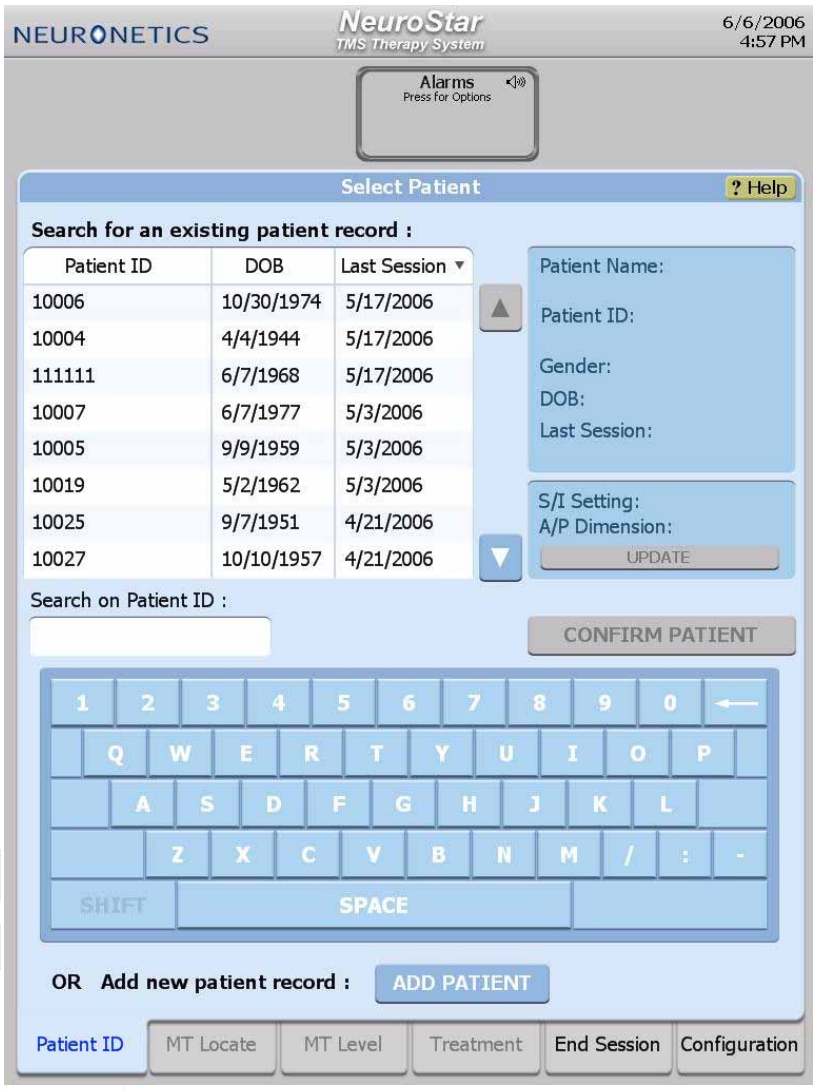
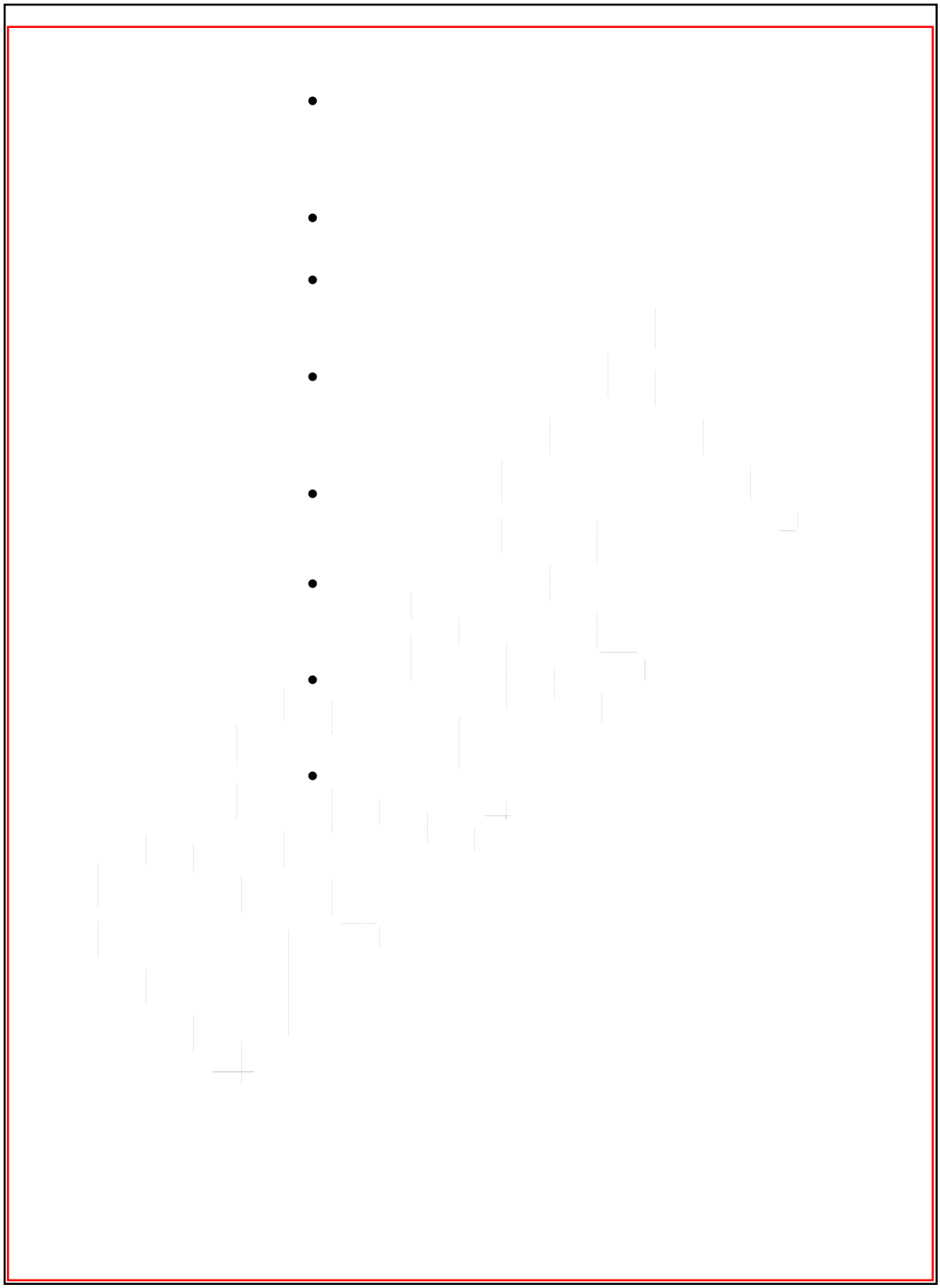
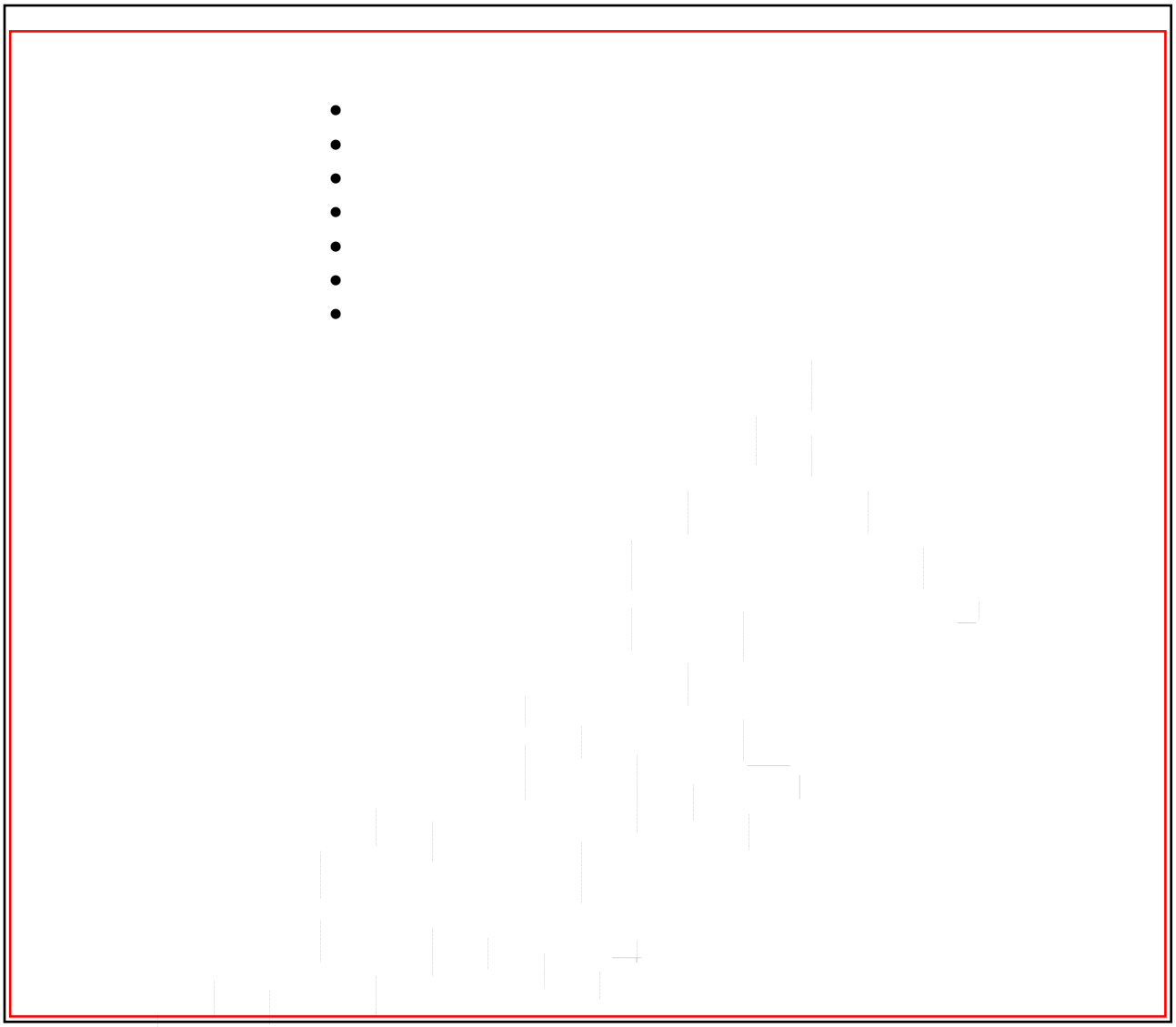
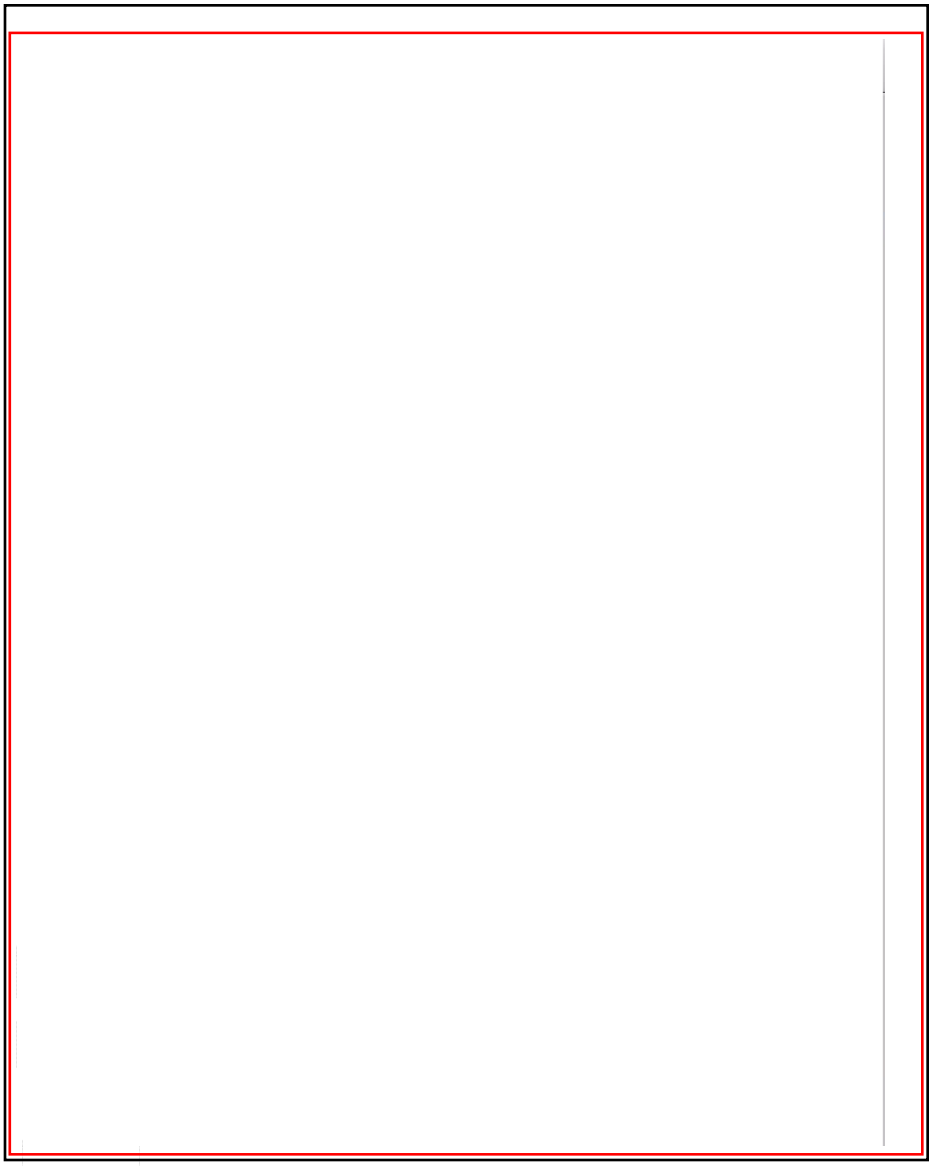


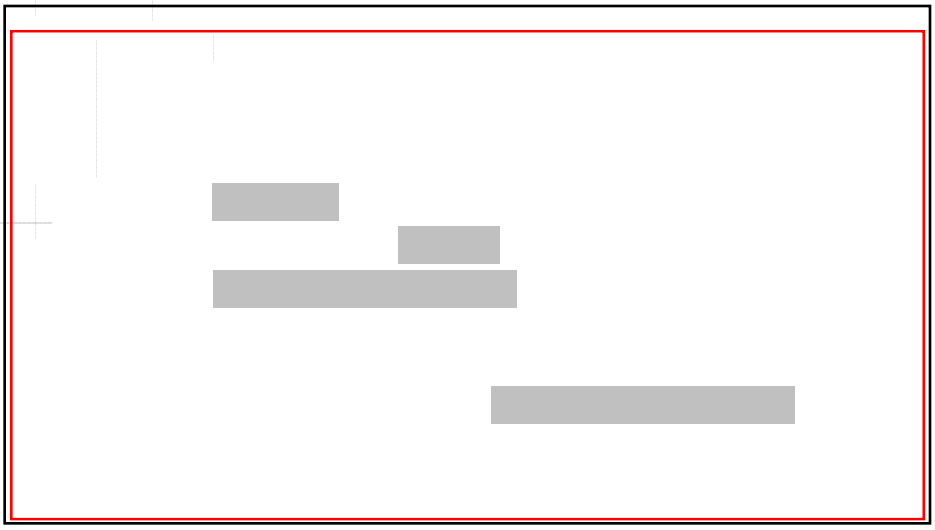
Figure 3-8. Select Patient Screen

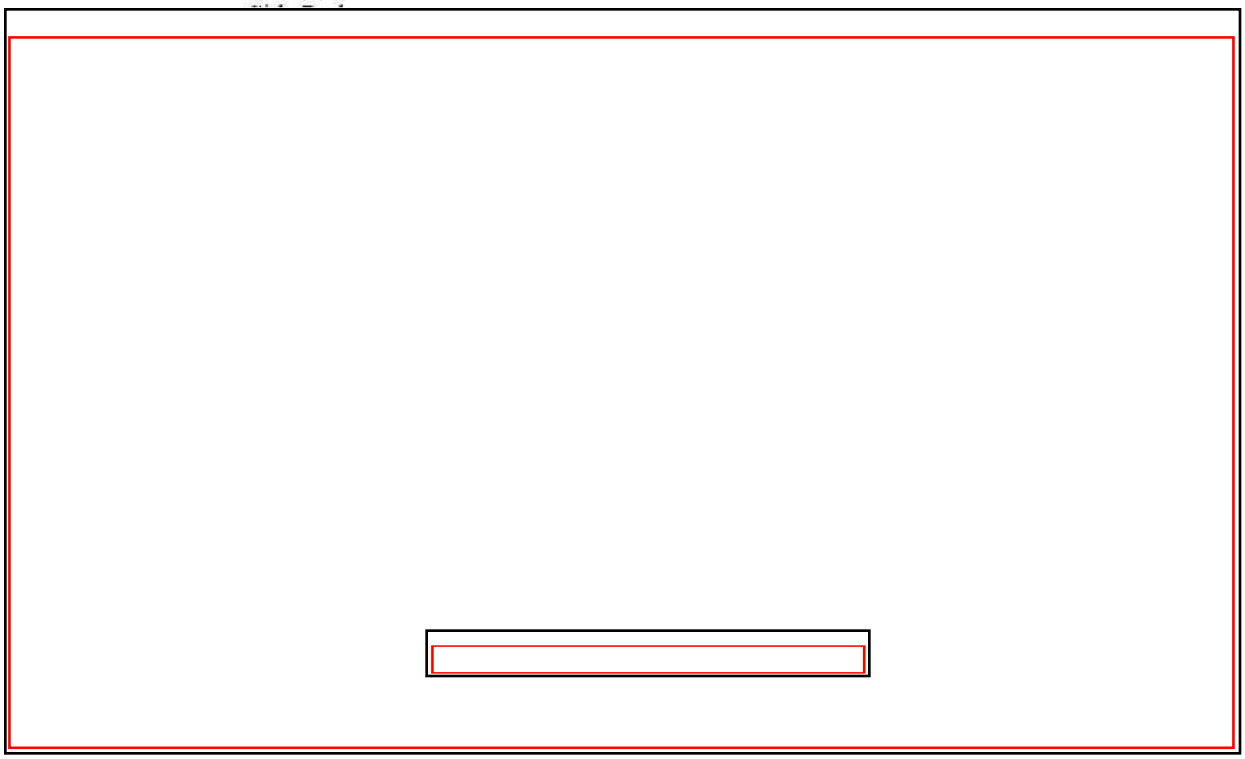
4. At this point, you can either follow the steps for an initial visit (Section 4.3) or for a return visit (Section 4.5).

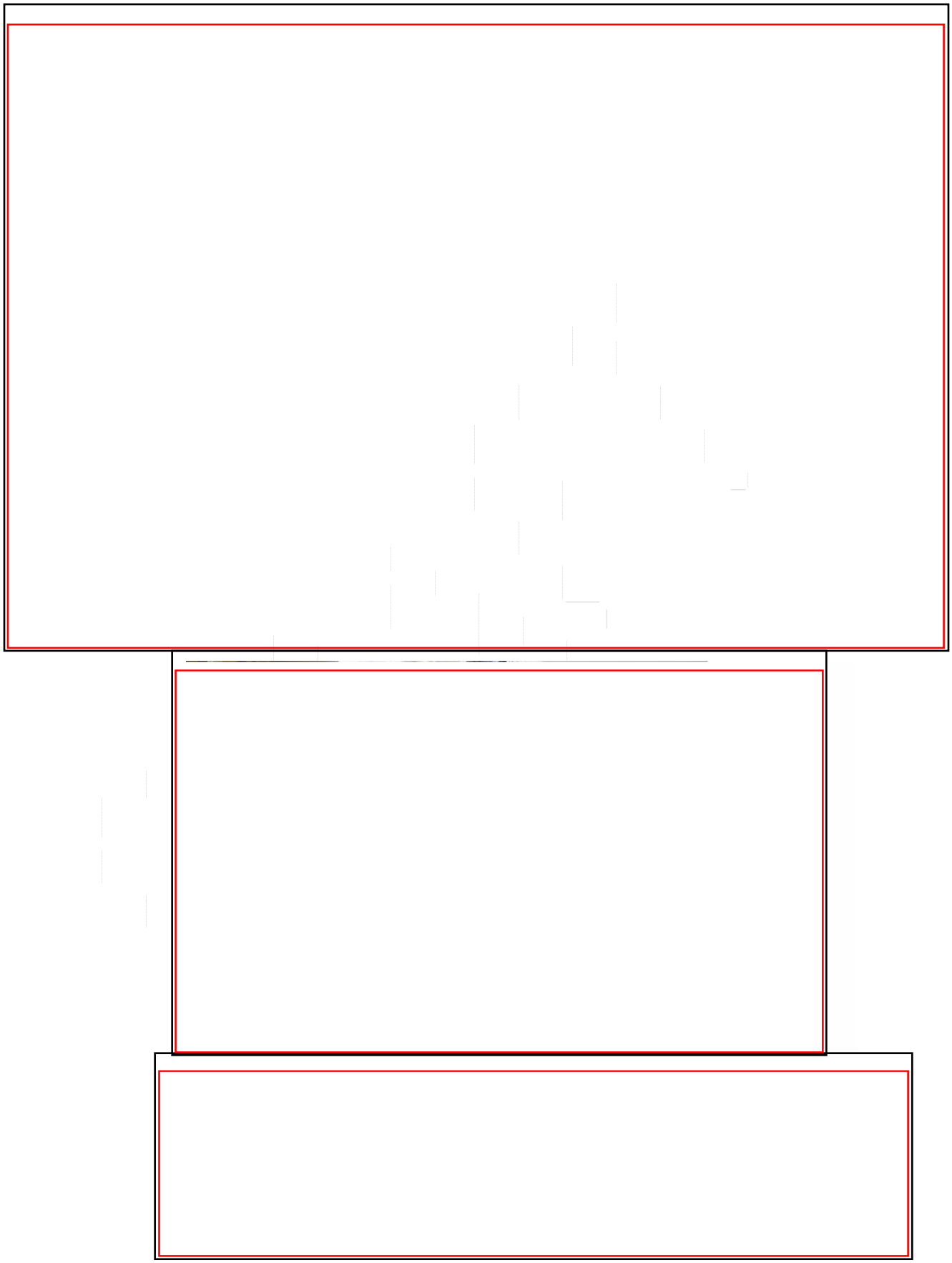


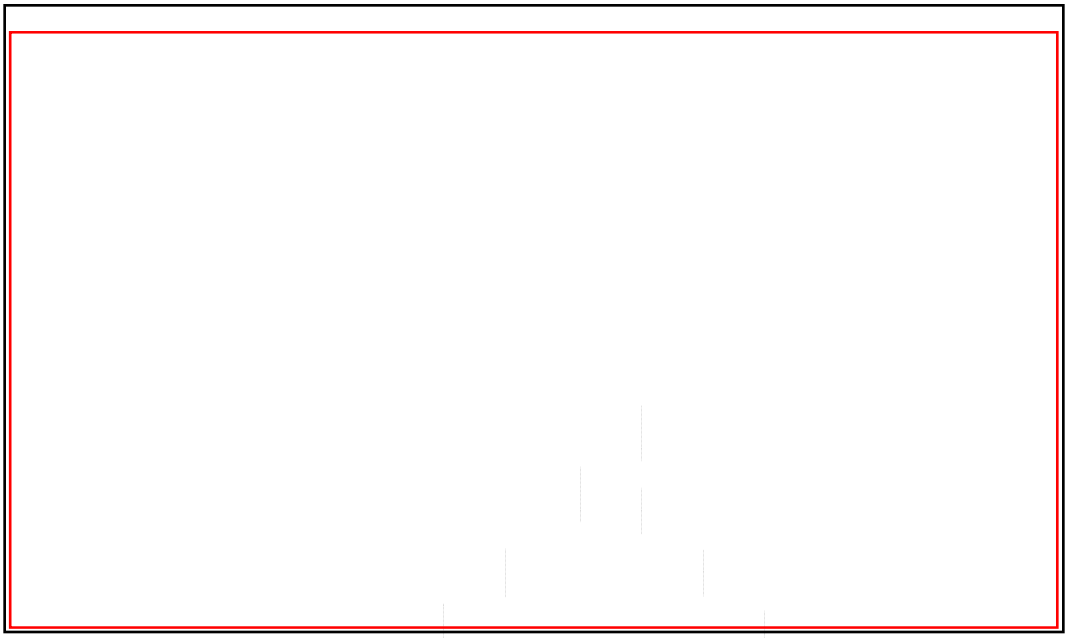


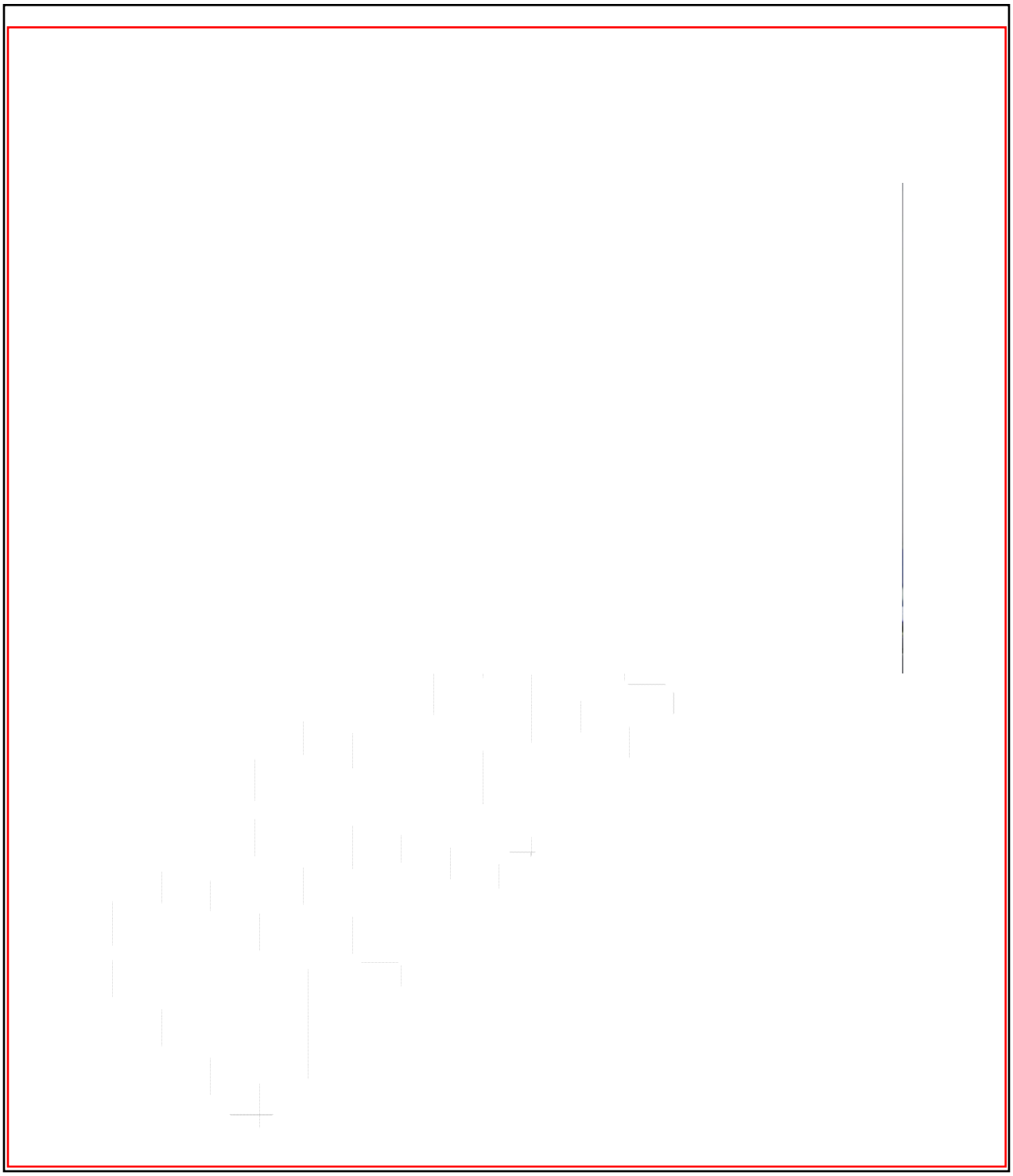


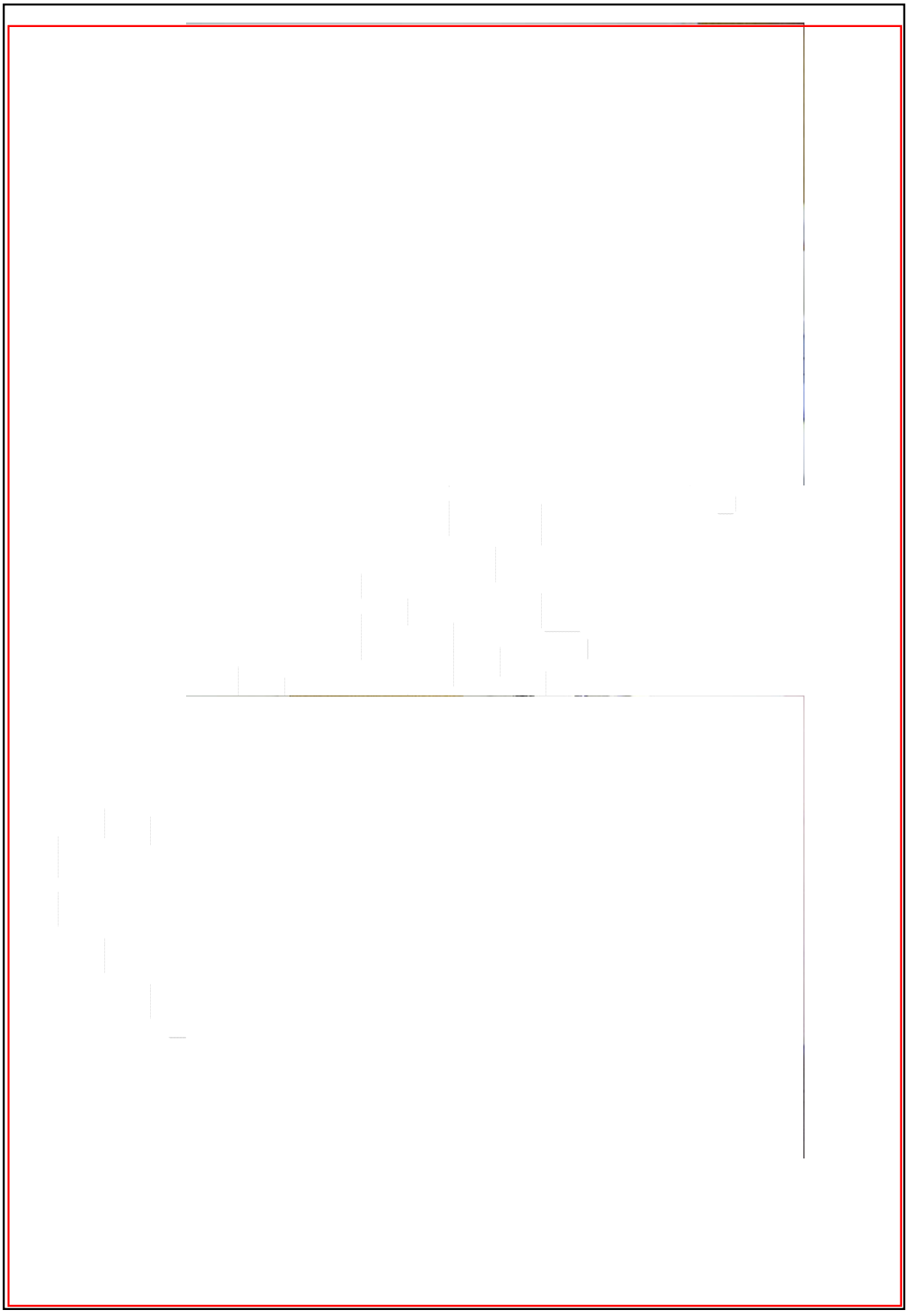


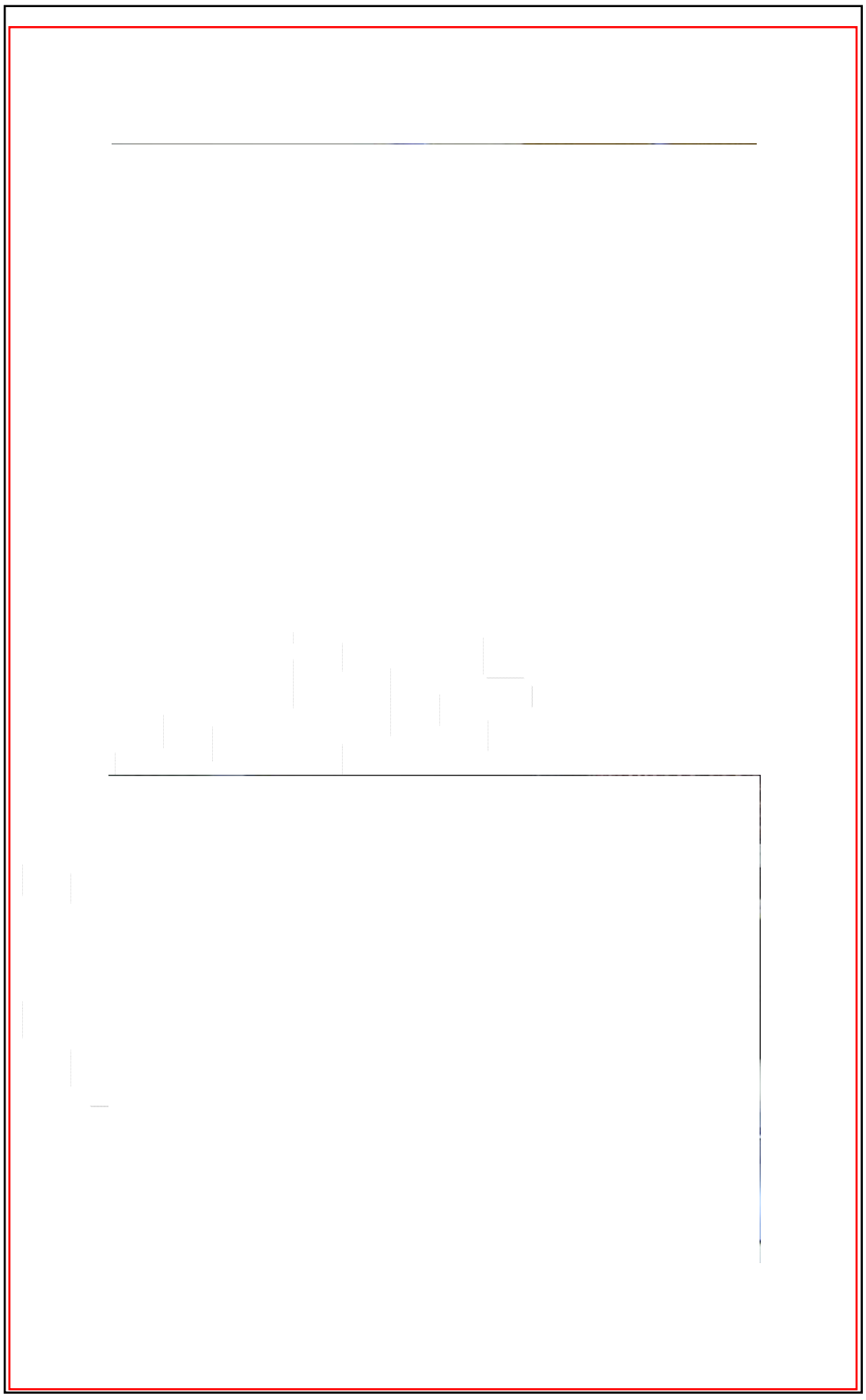


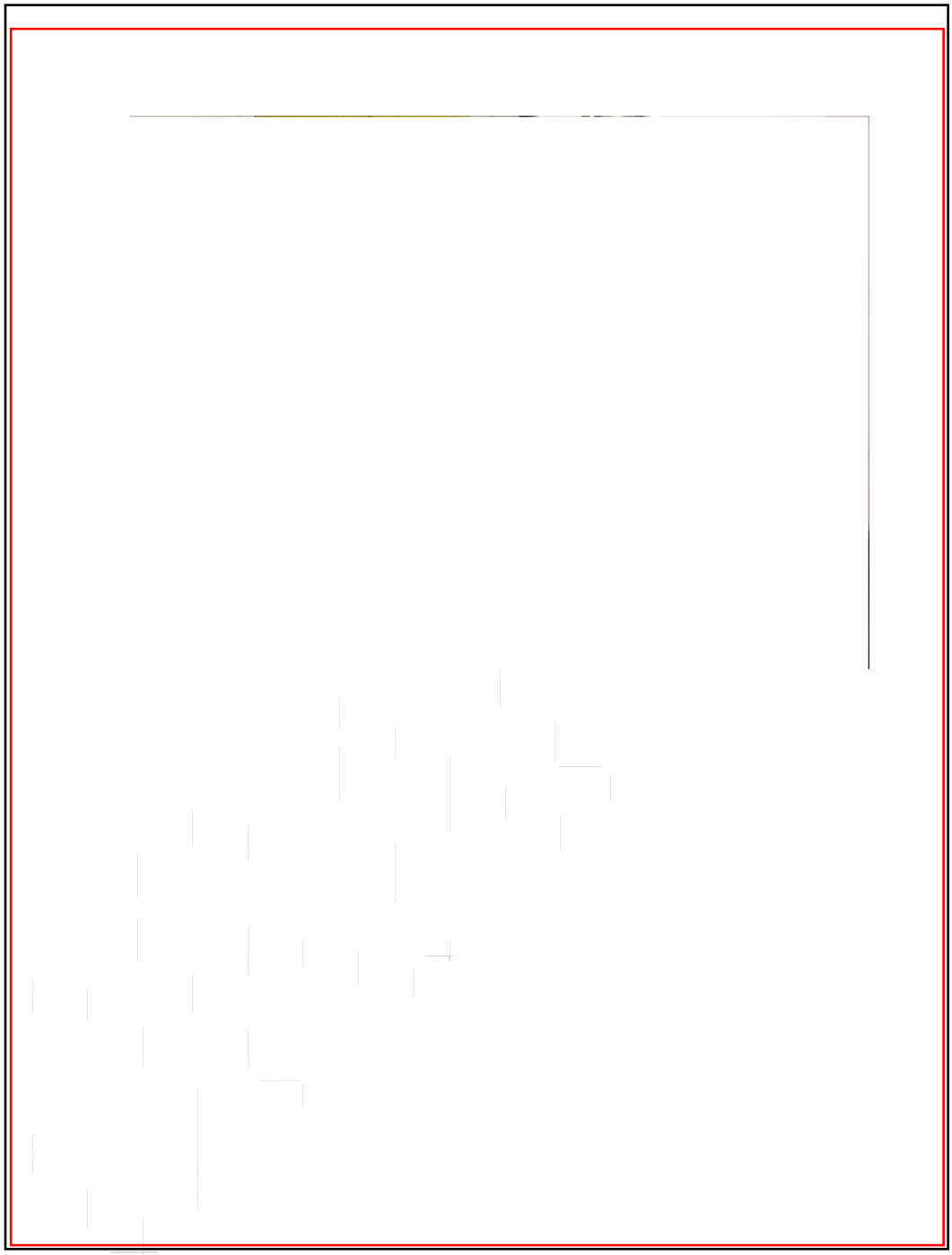


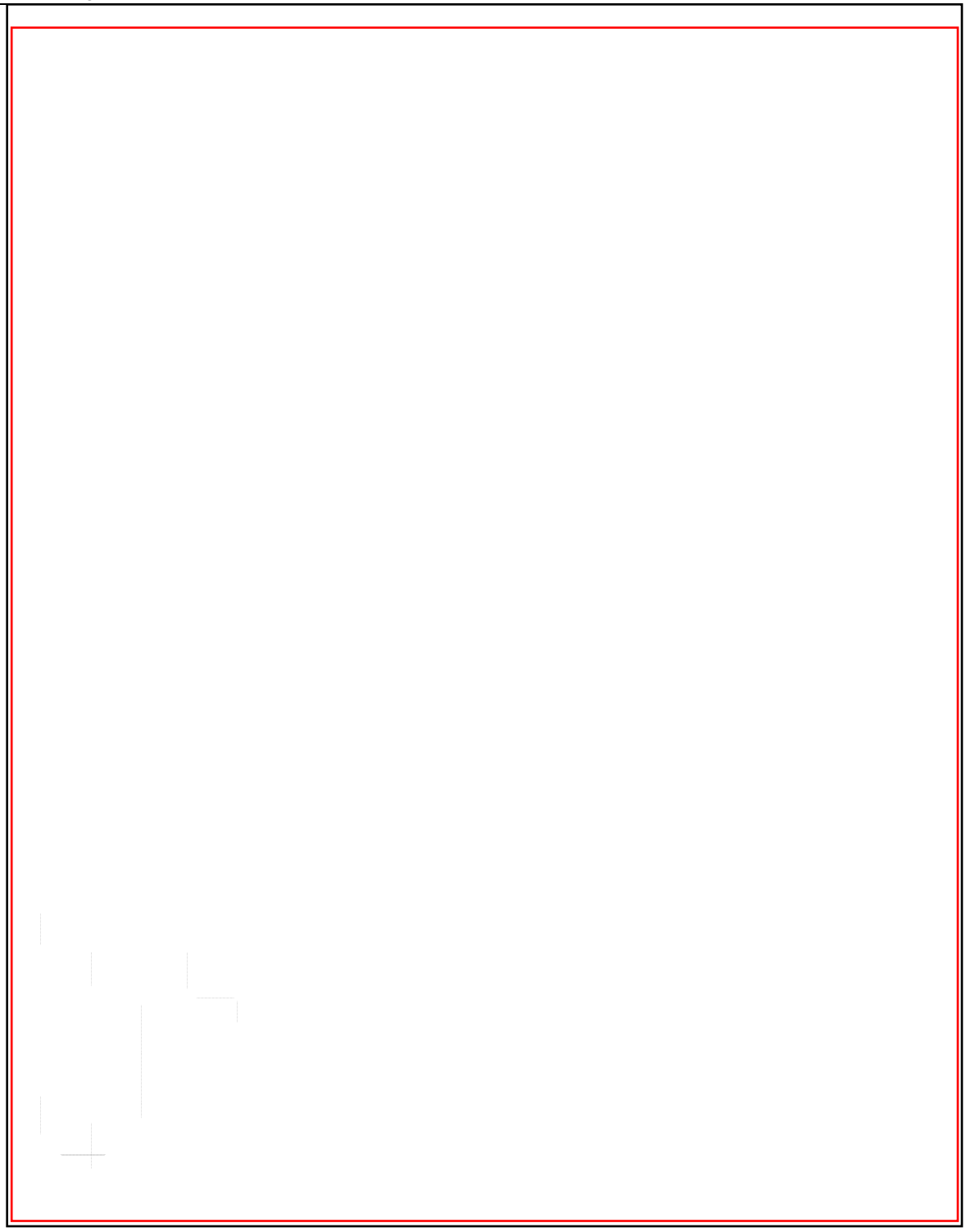


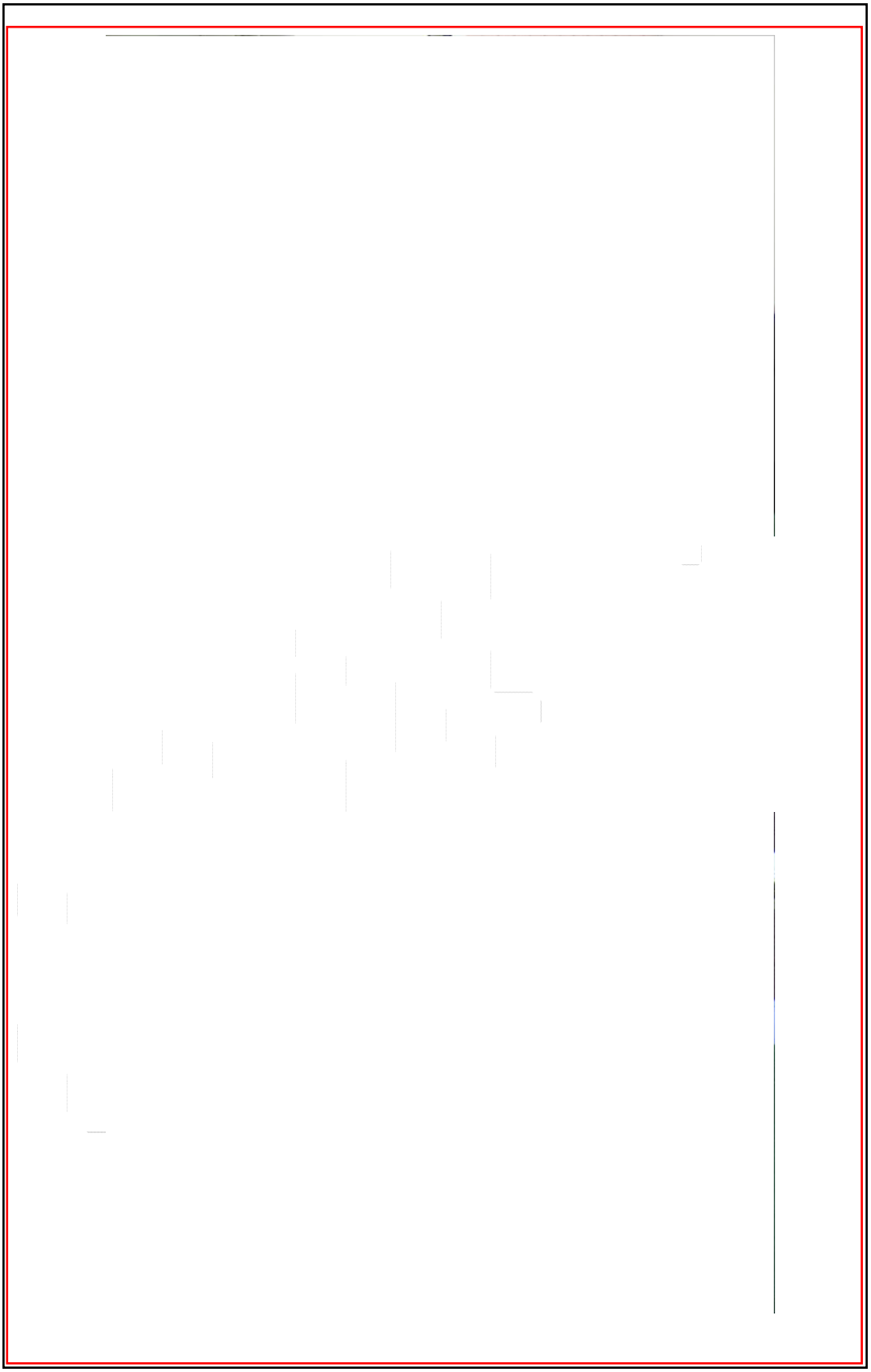


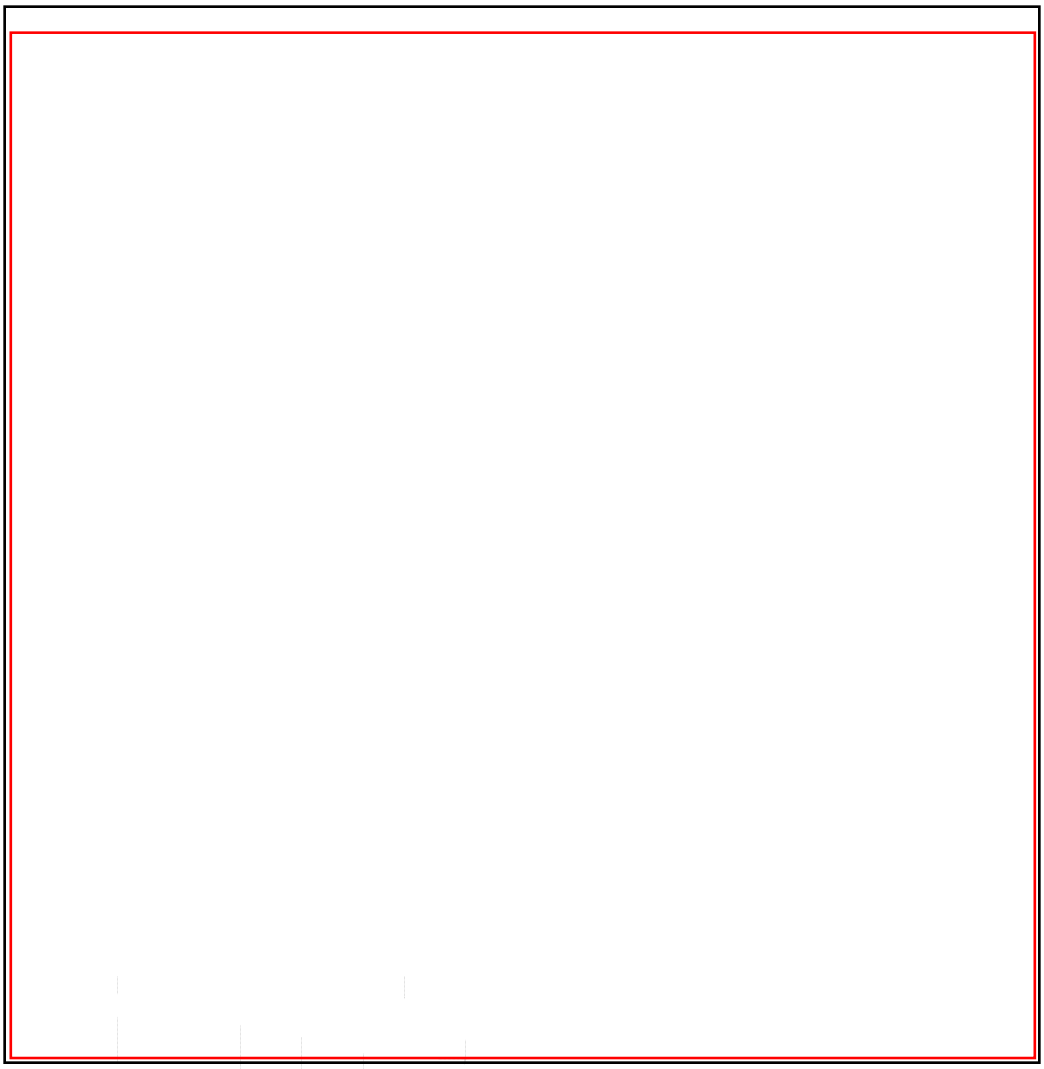


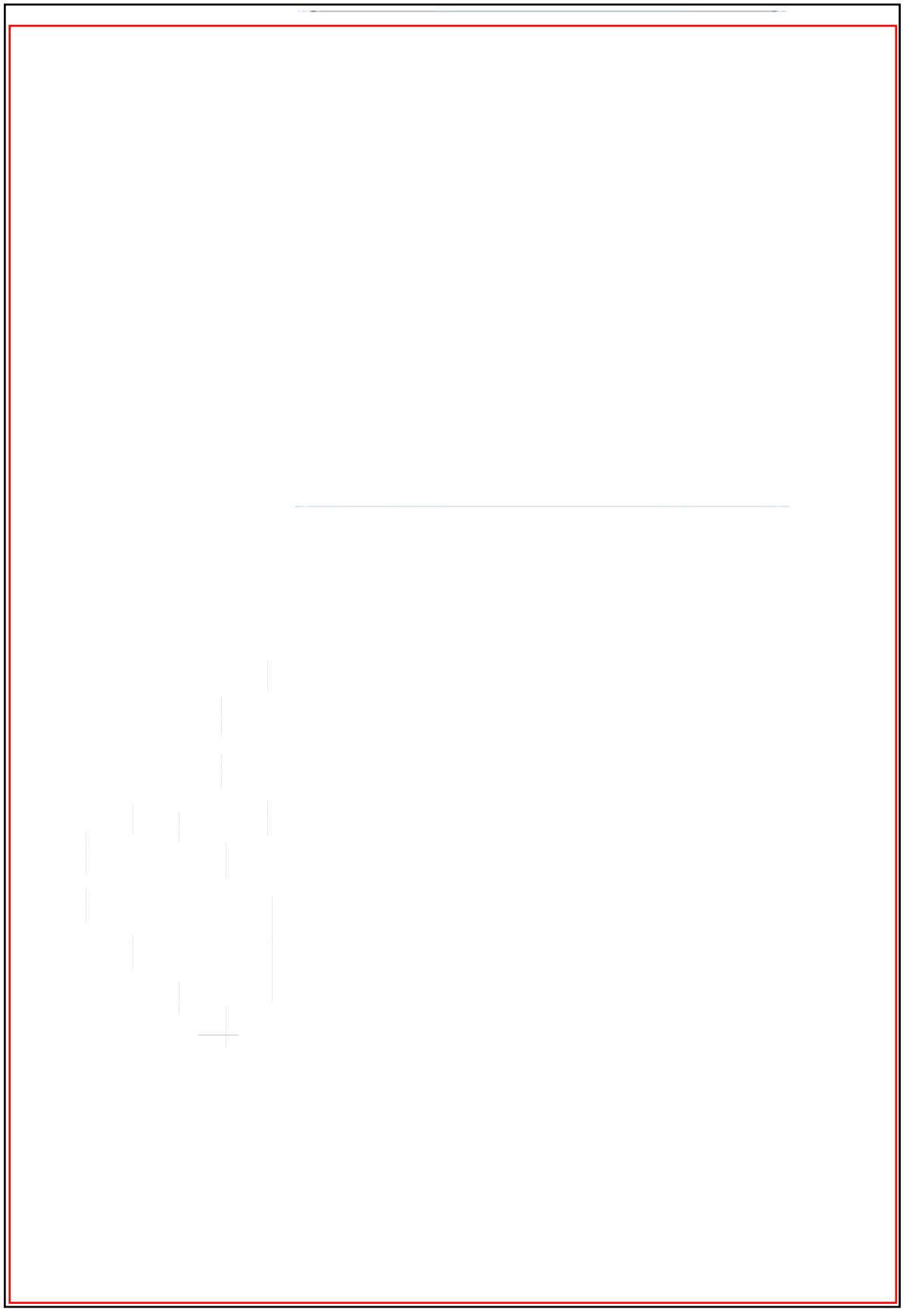


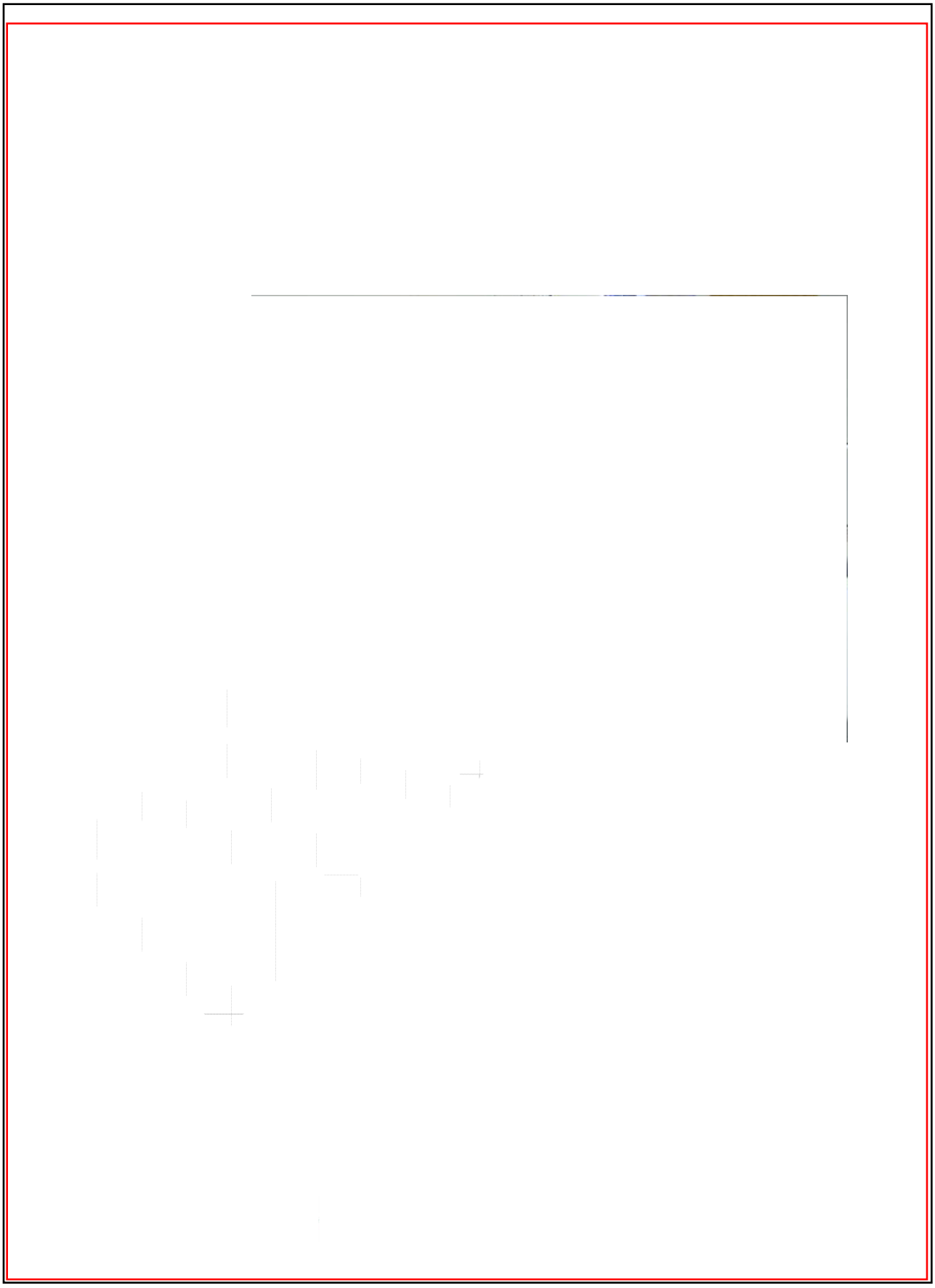


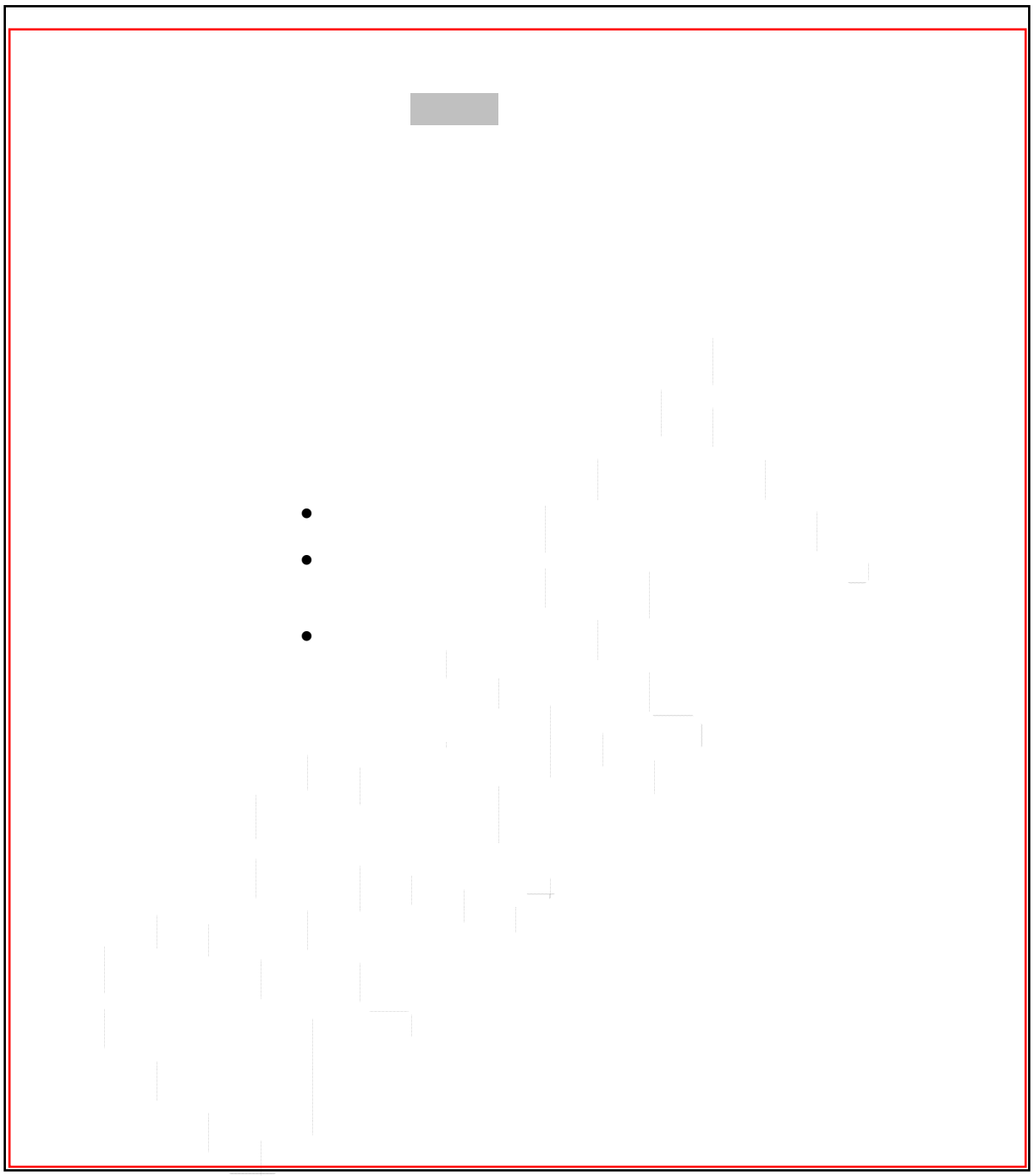


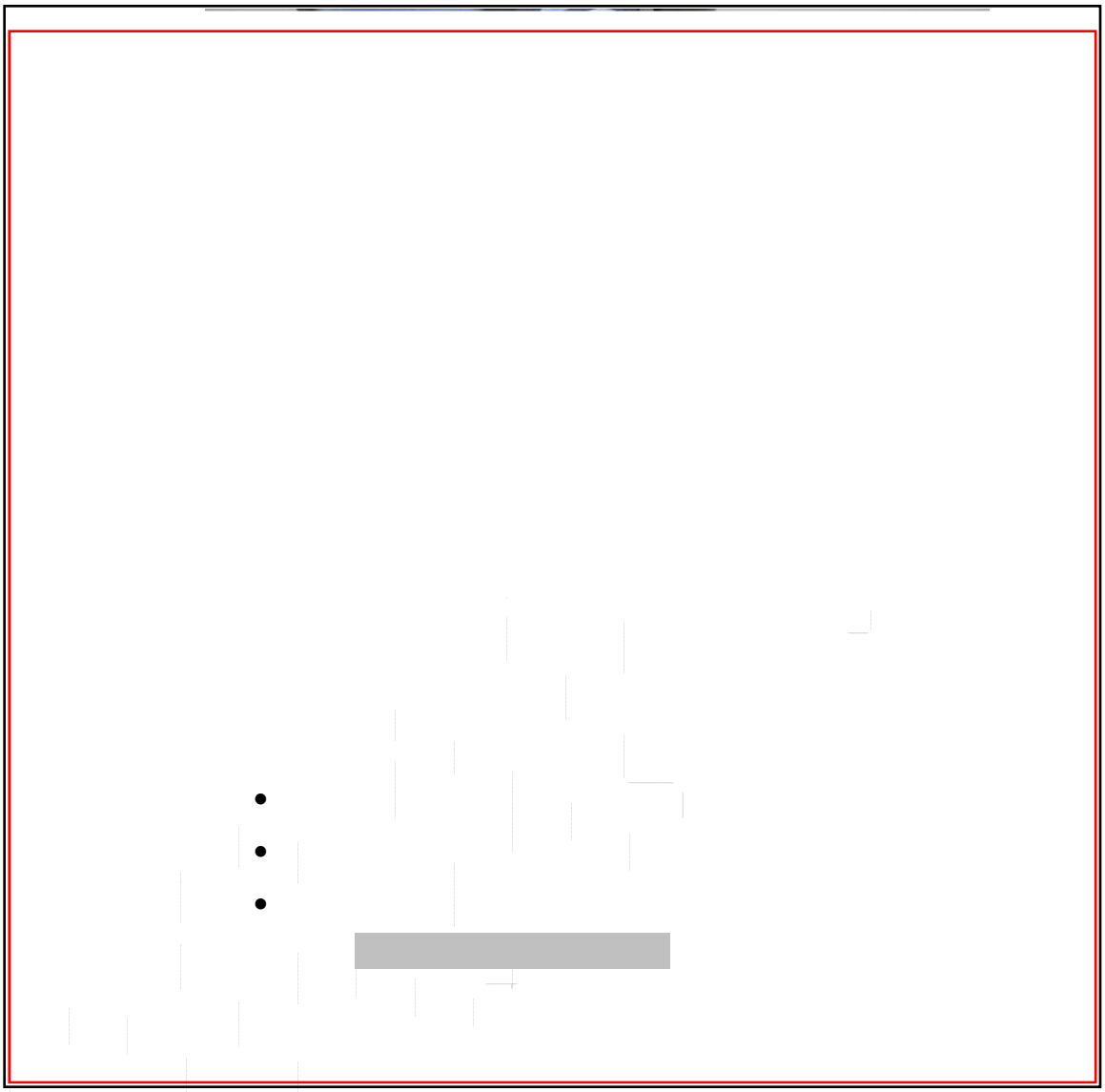


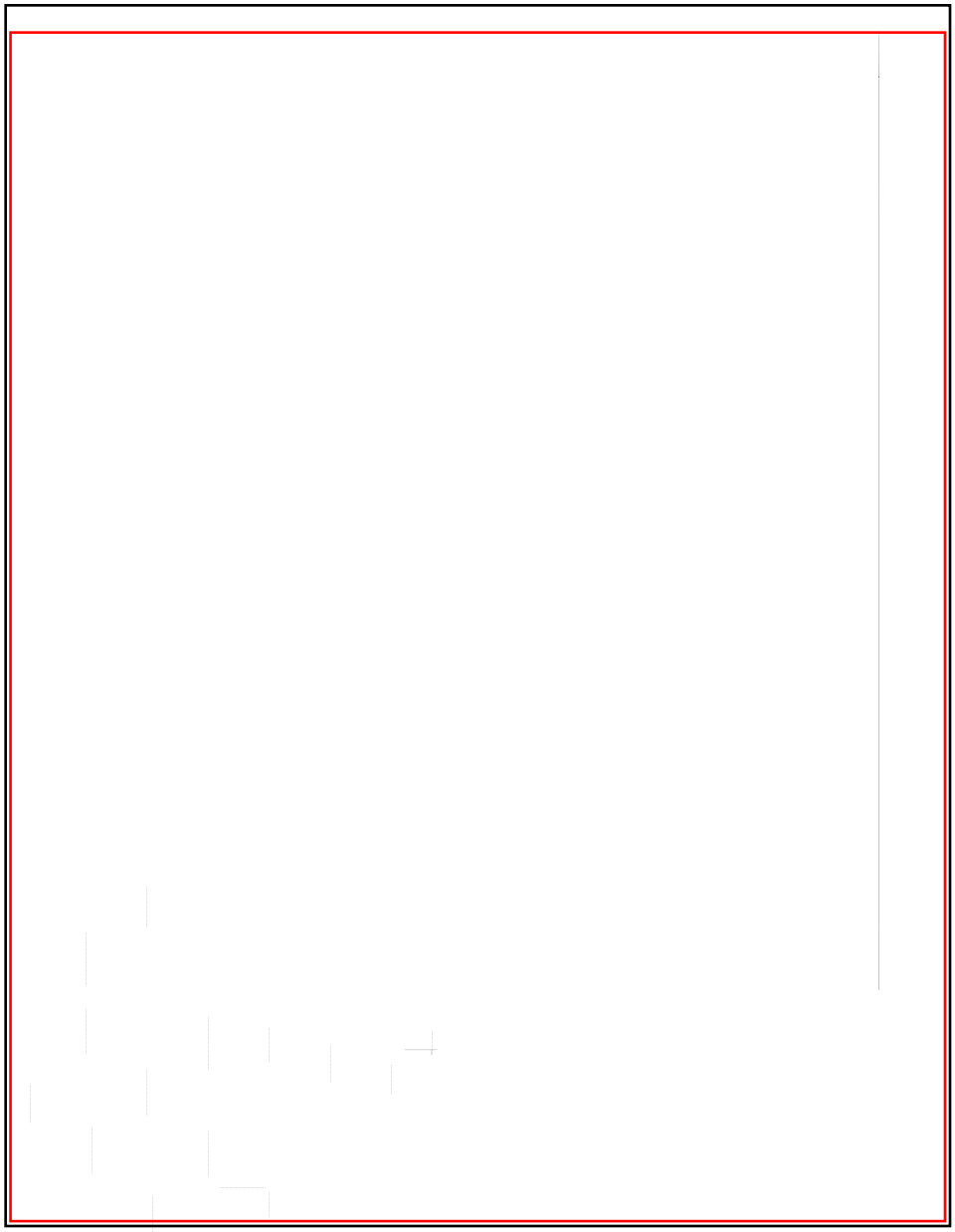


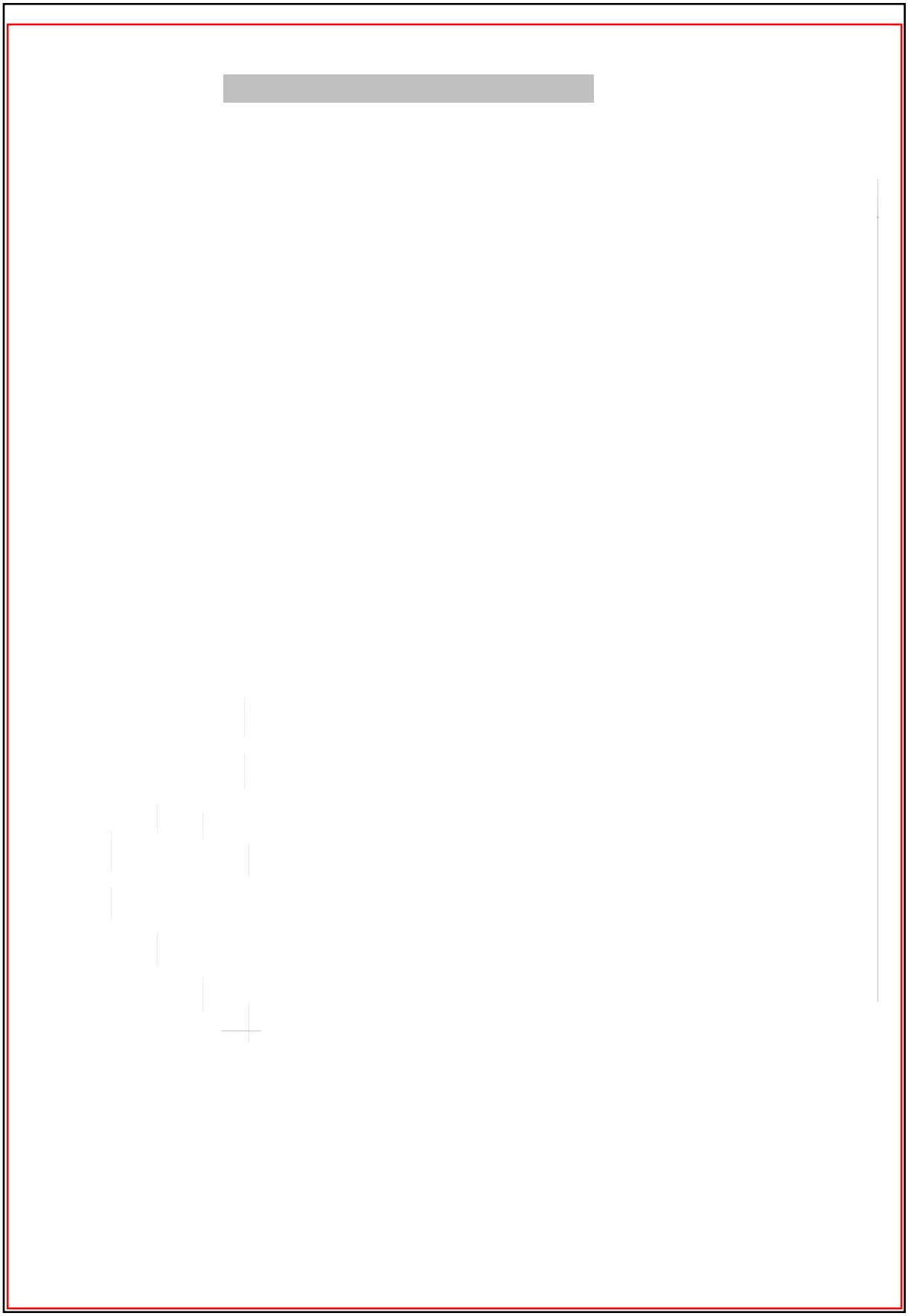


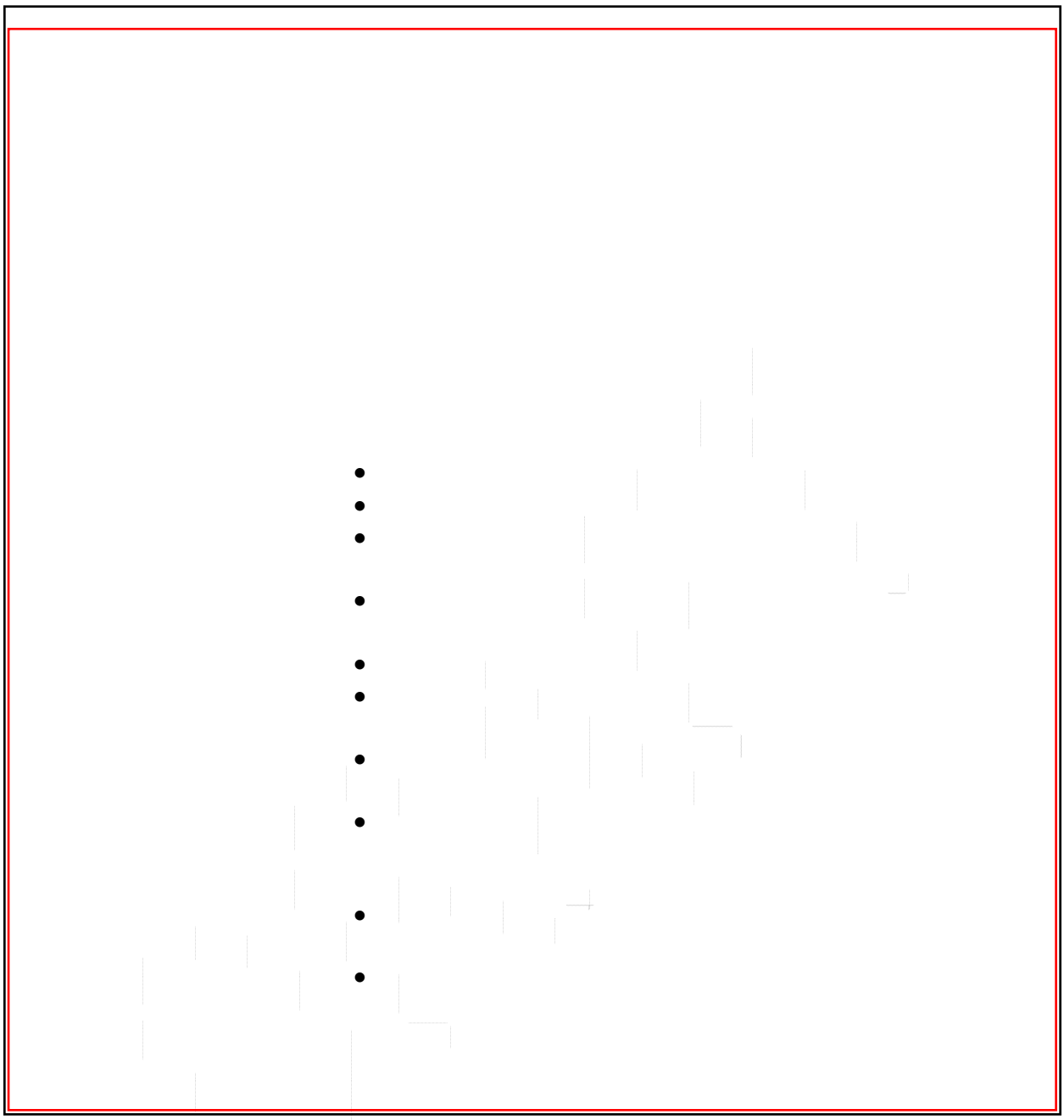


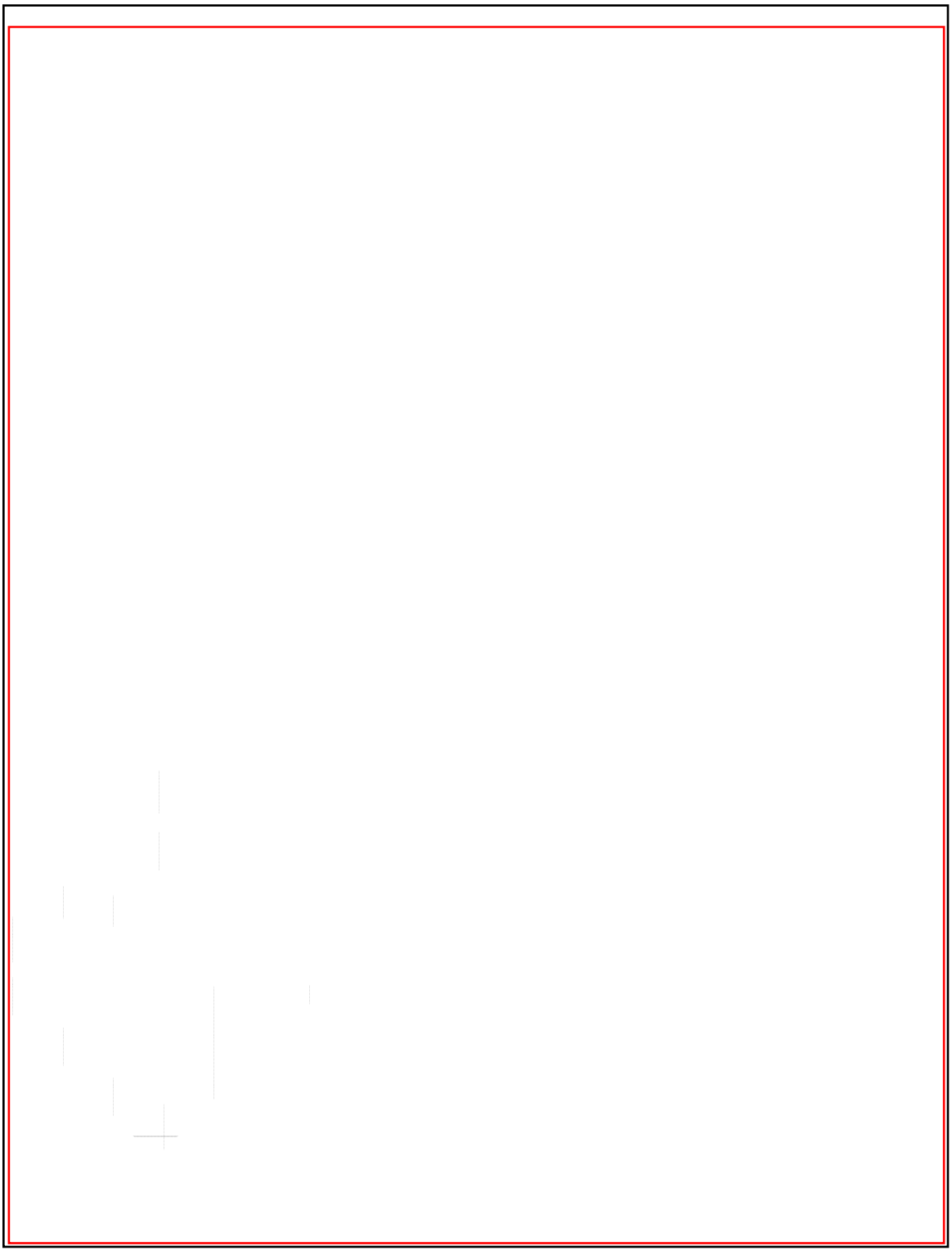


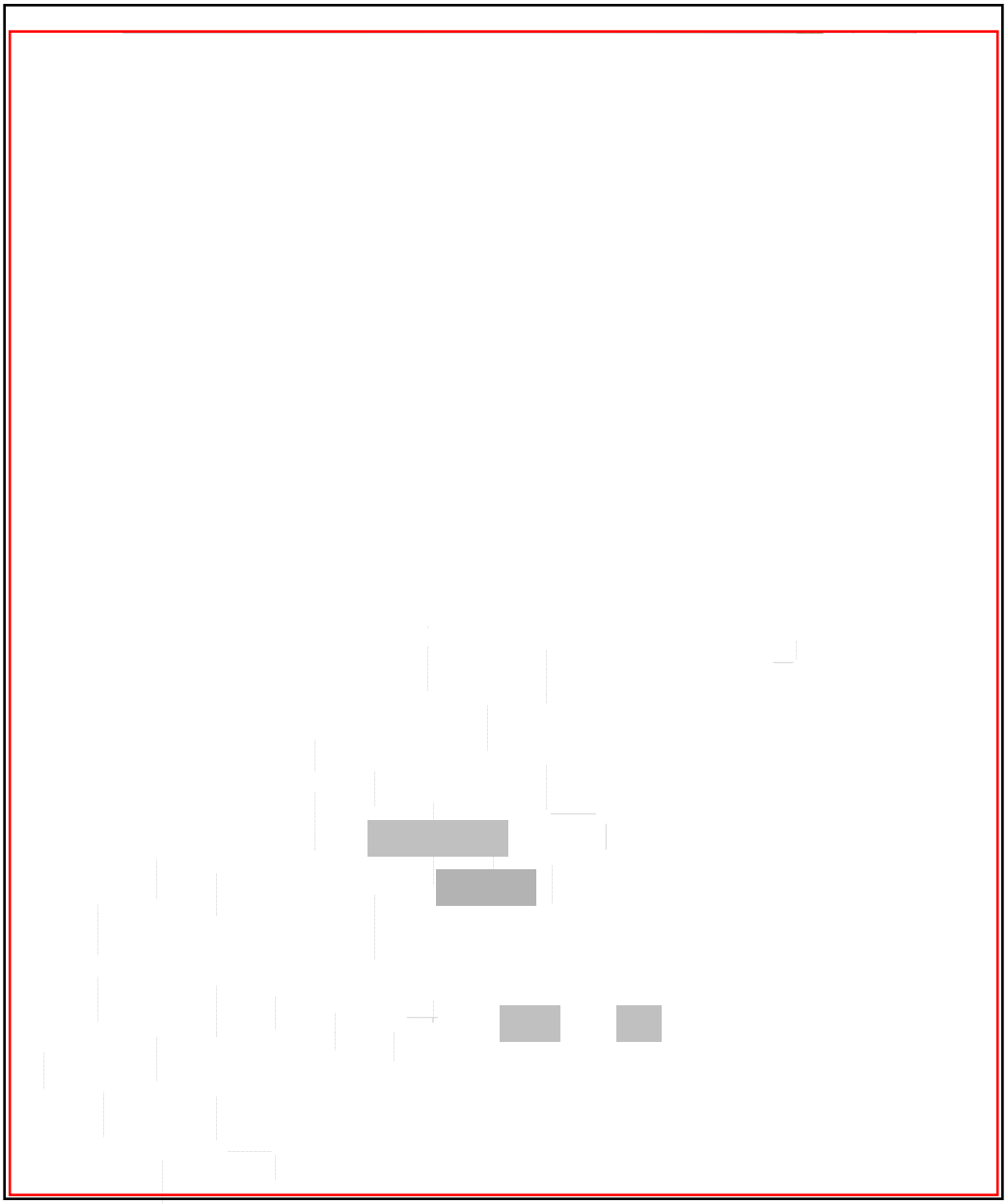


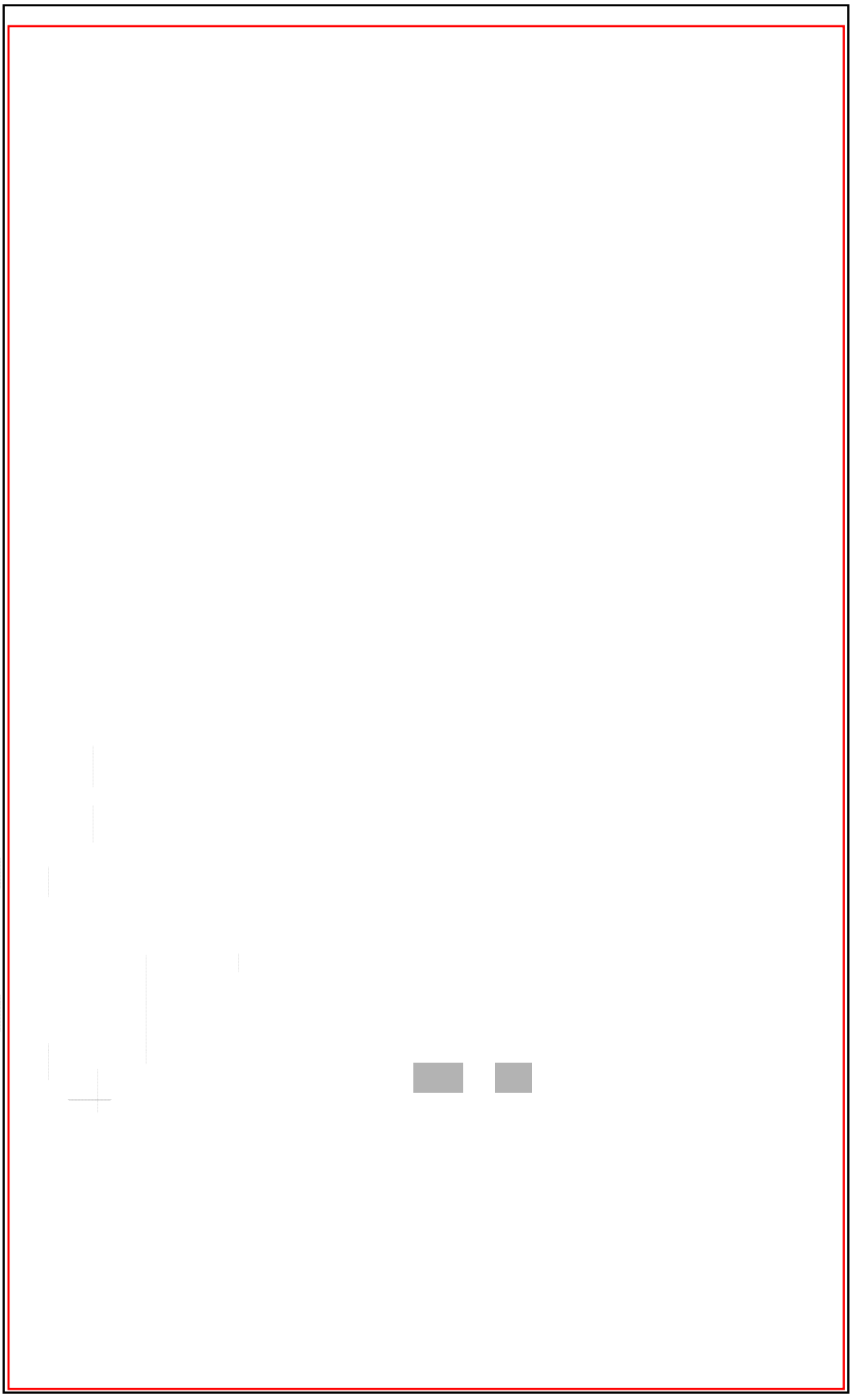


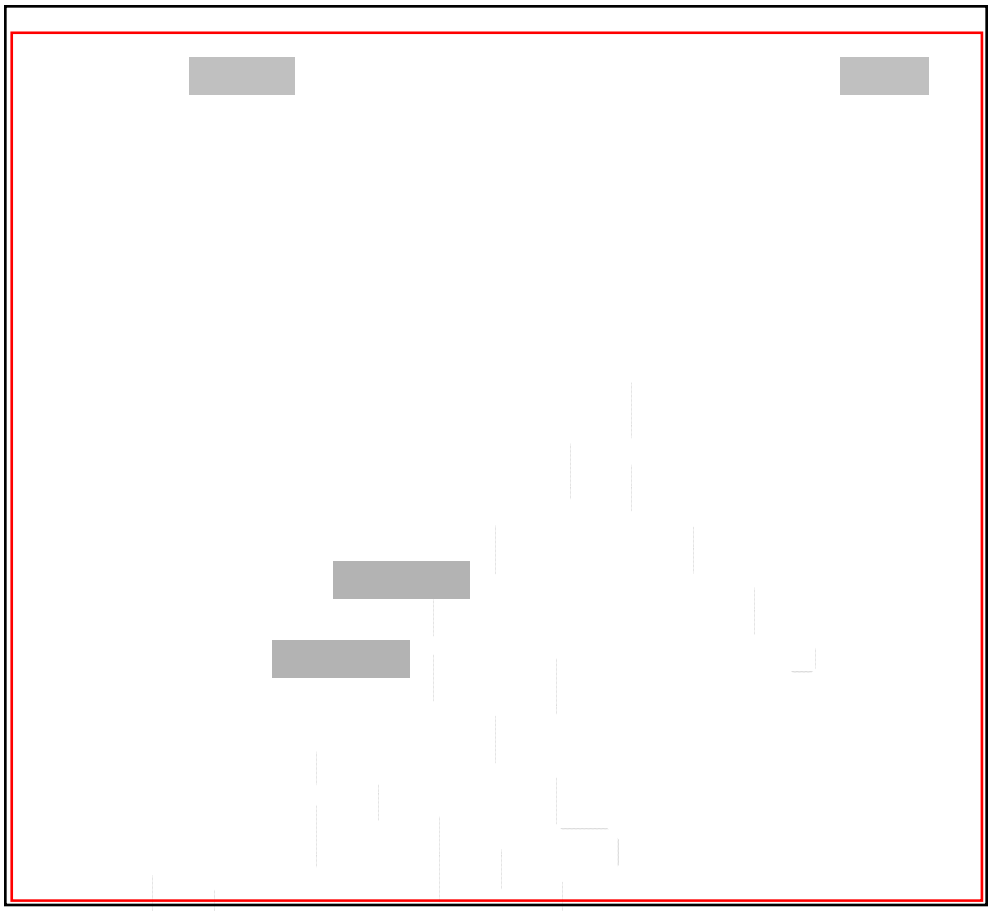


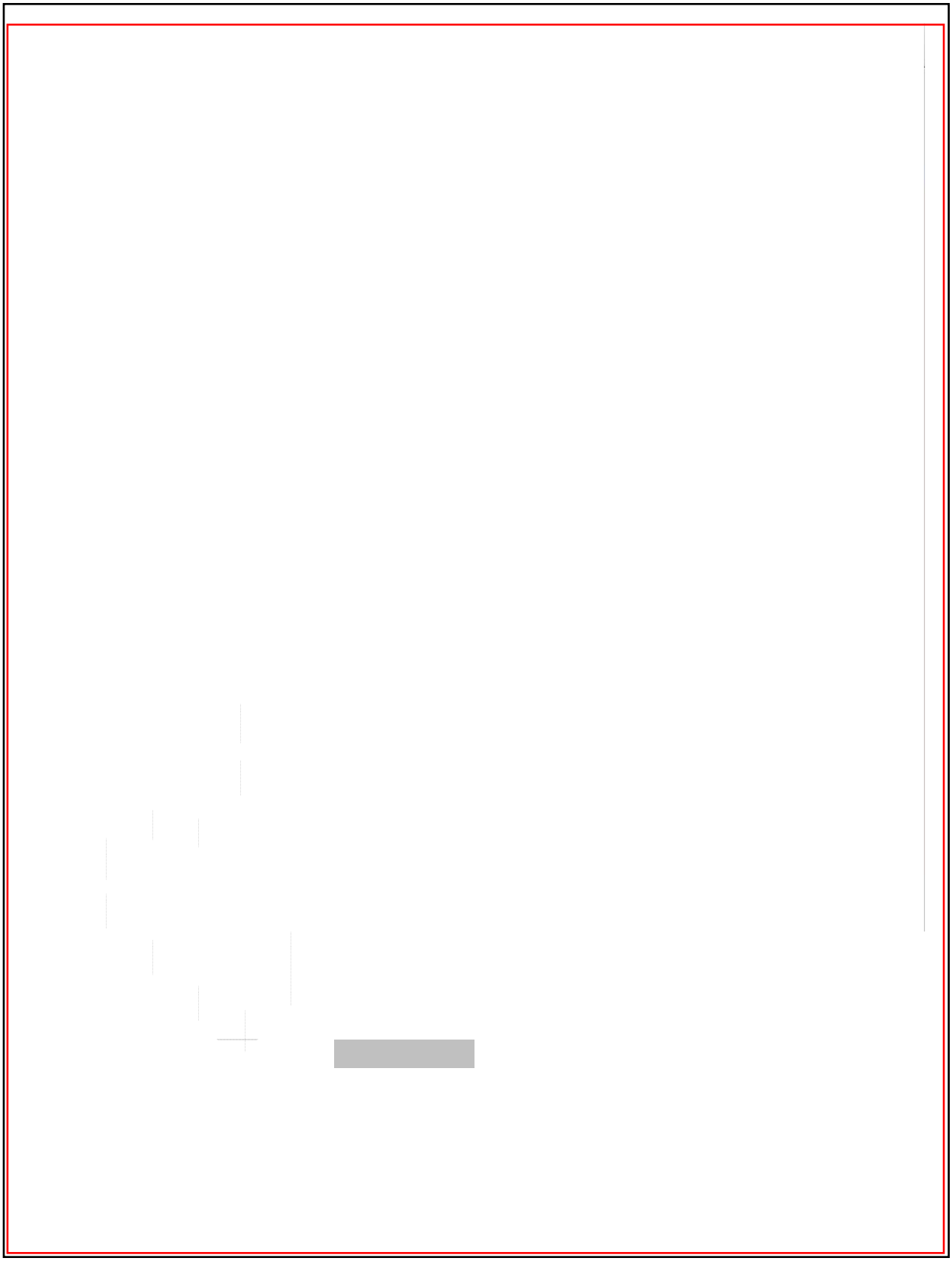


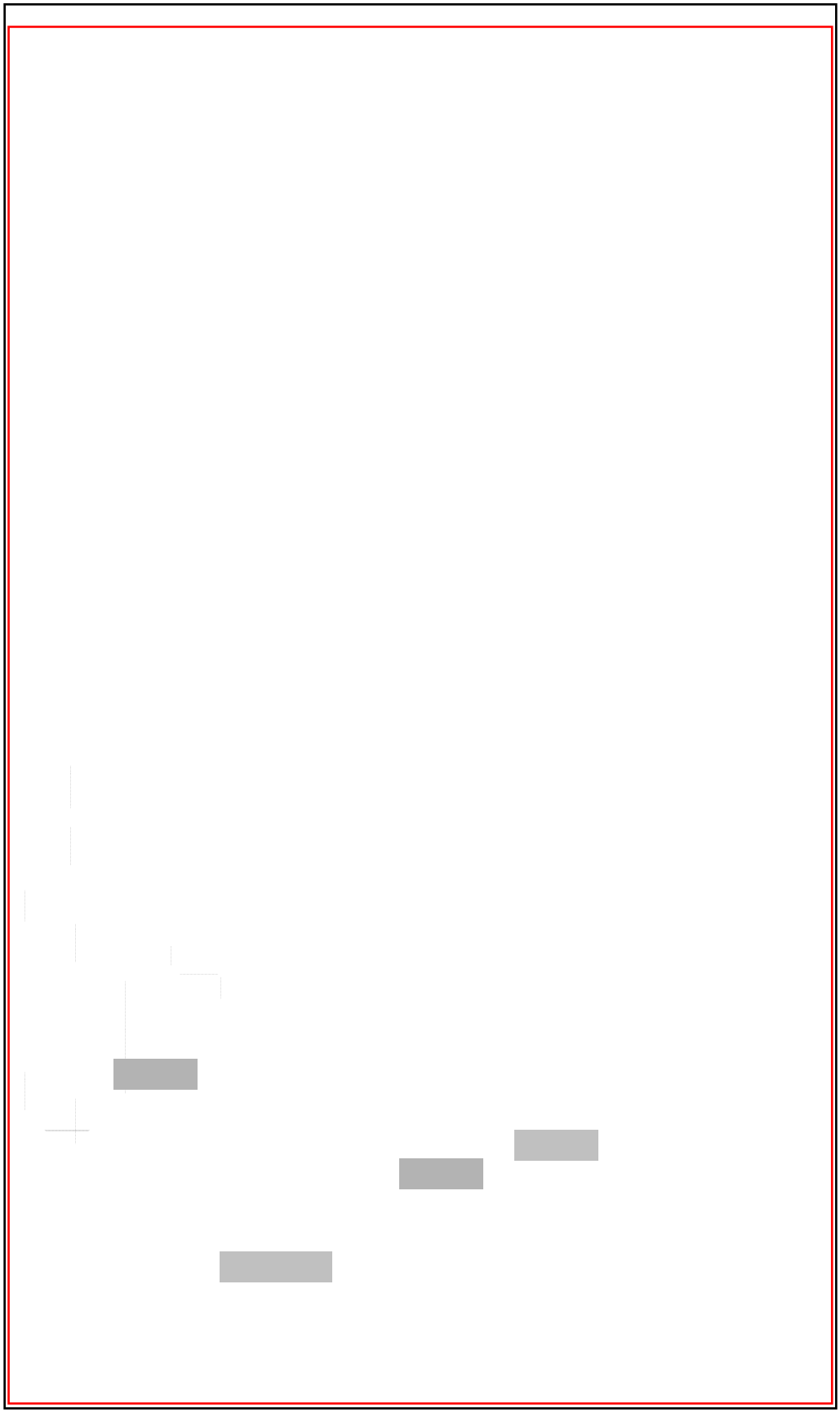


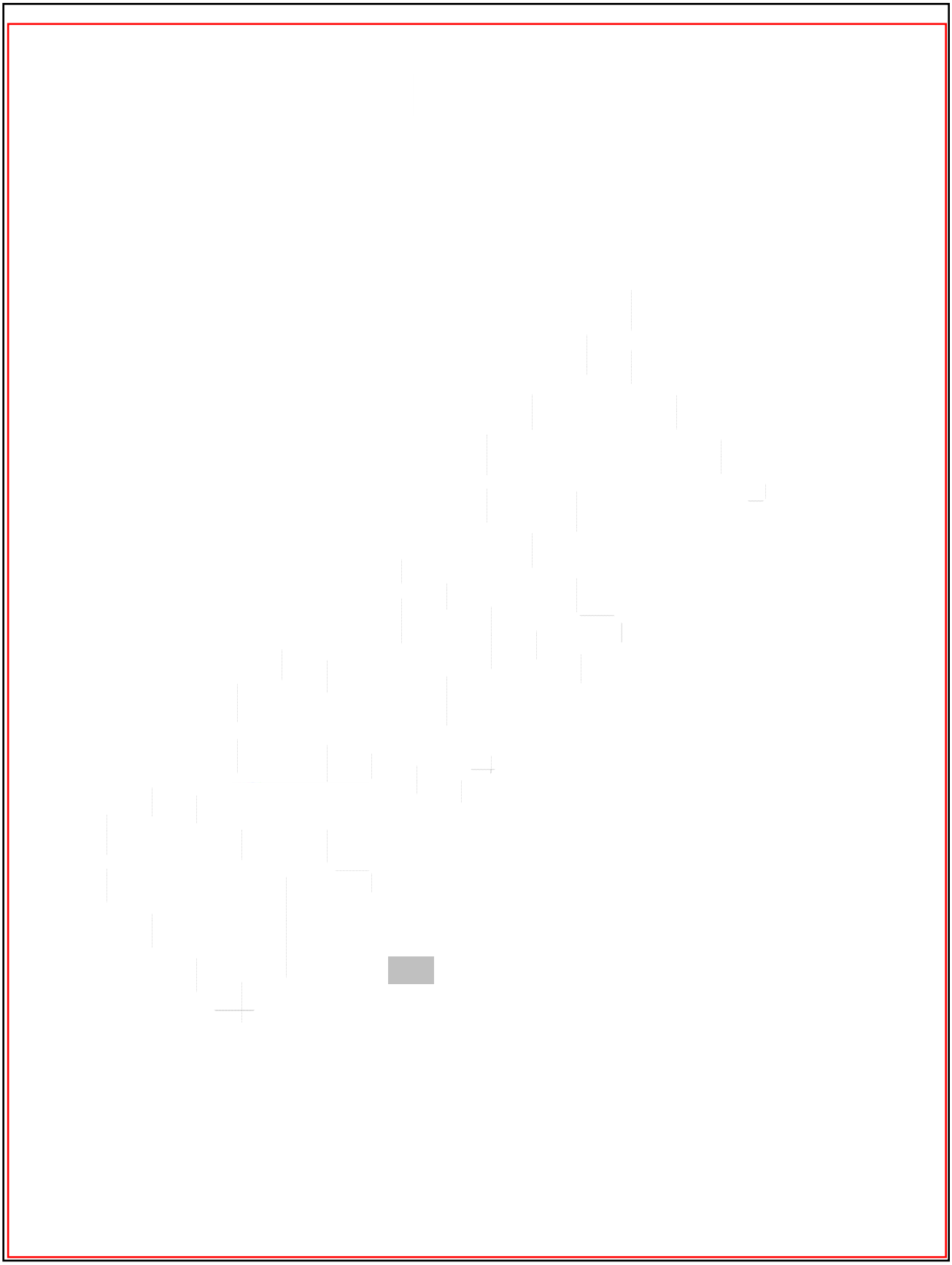


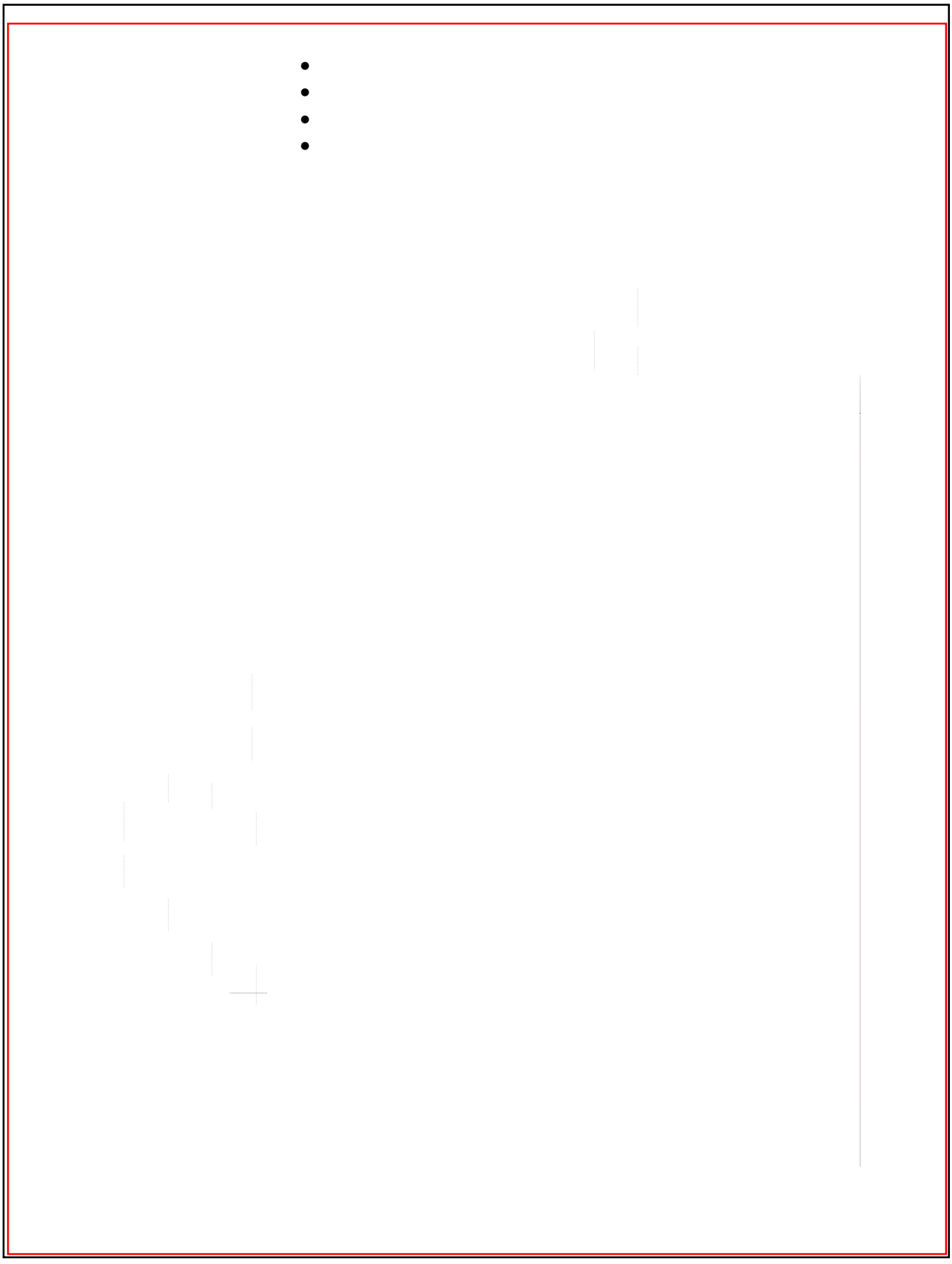


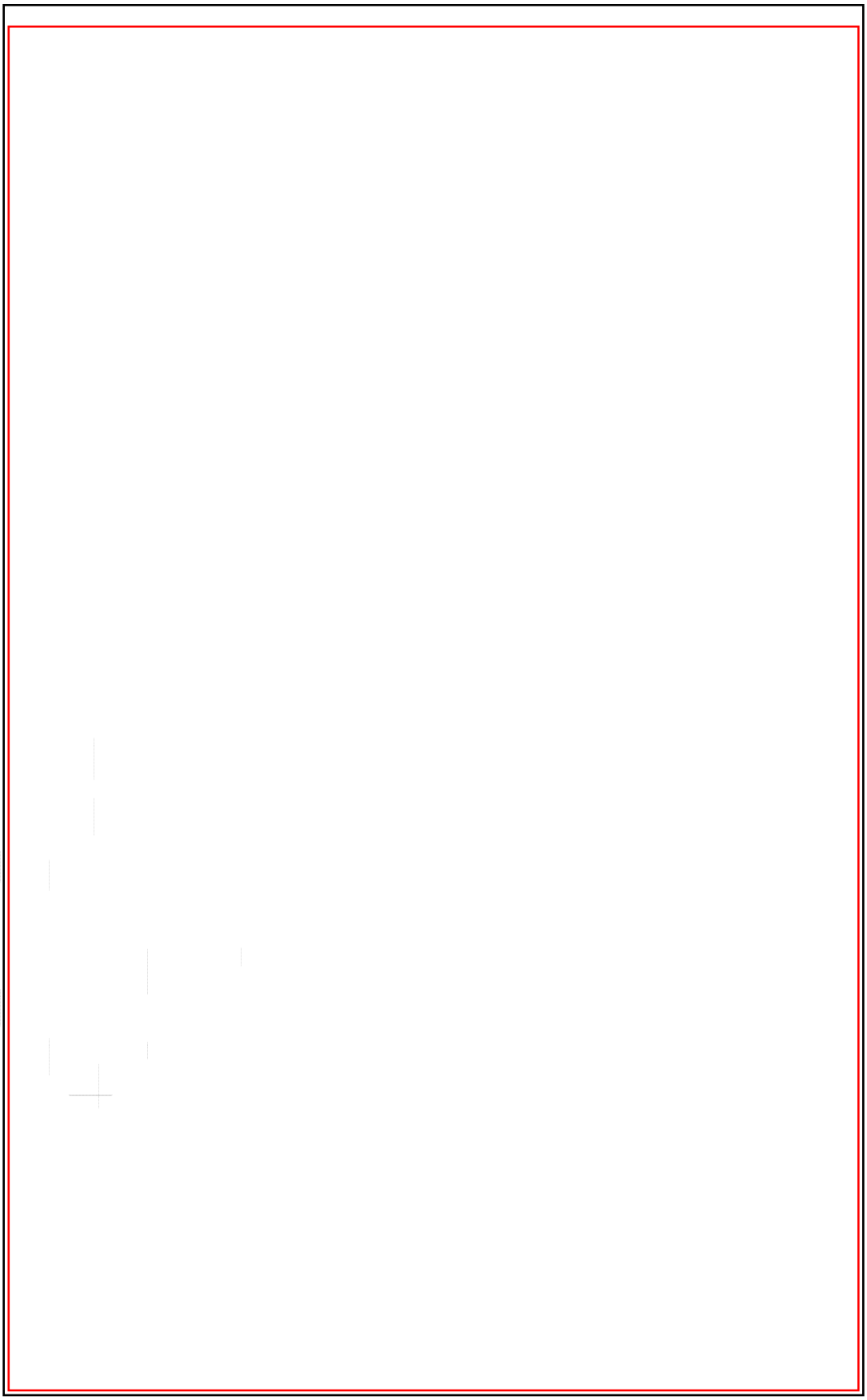


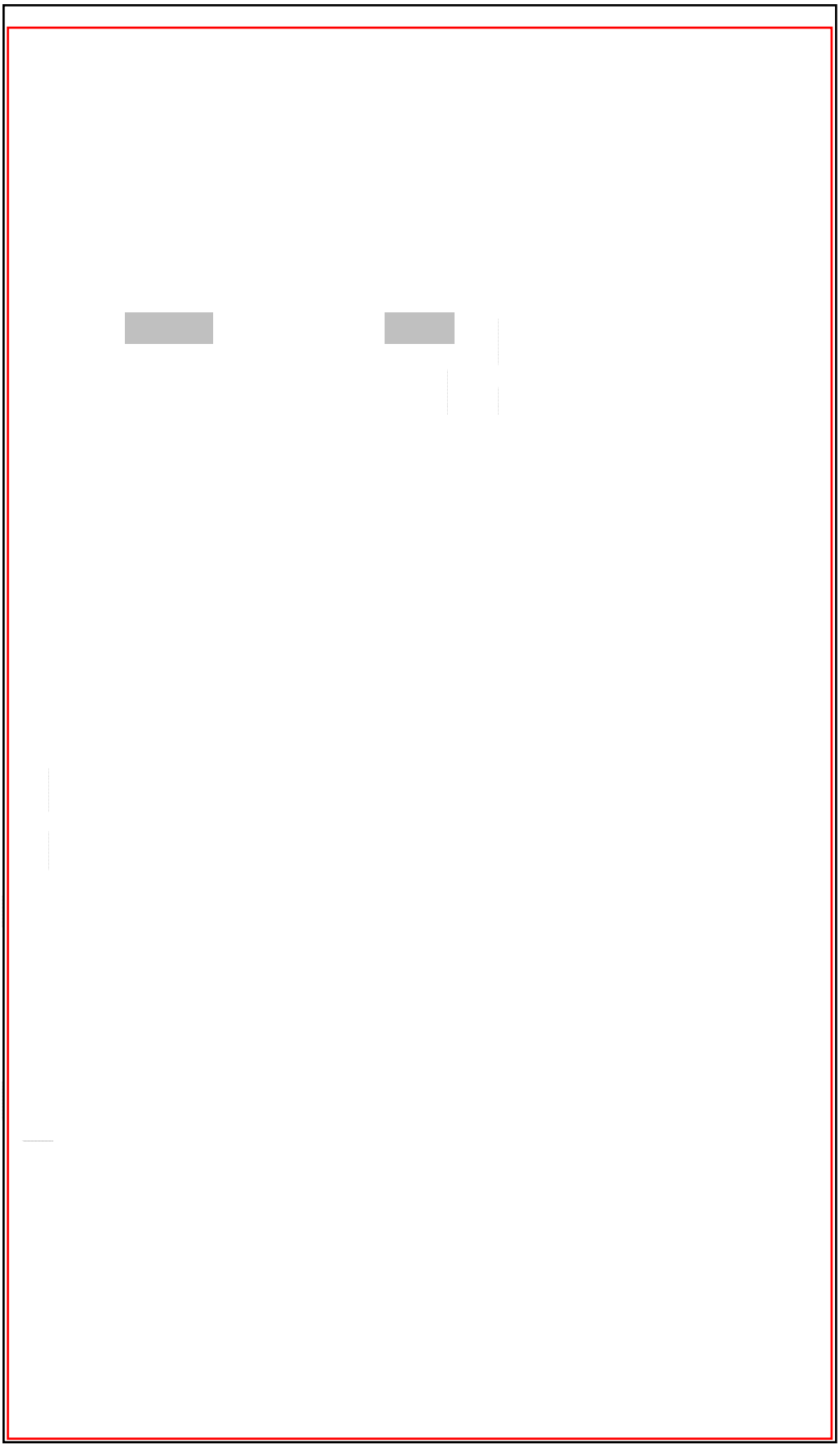


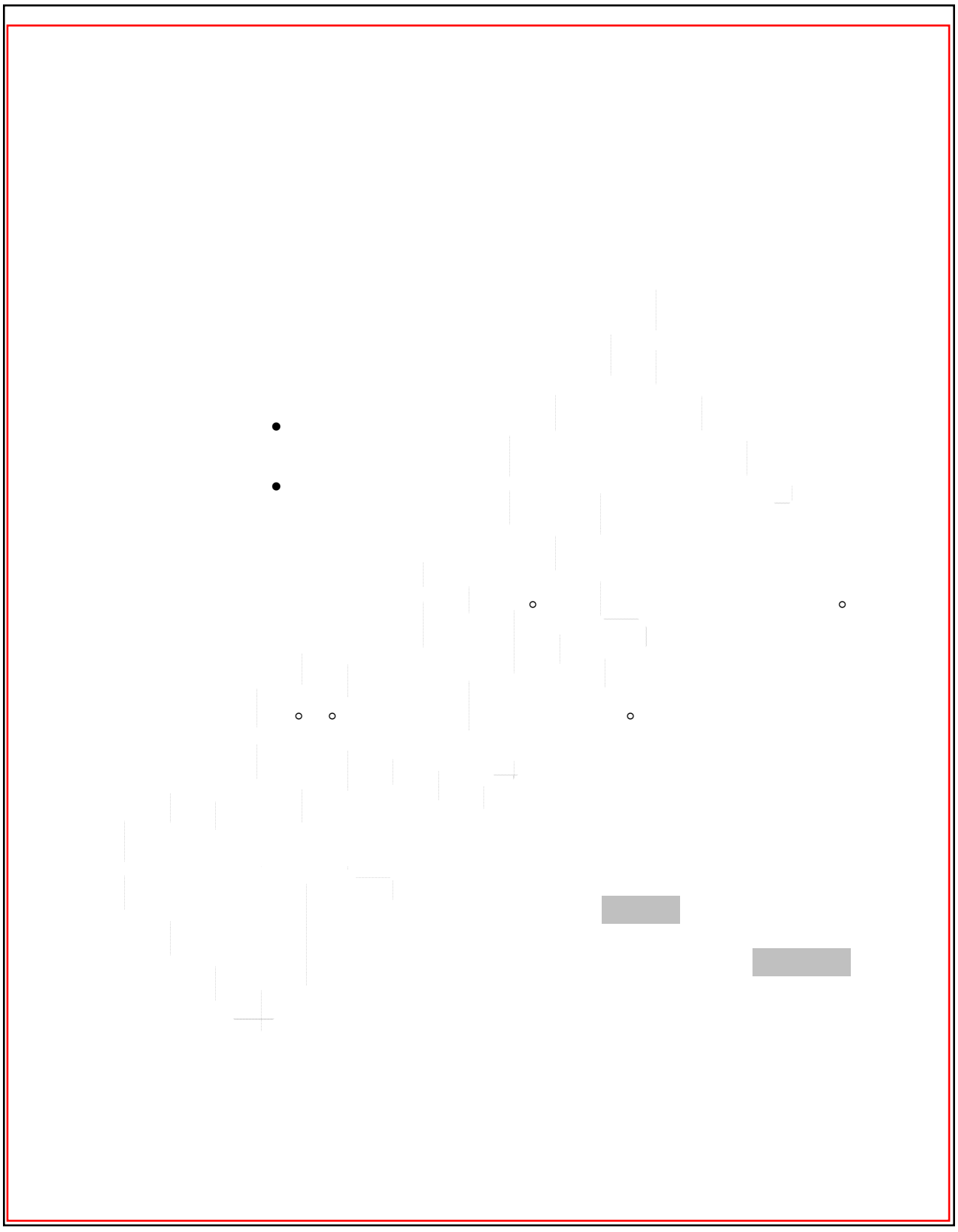


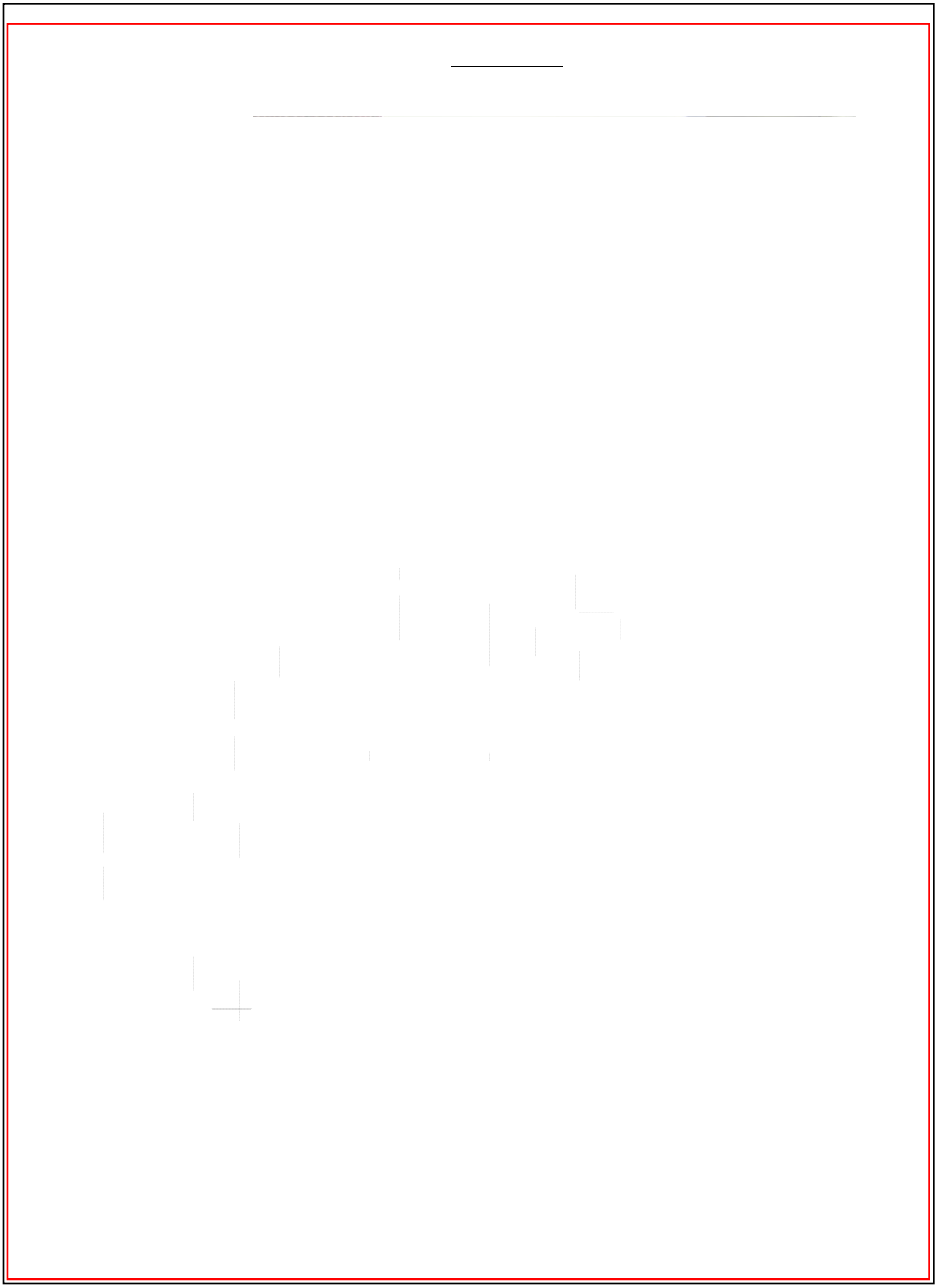


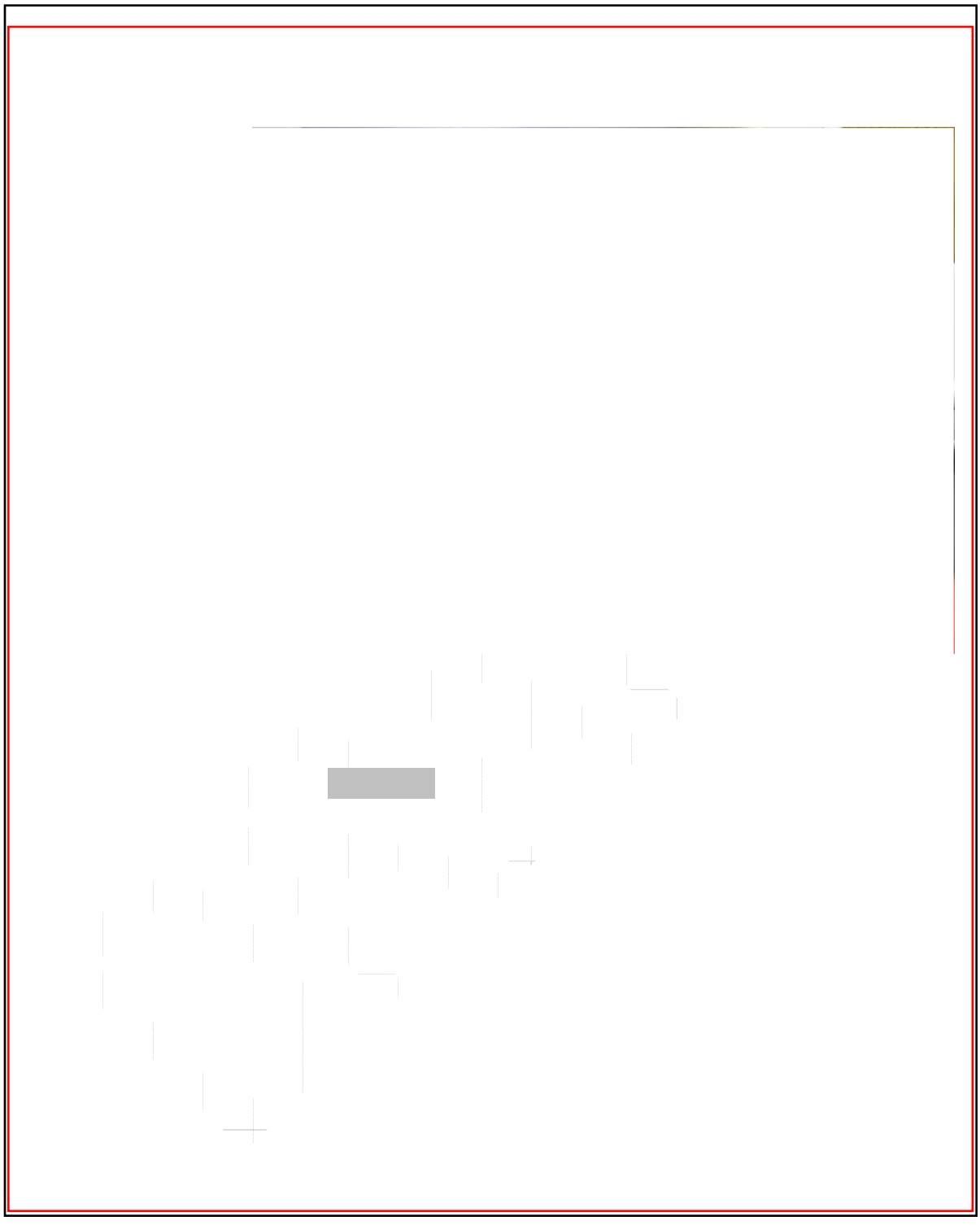


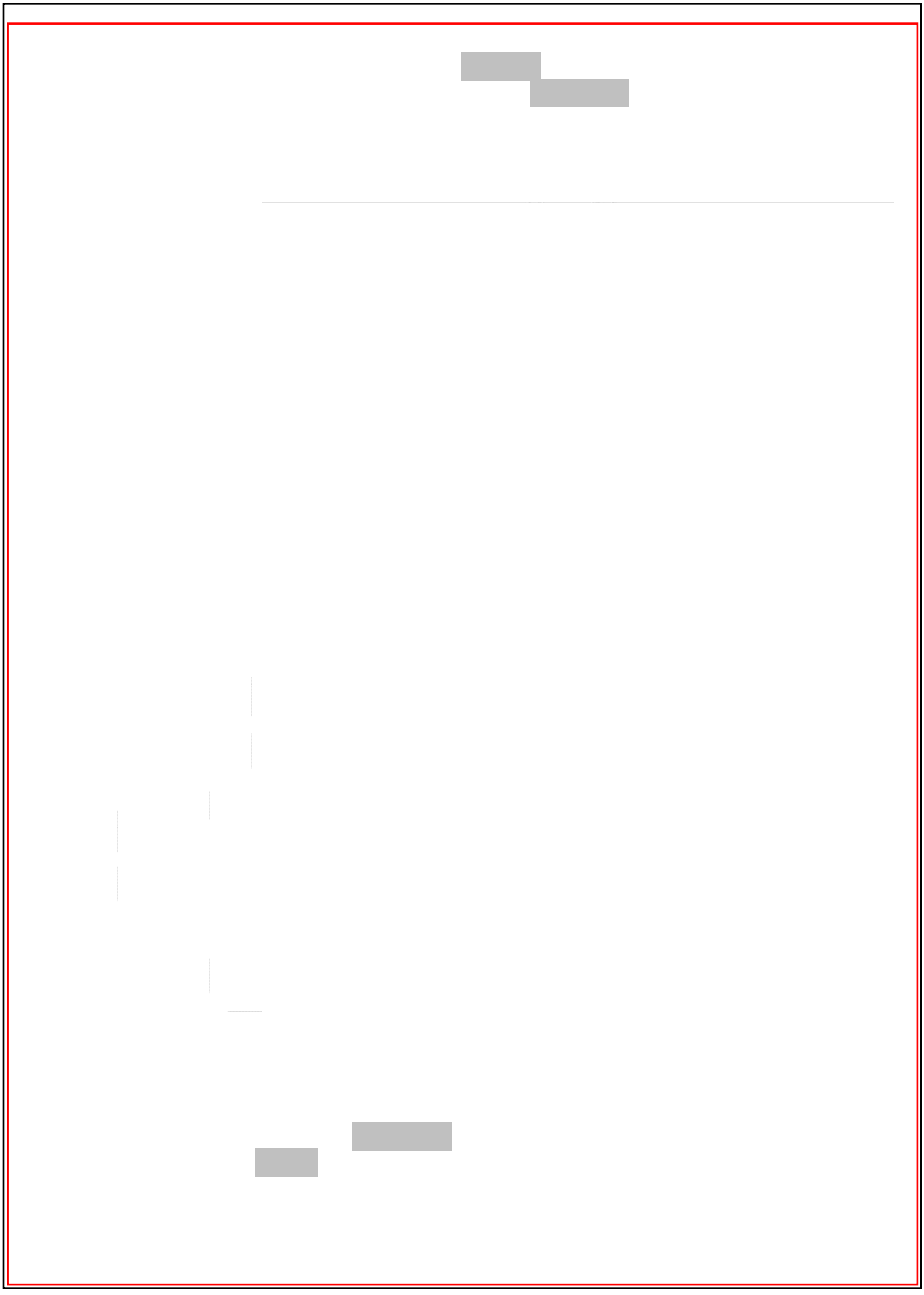


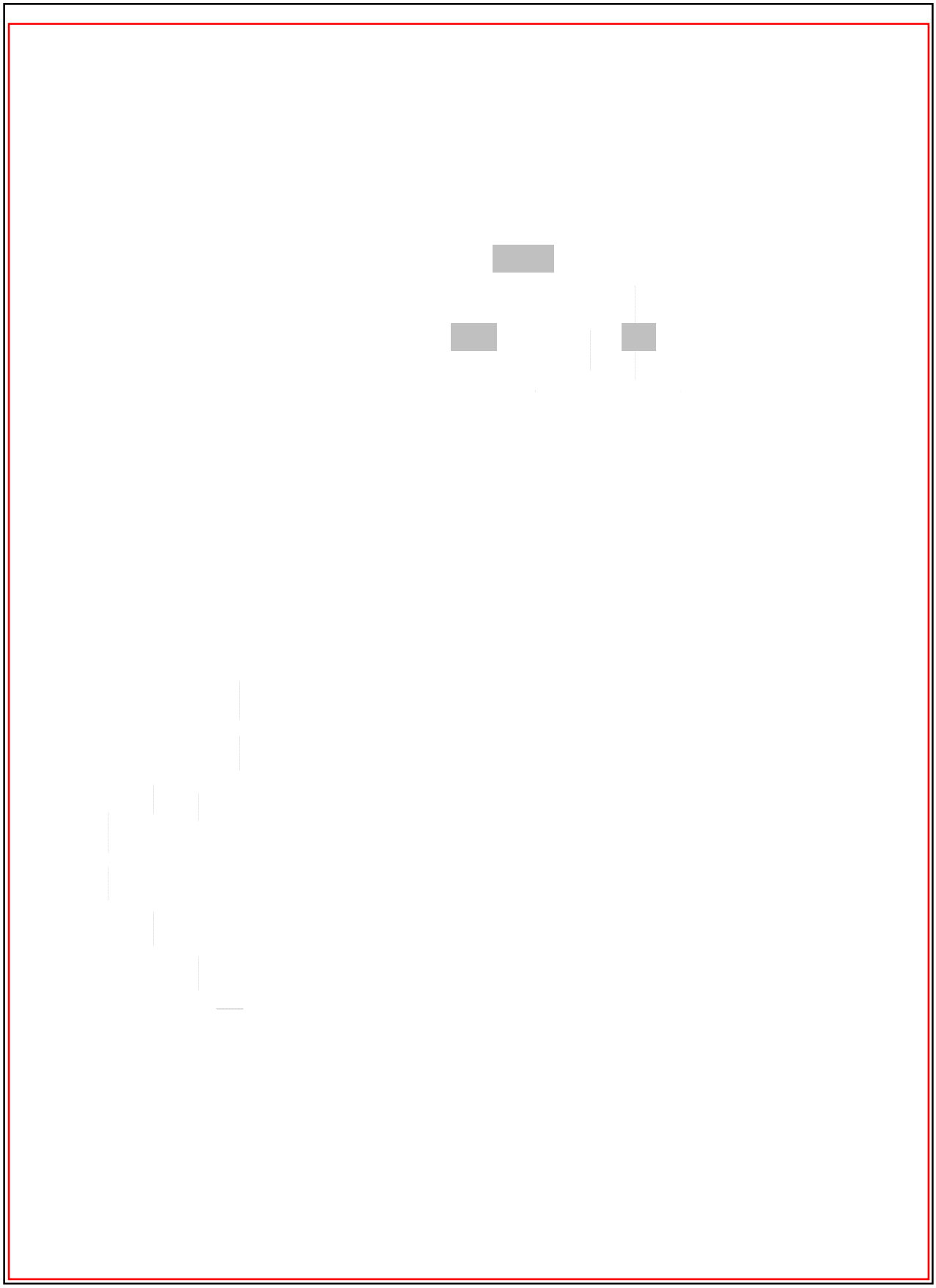


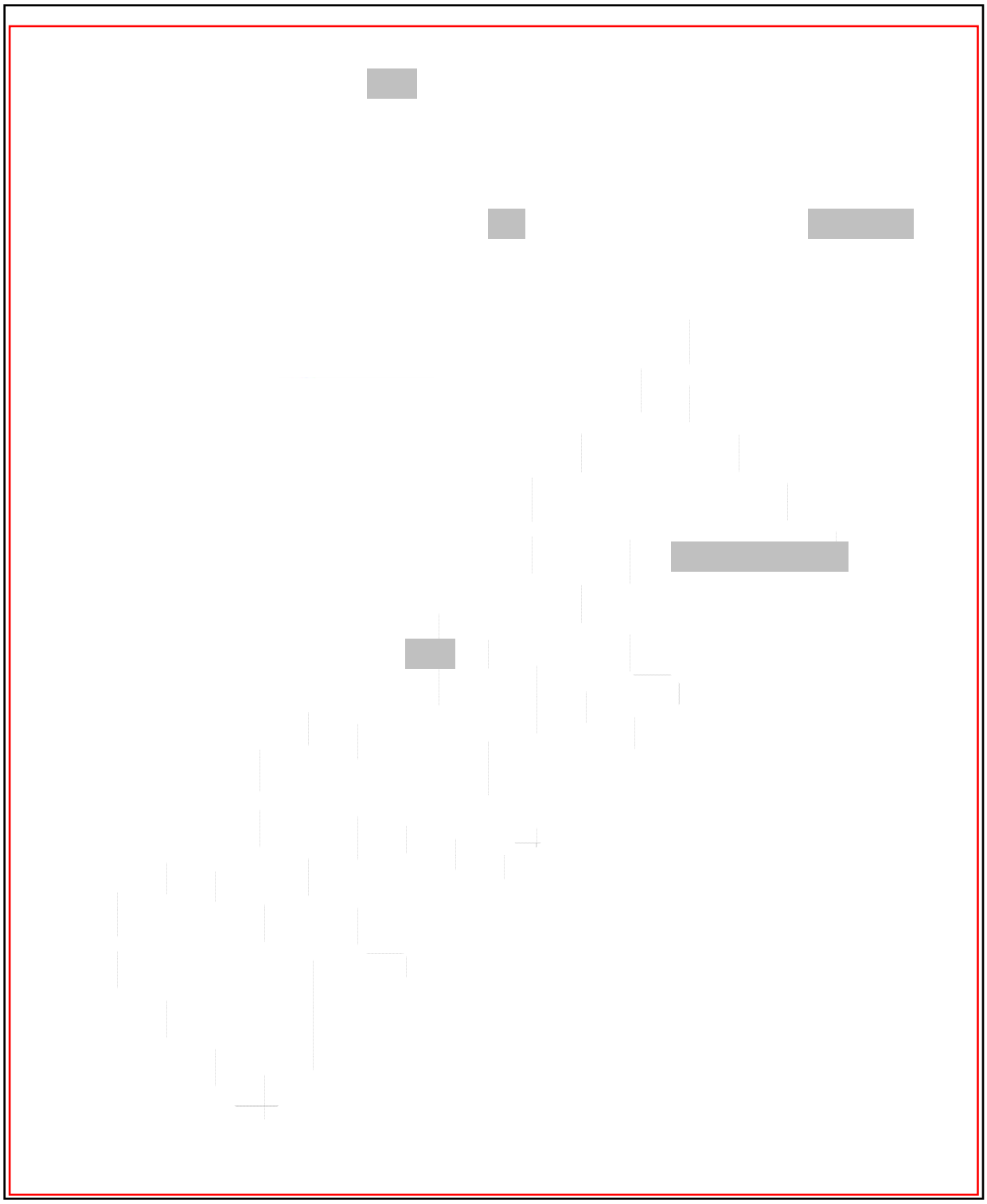


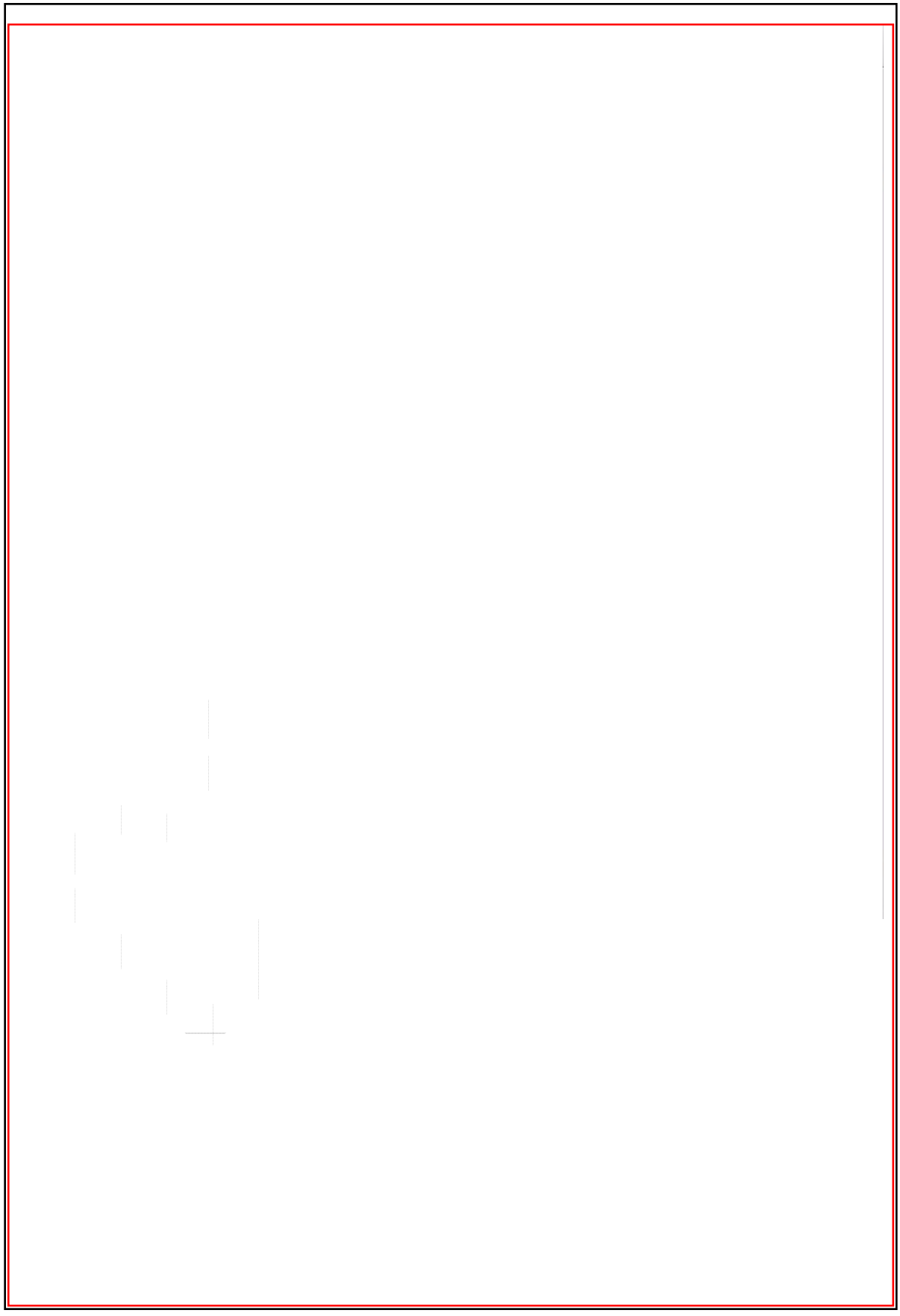


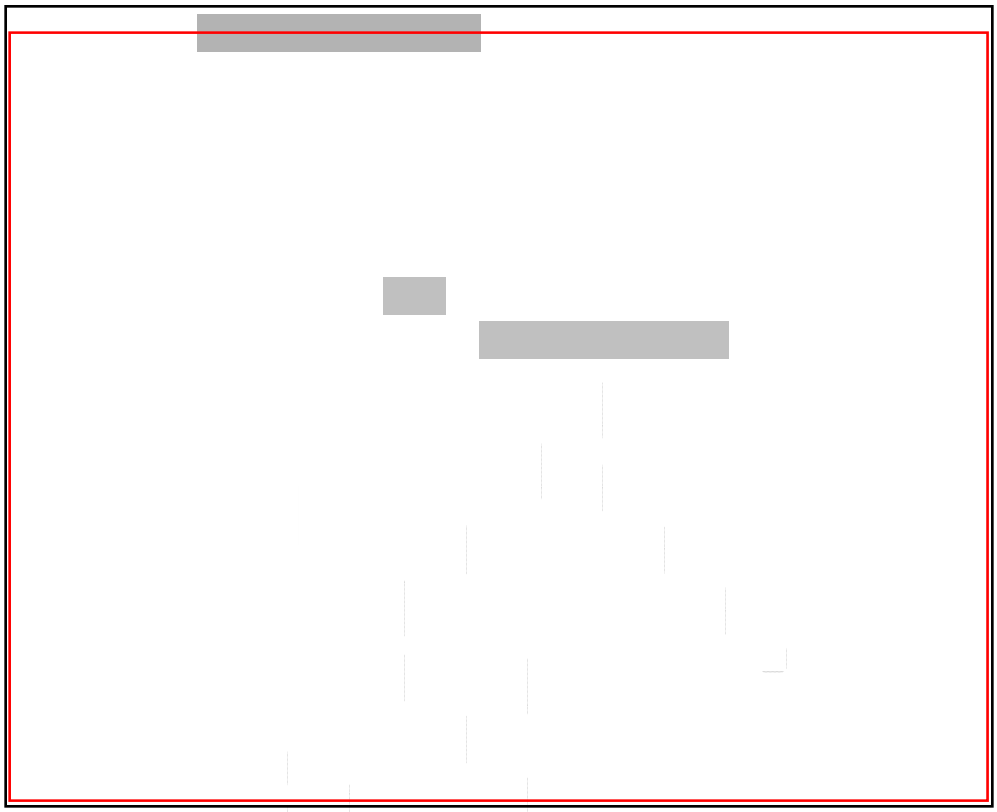


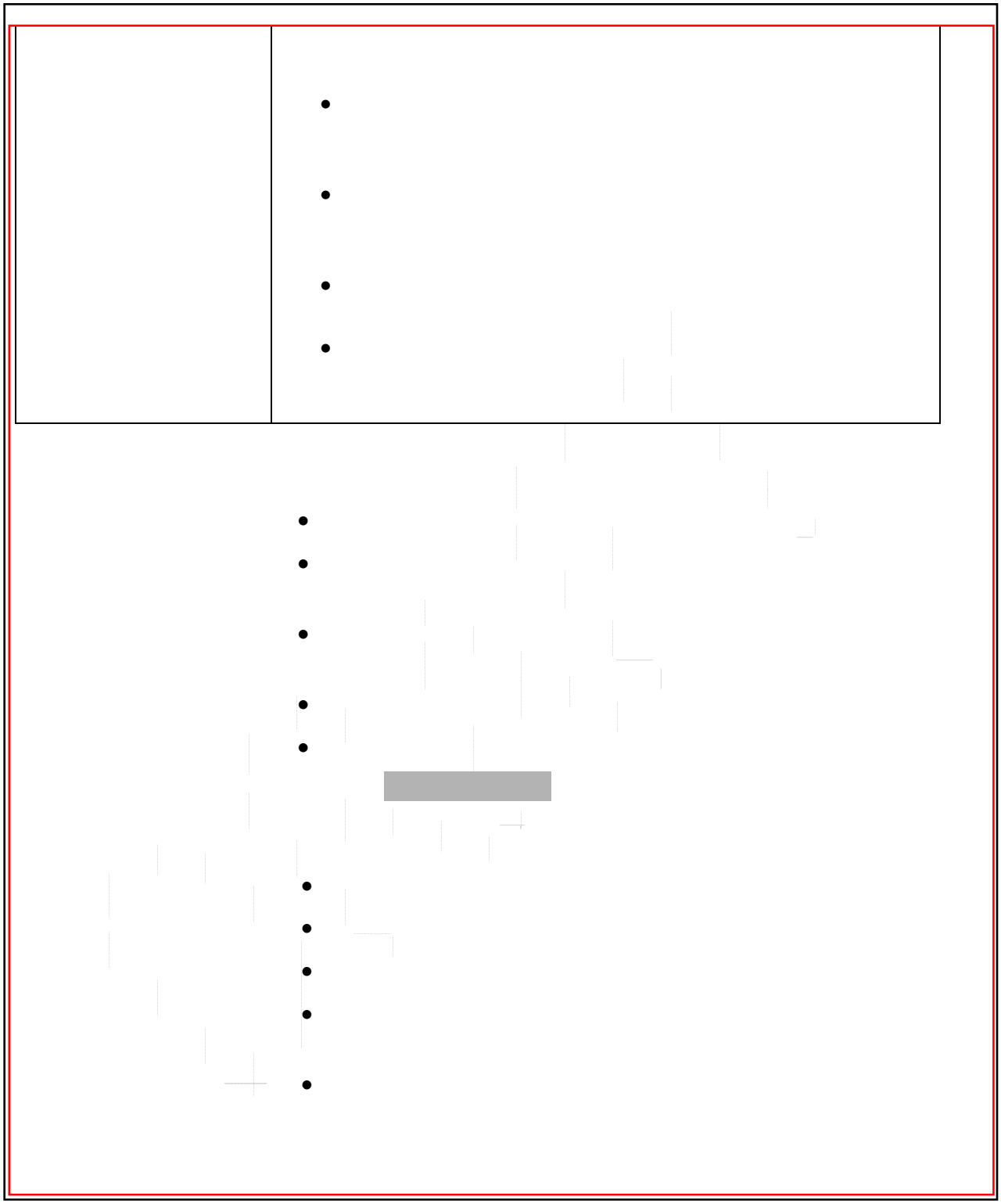


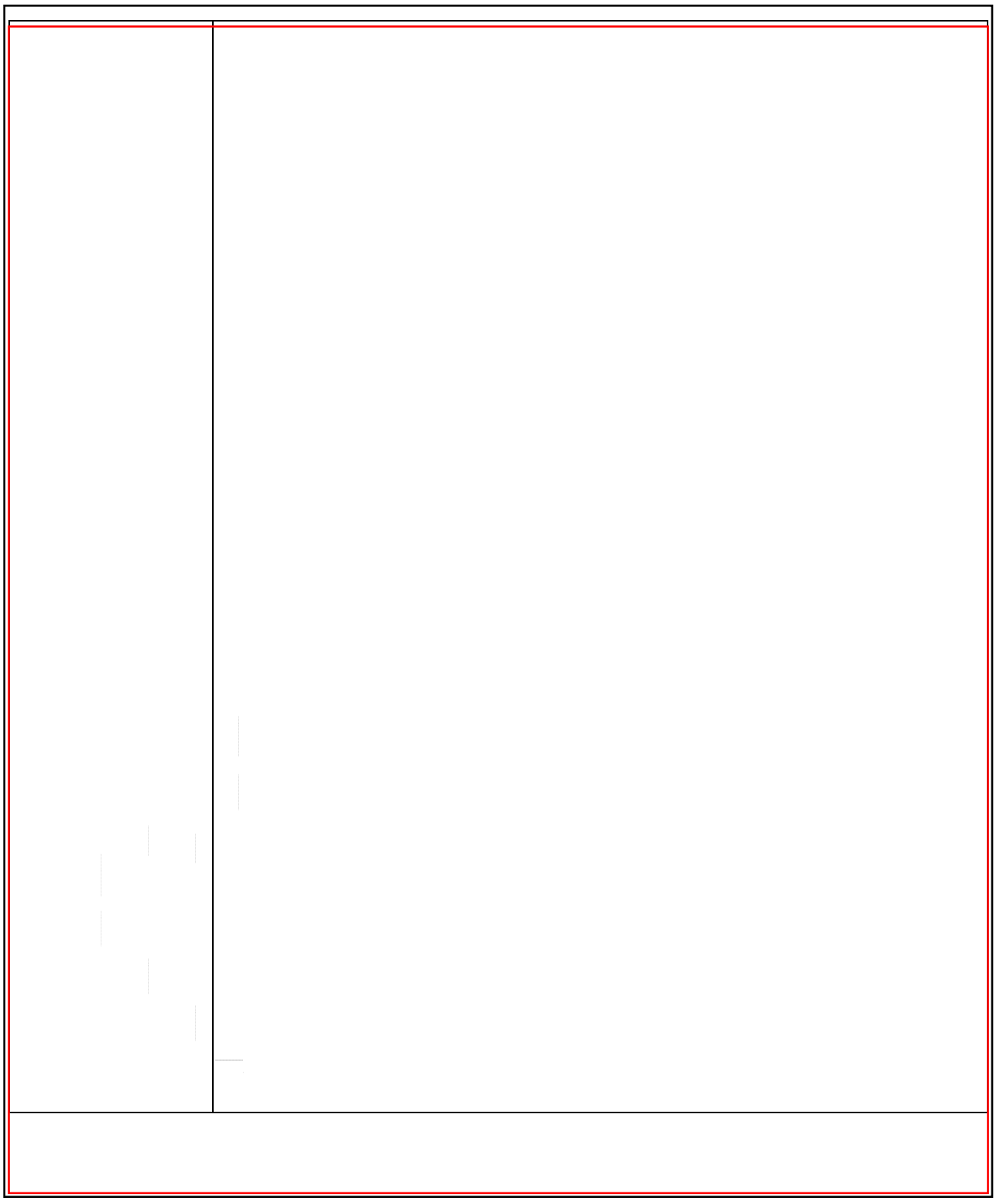


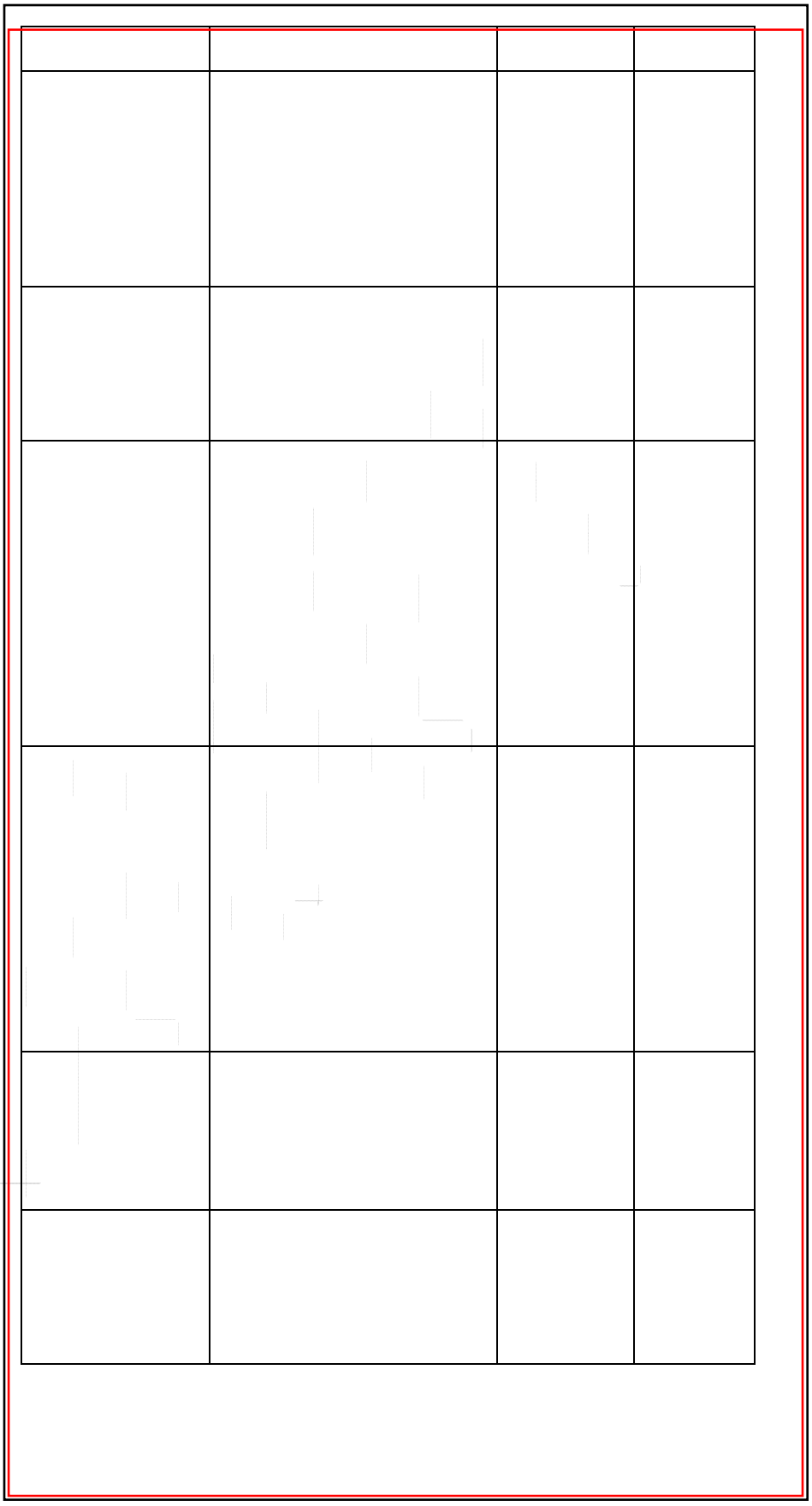


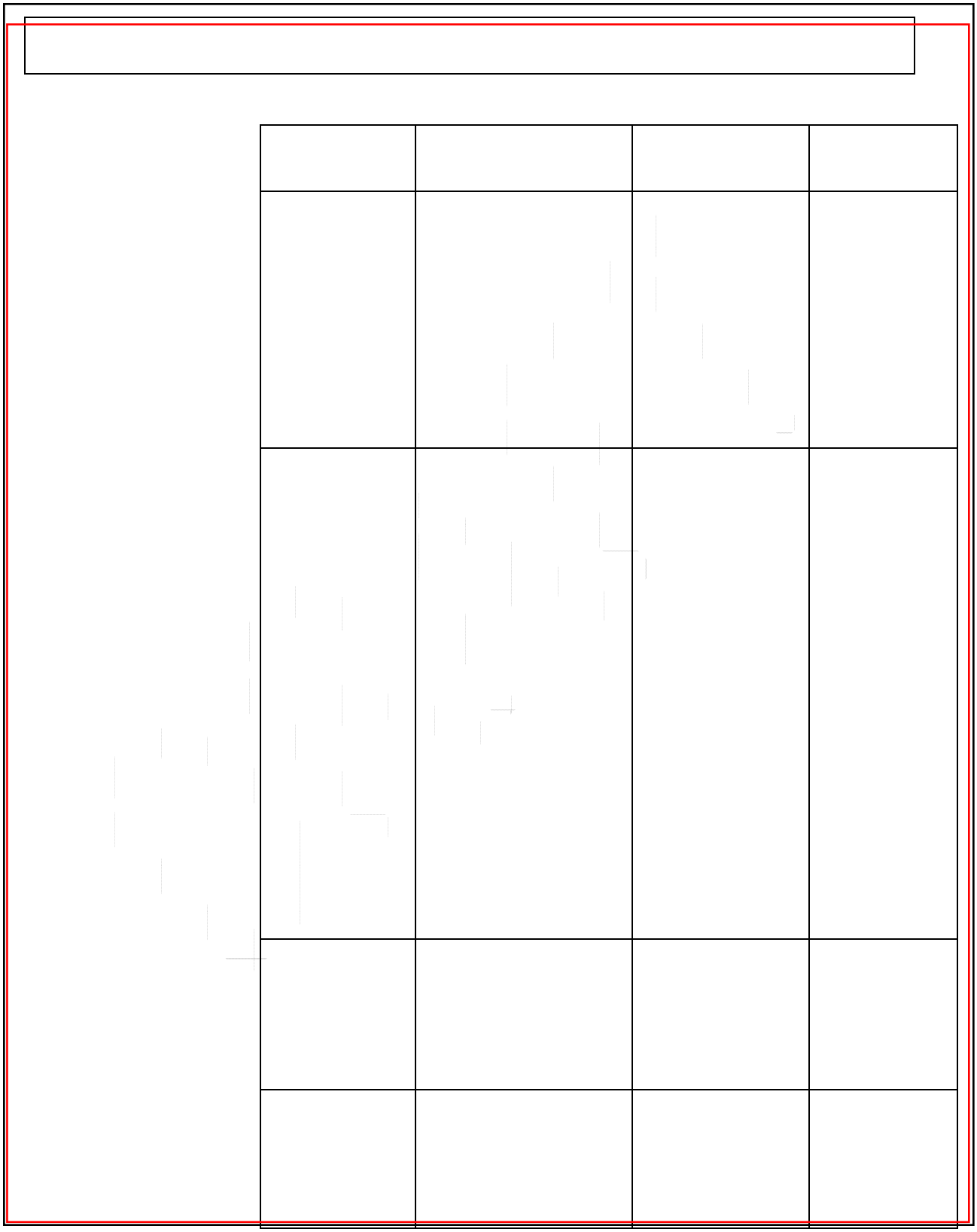


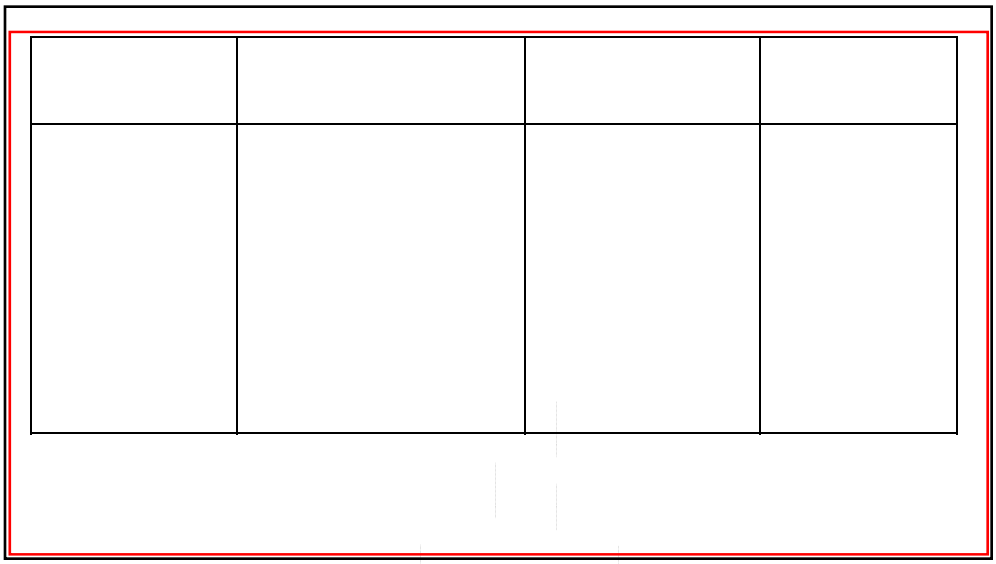


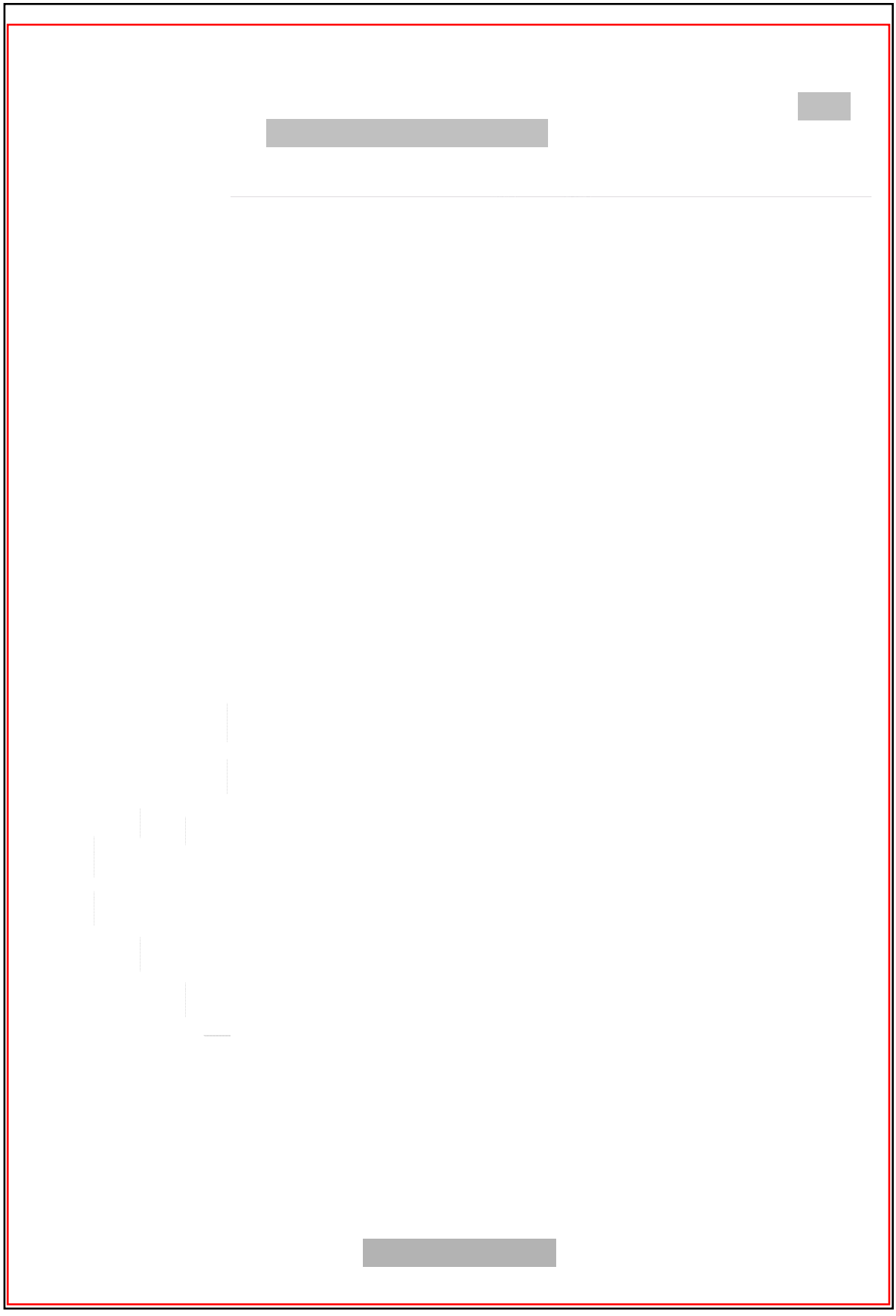


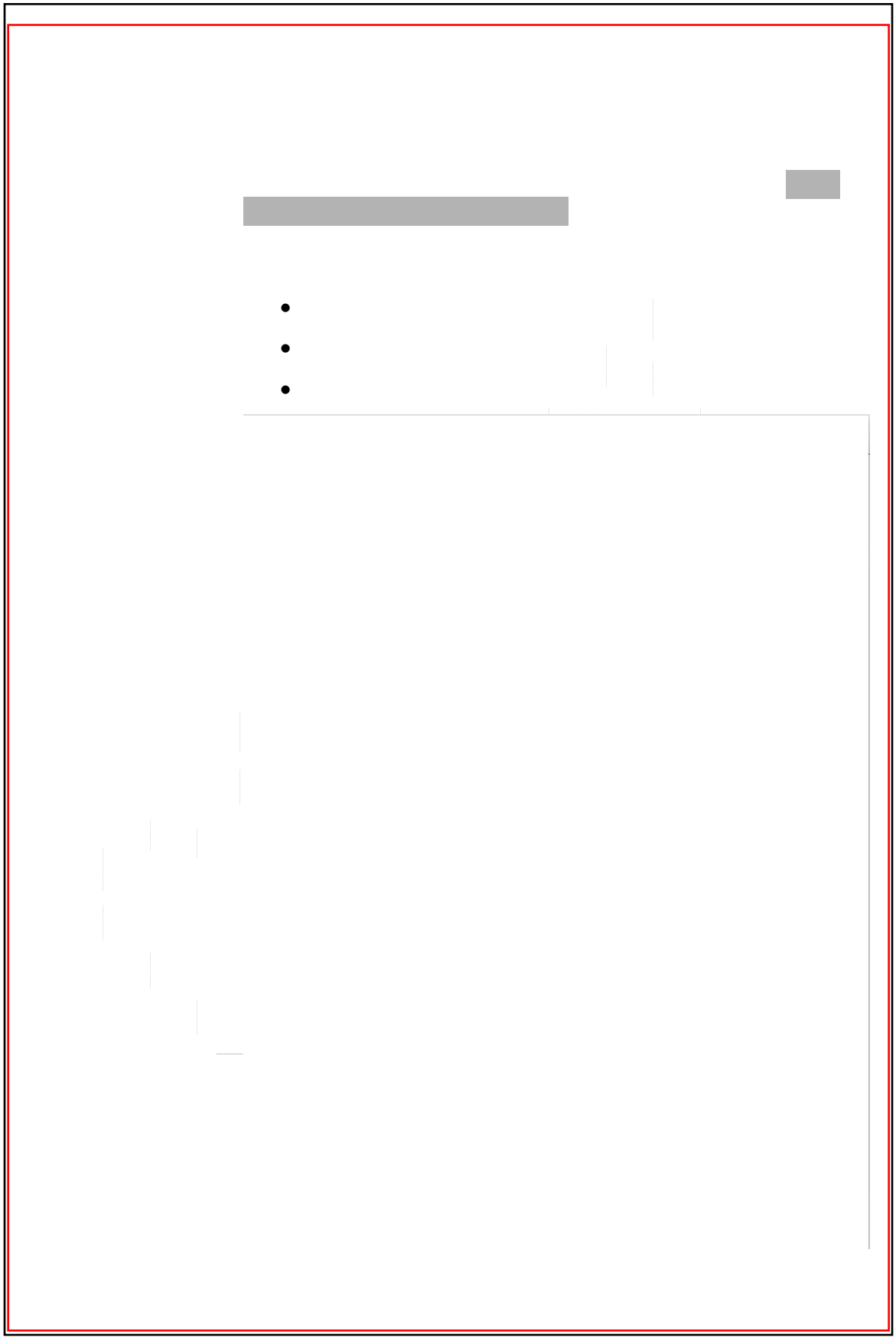


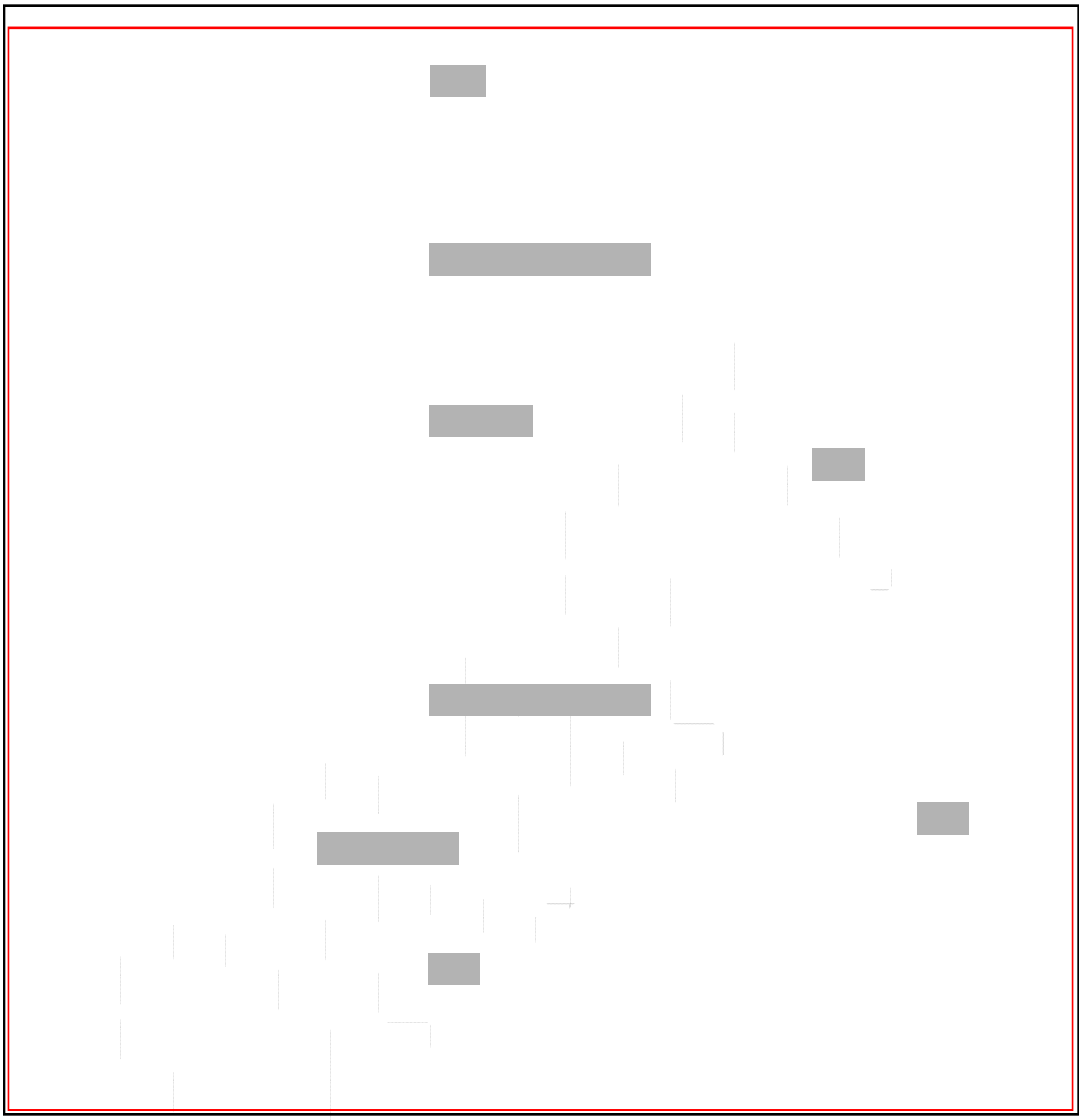


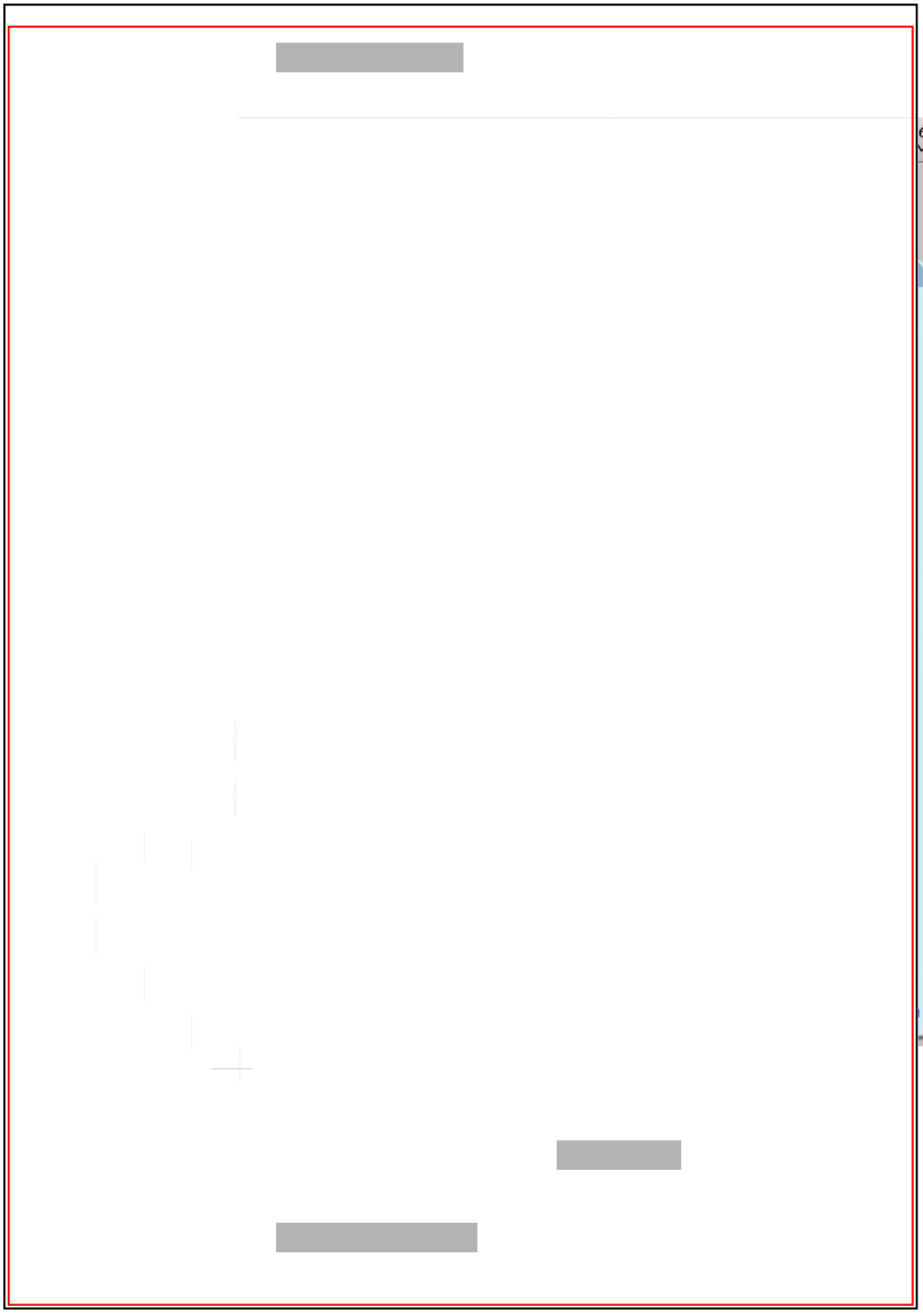


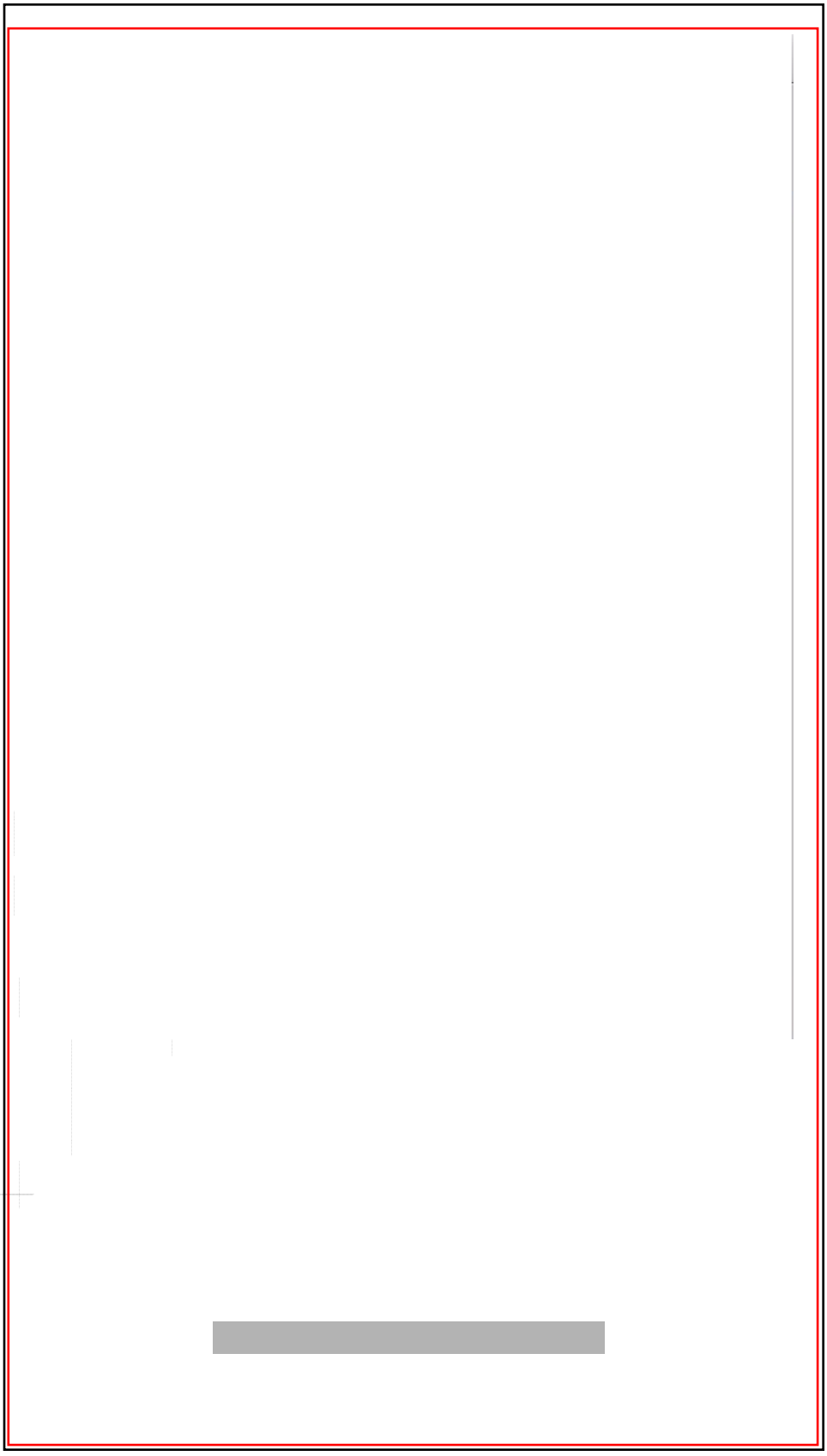


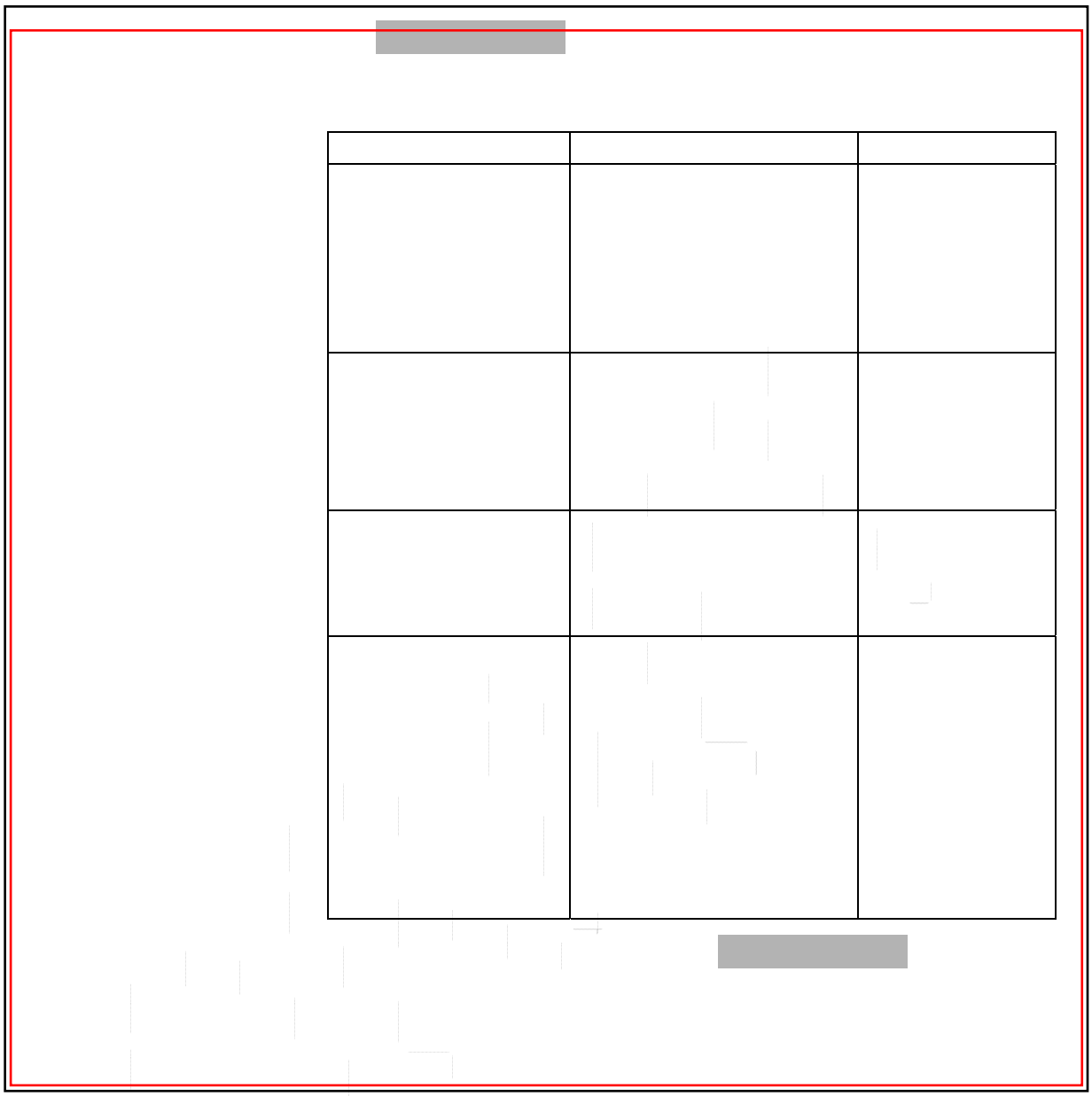


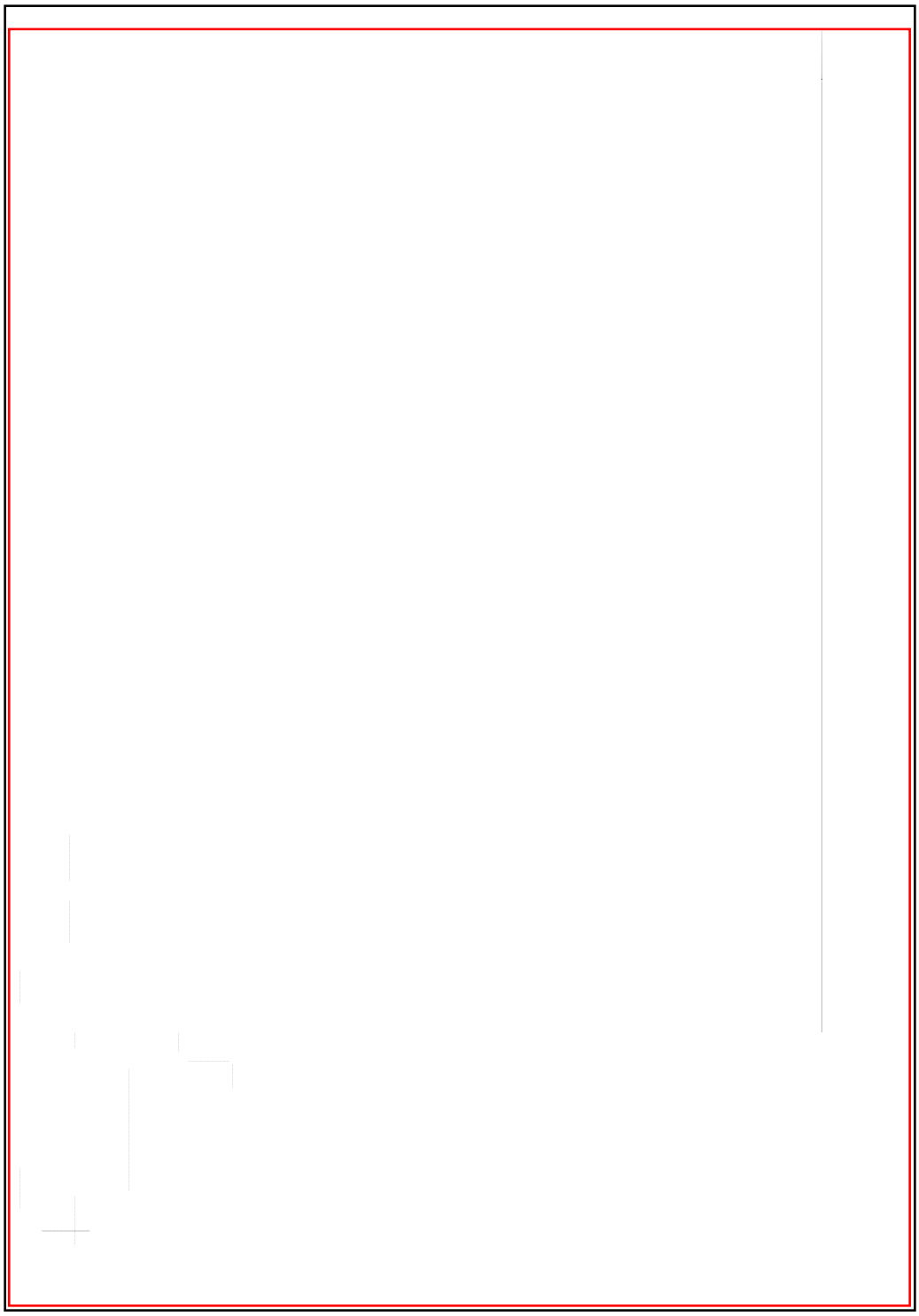


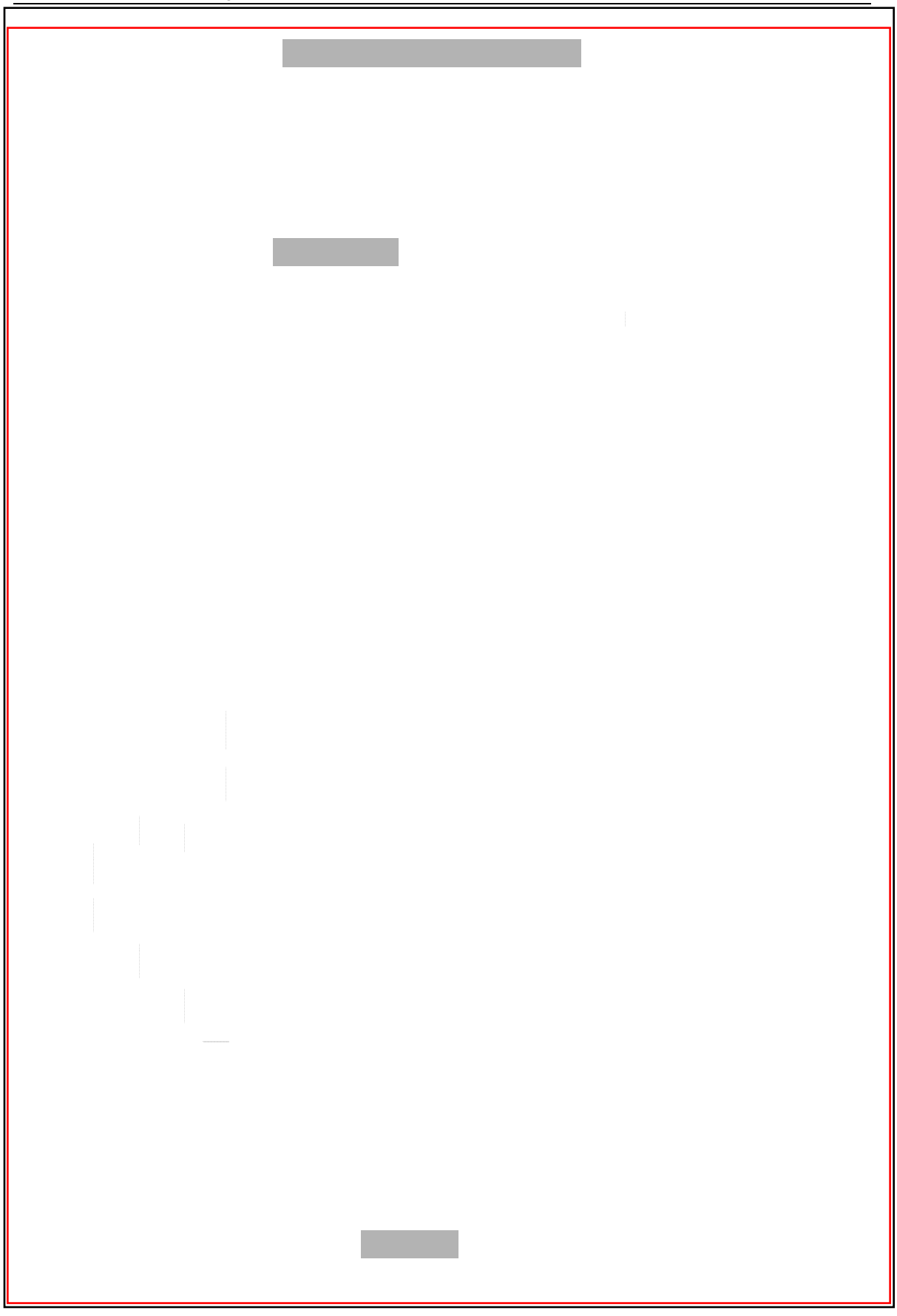


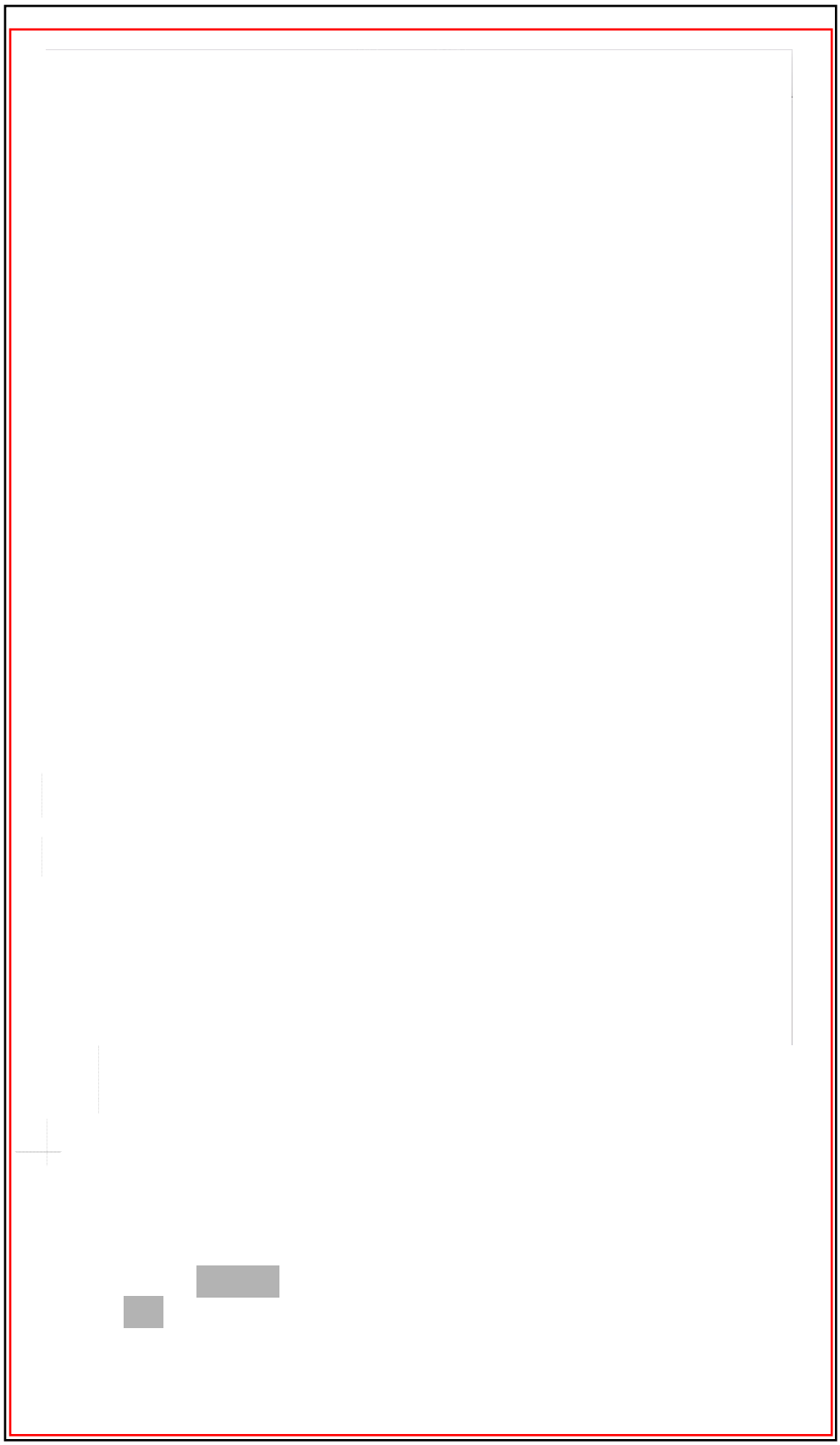


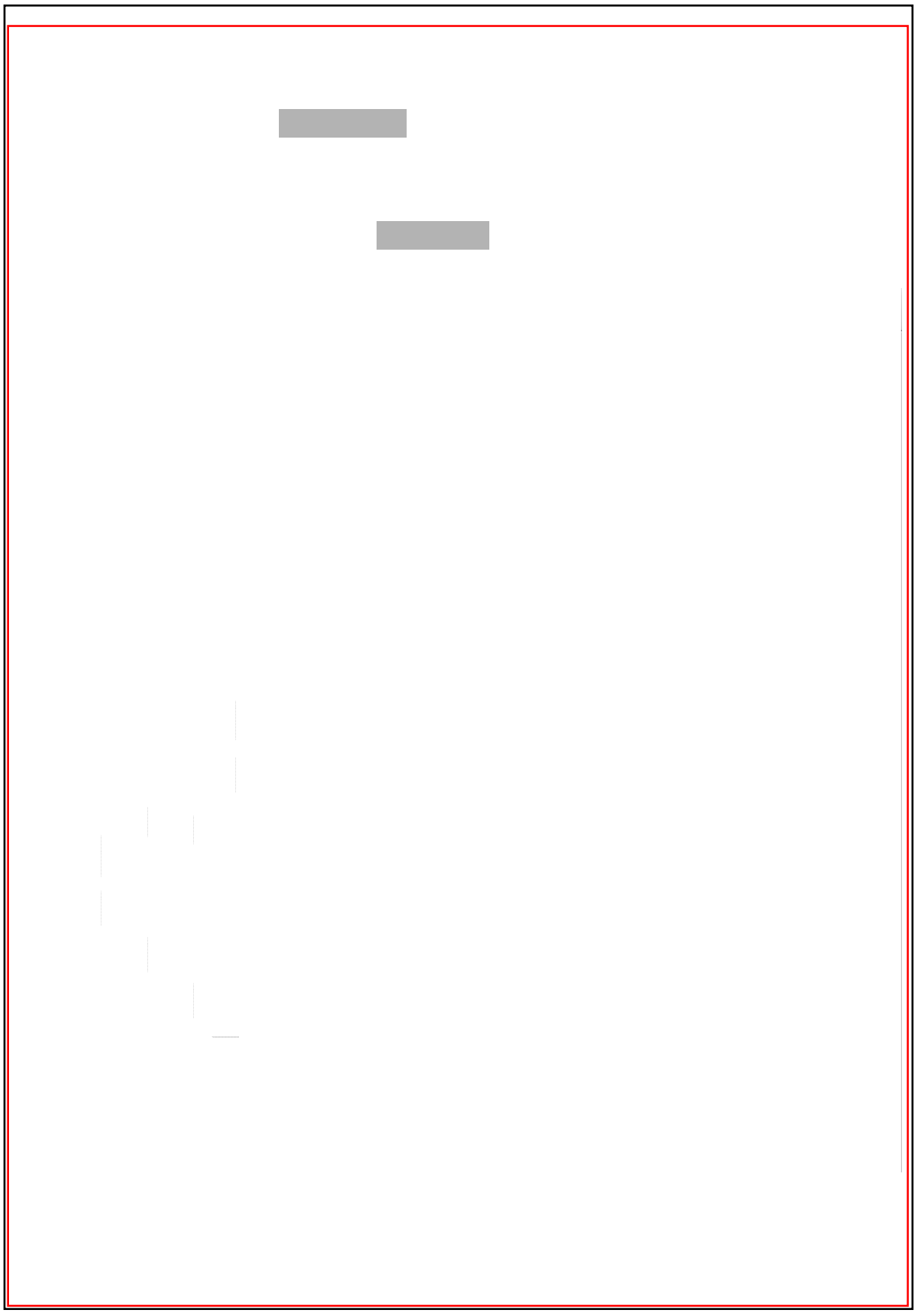


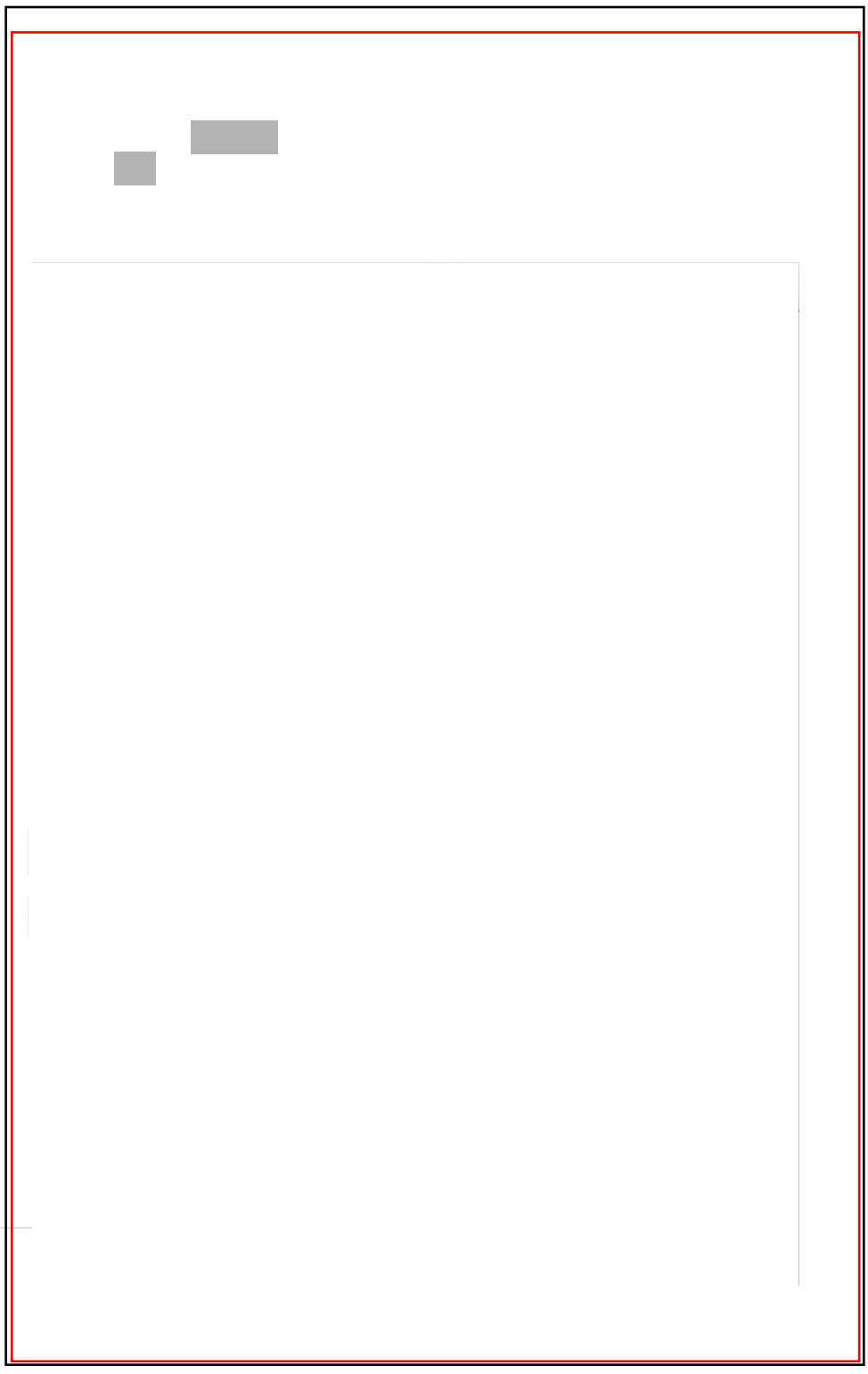


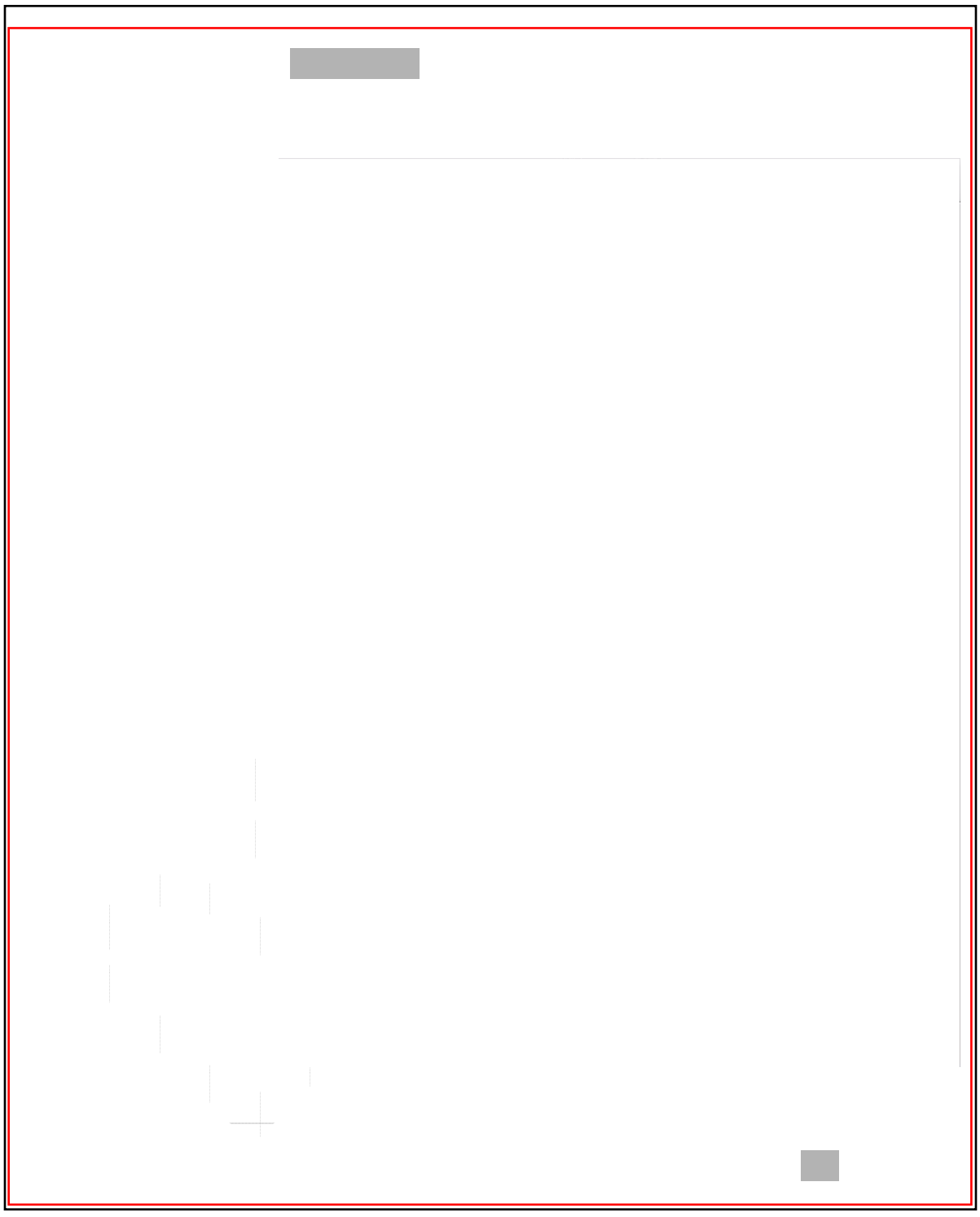


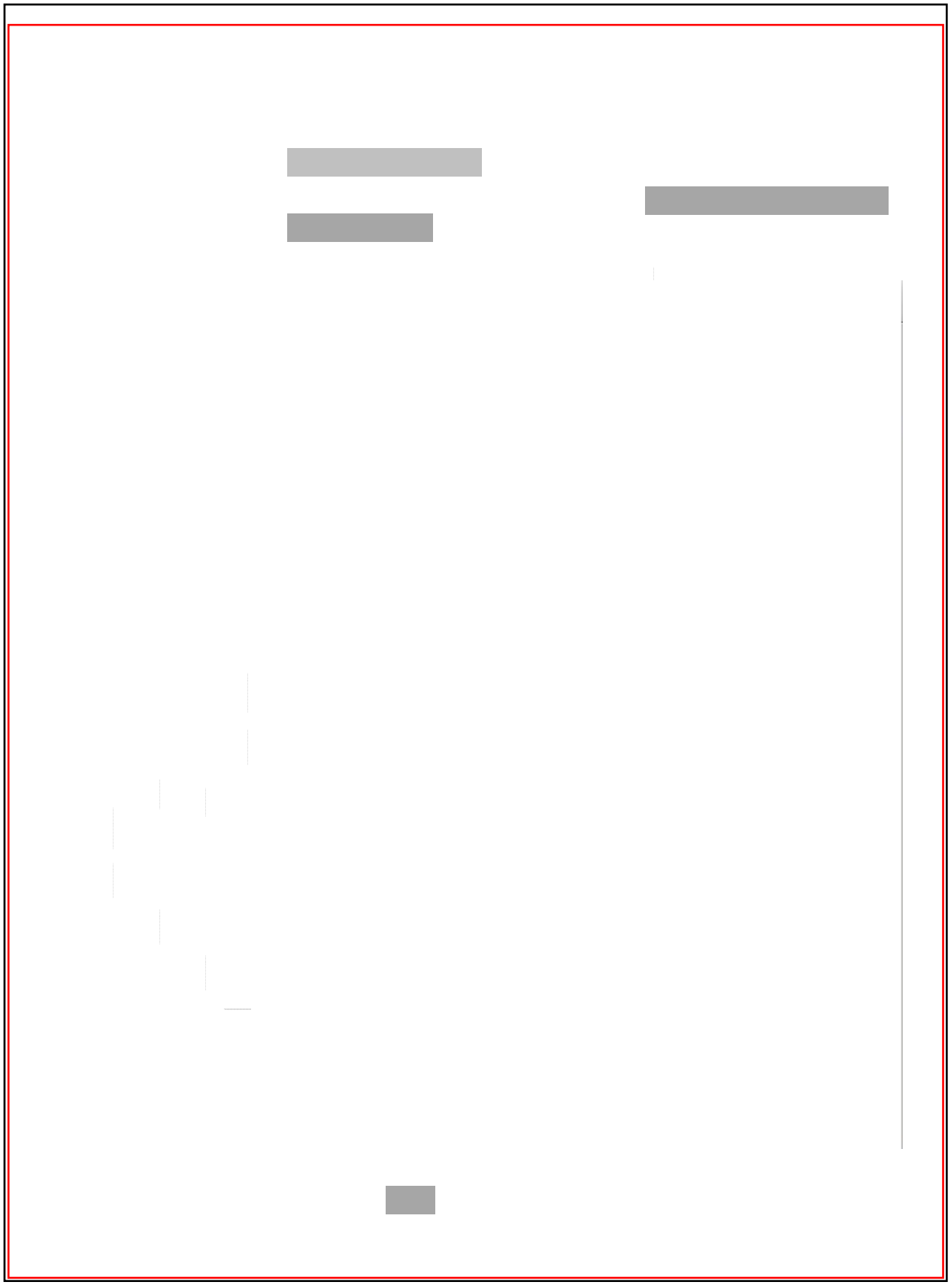


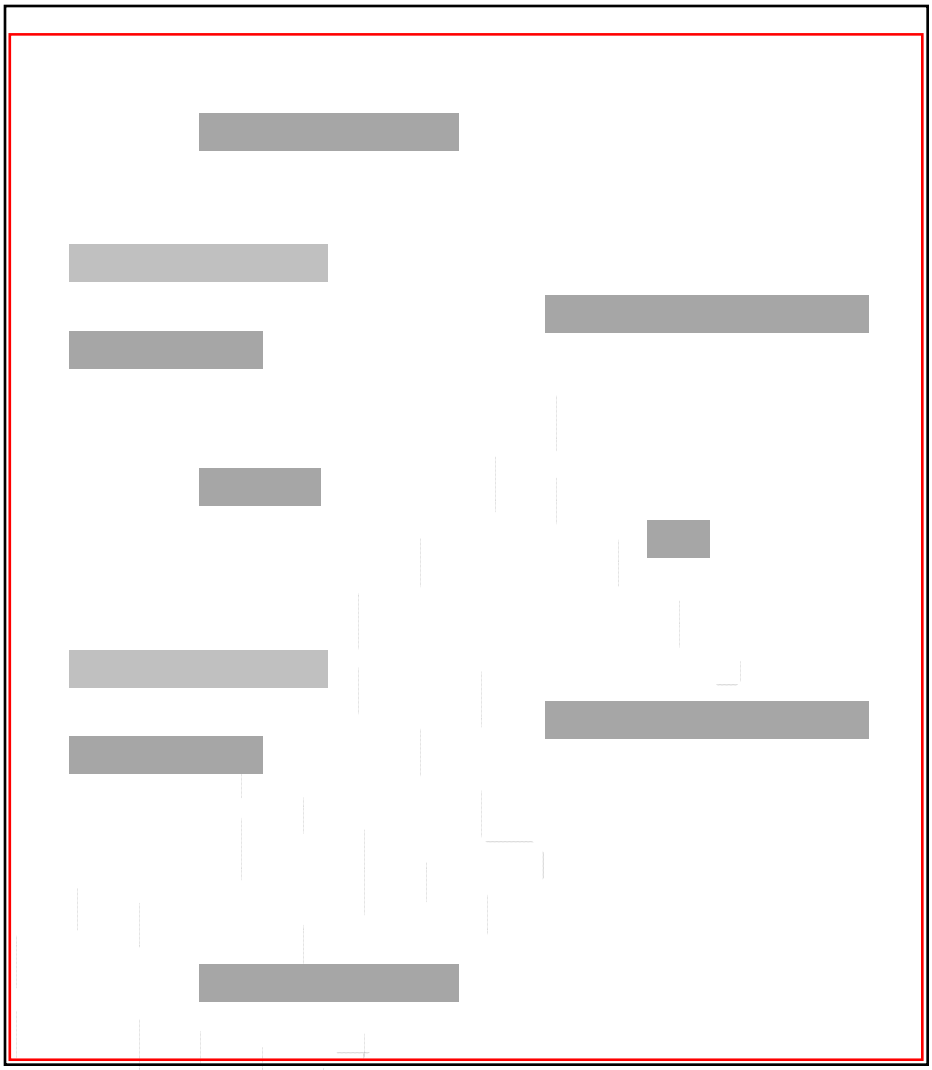












5.10 Understanding the Technical Design

This section contains technical and theoretical background information for individuals who want a better understanding of how the NeuroStar TMS System works.

5.10.1 Principles of Operation

Transcranial magnetic stimulation (TMS) is the non-invasive application of a localized pulsed magnetic field to the surface of the head causing depolarization of neurons in the cerebral cortex and connected regions of the brain. In simple terms, a TMS stimulator consists of a power supply, a single large capacitor for energy storage, a triggering component that allows the charge stored on the capacitor to discharge, and an inductive coil that receives the stored energy. (See Figure 5-1.)

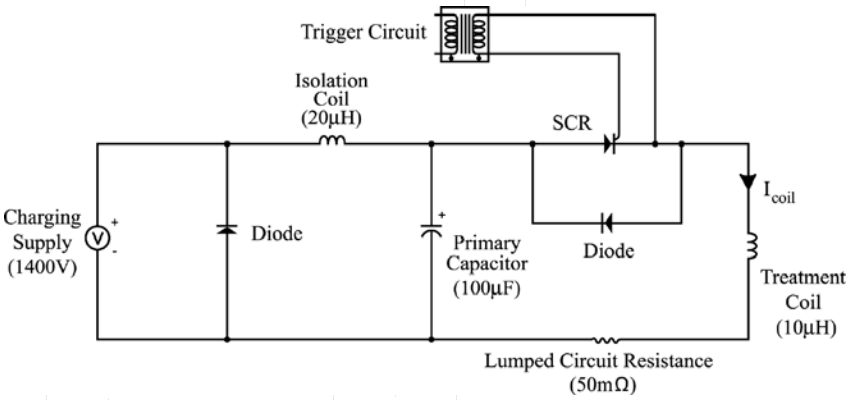


Figure 5-1. Simplified Schematic of a Representative Transcranial Magnetic Stimulator (Note: component values are not identical with the NeuroStar System)

The current flowing in the coil produces a time-varying magnetic field that can penetrate the brain. The magnetic permeability of biological tissue is approximately that of a vacuum. Therefore, human tissues have no noticeable effect on the magnetic field itself, allowing for a very predictable field to penetrate the brain.

Once the magnetic field penetrates the brain, it induces an electrical current in the brain as predicted by Faraday's Law of Magnetic Induction. (In 1831, Michael Faraday demonstrated that electric currents could be induced in a conducting medium by the application of a time-varying magnetic field.)

The NeuroStar TMS System technology stimulates cortical neurons (and connected sub-cortical tissues) by using a time-varying magnetic field to induce an electrical potential that causes ion flow, or eddy currents in the cortex. If oriented correctly relative to the membrane of the axon of a neuron, this ion flow results in a brief depolarization of the membrane, causing the neuron to fire. Stimulating neurons in the cortex with this technique has been shown to modulate neuronal excitability with effects that last beyond the time of direct stimulation.

Multiple stimulations delivered over a short period of time are called repetitive transcranial magnetic stimulation, or TMS. TMS can facilitate or inhibit neuron excitability as a function of stimulation frequency. In the case of frequencies greater than 1 Hz, it has been shown that TMS will facilitate firing, or lower the firing threshold of the stimulated neuron. It is hypothesized that this durable modulation effect may have therapeutic properties for the treatment of depression.

The total magnetic field exposure that a patient experiences over a four-week course of therapy (3000 pulses per day) is about 12 seconds. The patient is exposed to a peak magnetic field strength of approximately 0.5 Telsa.

The discrete regions of the brain that are directly affected by the NeuroStar TMS System therapy are illustrated in Figure 5-2.

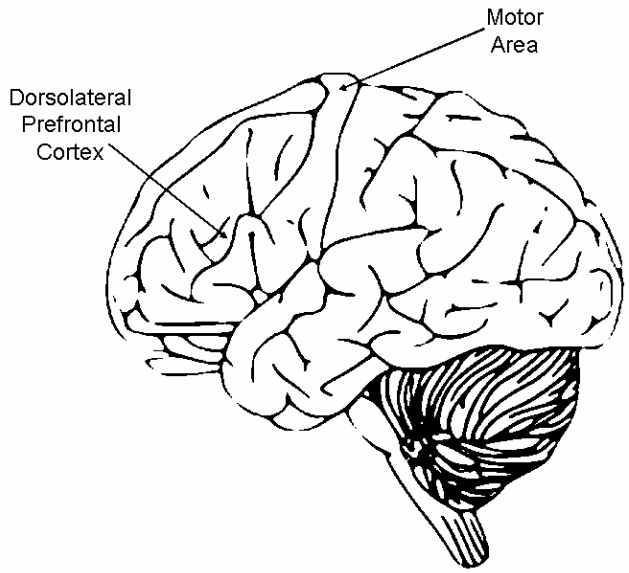
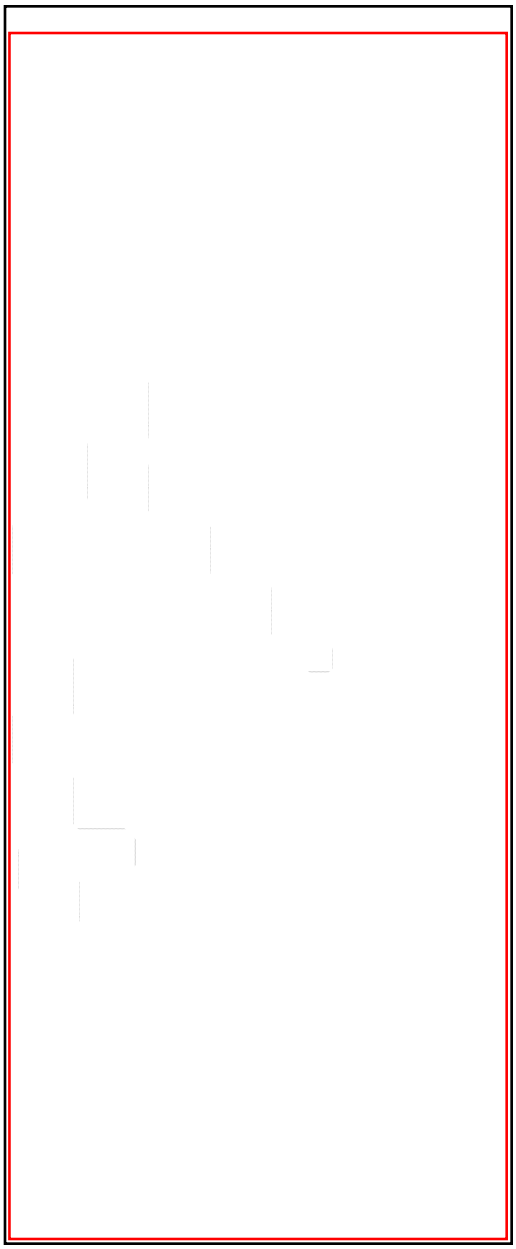


Figure 5-2. Brain Regions Relevant to TMS Therapy

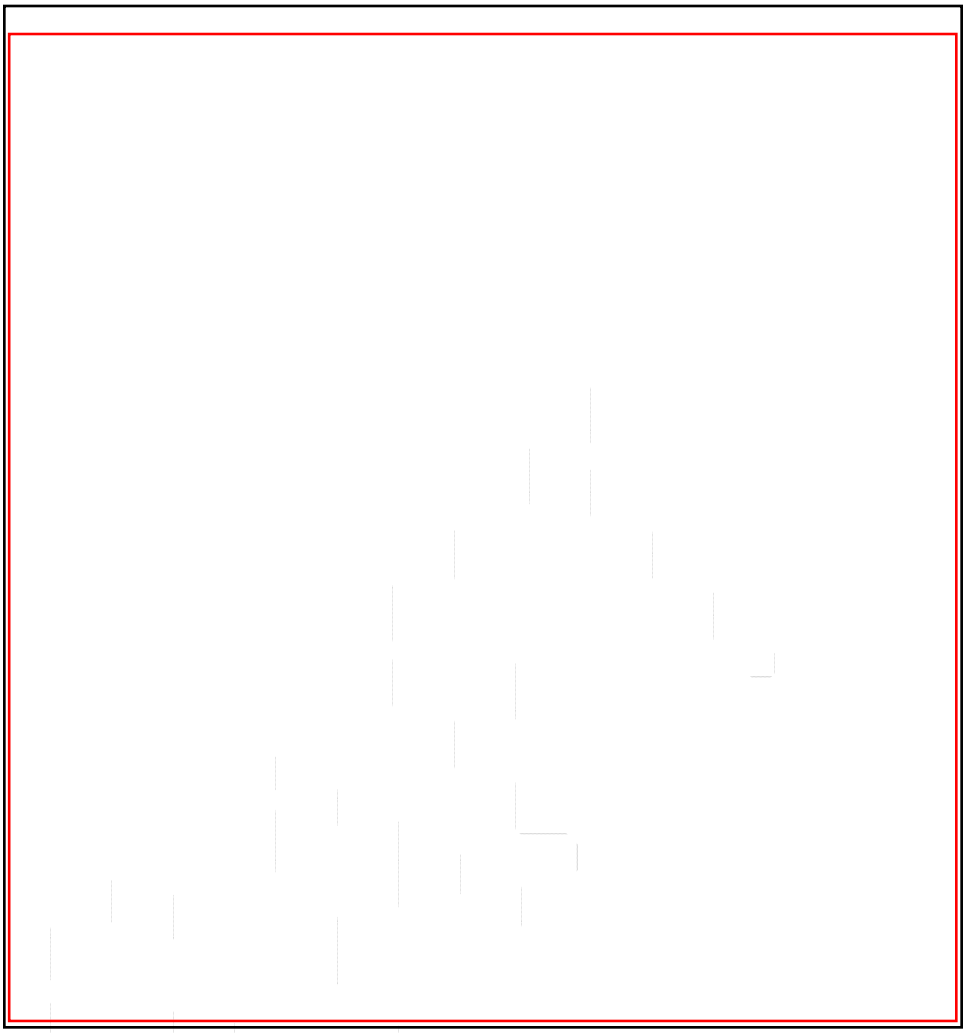
5.10.2 Main Technical Specifications

Processor:
Memory:
Storage:
Input Power:
Input Frequencies:
Operating System:
Input Device:
Touch Screen Specification:
Touch Screen Display Size:
Coil Weight:
Footprint:
Gantry Length:
Display arm Length:
Mast Length:
Mobile Console Weight:
Chair Length:
Chair Height:
Chair Width:
Chair Weight:
Chair Back Range of Movement:
Chair Leg Range of Movement:
Interface Ports :

Electrical Switches:



PDMS System Requirements



PDMS Transceiver Specifications

Field Replaceable Units

The following items are replaceable by the clinical user:

- Head Support Unit
- Head Cushion
- Coil
- Cushion Set
- PDMS Software

The following items are designed to be replaceable by Neuronetics Field Service personnel:

- Power Module
- Processor Module
- Display
- Covers
- Cables
- NeuroStar TMS System Software
- Treatment Chair
- Wireless Transceiver
- Printer

Operating Environment

The NeuroStar TMS System was designed to operate optimally in a typical clinical office environment.

Transport and Storage Environment

FDA Classification

The NeuroStar TMS System is a class (TBD) medical device. It is an active medical device that has no measuring function and that is noninvasive and designed for intermittent use.

Industry Standard Classification (IEC 60601-1)

Classification Area	Classification
Type of Electric Shock Protection	Class I Equipment
Degree of Electric Shock Protection	Type BF

Industry Standard Classification (IEC 60601-1)

Classification Area	Classification
Degree of Protection Against Harmful Ingress of Water	Ordinary Equipment
Safety in the Presence of Flammable Material	Equipment is NOT suitable for use in the presence of a flammable anesthetic mixture with air or with oxygen or with nitrous oxide.
Mode of Operation	Continuous Operation with Short-Term Loading

Electro-magnetic Compatibility (EMC)

This equipment has been tested and been found to comply with the requirements of EN60601-1, Medical Electrical Equipment Part 1: General Requirements for Safety, and Collateral Standard: Electromagnetic Compatibility – Requirements and Tests (EN60601-1-2). These requirements are designed to provide reasonable protection against harmful interference when the equipment is installed and operated as specified by Neuronetics. (See Appendix F for details.)

- The NeuroStar TMS System generates, uses, and can radiate electromagnetic energy if not installed and used in accordance with the instructions in this manual.
- If it is determined that the NeuroStar TMS System is generating interference with other equipment contact the Neuronetics Service Department.

Waste Disposal

Used head cushion liners and side pad liners may be mixed with regular trash. Used SenStar™ Treatment Links should be disposed of in the container provided by Neuronetics.

At the end of the NeuroStar TMS System's useful life, call the Neuronetics Service Department for disposal instructions.

6 Maintaining the System

This section provides instructions for maintaining the NeuroStar TMS System.

- ***Basic Maintenance***
  Section 6.1 provides instructions for changing system configuration parameters
- ***System Alarms***
  Section 6.3 provides instructions for addressing system alarms and alarm messages
- ***Diagnostics***
  Section 6.4 provides the possible display messages on the touch screen
- ***Troubleshooting***
  Section 6.5 provides routine system observations and suggested corrective actions.

The NeuroStar TMS System is designed to provide reliable service in a convenient self-contained package. The instructions in this section cover preventive maintenance steps and the most basic diagnostic and troubleshooting steps.

The NeuroStar TMS System software has many self-checking features and displays error messages in the unlikely event that it encounters problems.

There are NO user-serviceable parts in the NeuroStar TMS System mobile console. If you encounter a problem that is not covered in this section, call the Neuronetics service line. If you suspect that a system malfunction has created a hazardous condition, unplug the power cord from the wall outlet and call the Neuronetics Service Department for assistance.

6.1 Routine Maintenance

Cleaning and Disinfecting	• With the power off and the system unplugged from the wall receptacle, use a damp cloth to wipe away dust or dirt on the mobile console, the power cable, the signal cable, the therapy coil, and the coil halo, gantry, and mast. • Clean the surface of the therapy coil by wiping it with a damp sponge and/or by blotting with a clean cloth, using a water-based cleaning product or mild soap and water.

	• Do NOT use any type of solvent or lubricant on the component parts. • Do NOT use acetone to clean any part of the system. • Do NOT attempt to sterilize any part of the system. Do NOT use glass cleaner, cleanser, or any abrasive substance on the touch screen.

User Routine Maintenance

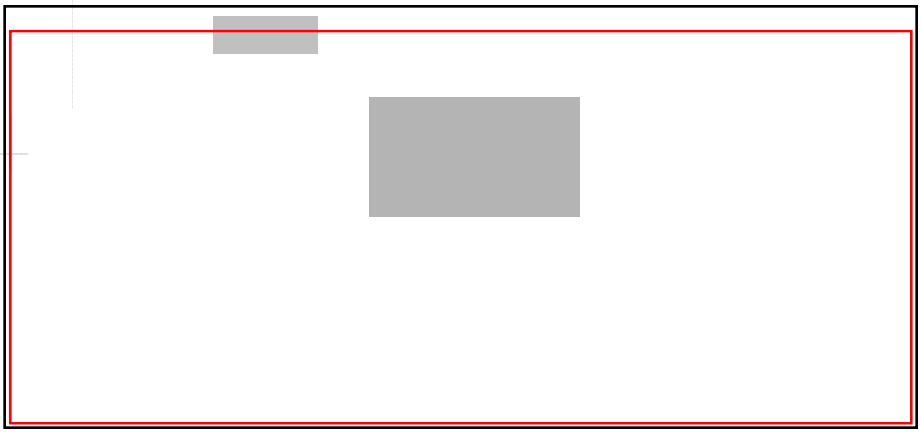
- Ensure that the system is set for the proper local voltage level and that it has the proper power cable.
- Ensure that the power cable plug is intact and that you are connecting the system only to a grounded wall receptacle.
- Ensure that the mobile console housing, the gantry covers, and the display case are intact. If there are any cracked or broken areas, call Neuronetics for service.
- Use a sponge or cloth to soak up any small spills on the equipment. If the spill includes bodily fluids, observe all biohazard precautions.
- If a large amount of liquid is spilled on the unit, turn off the system, disconnect the power cable from the wall receptacle, and call the Neuronetics Service Department for assistance.

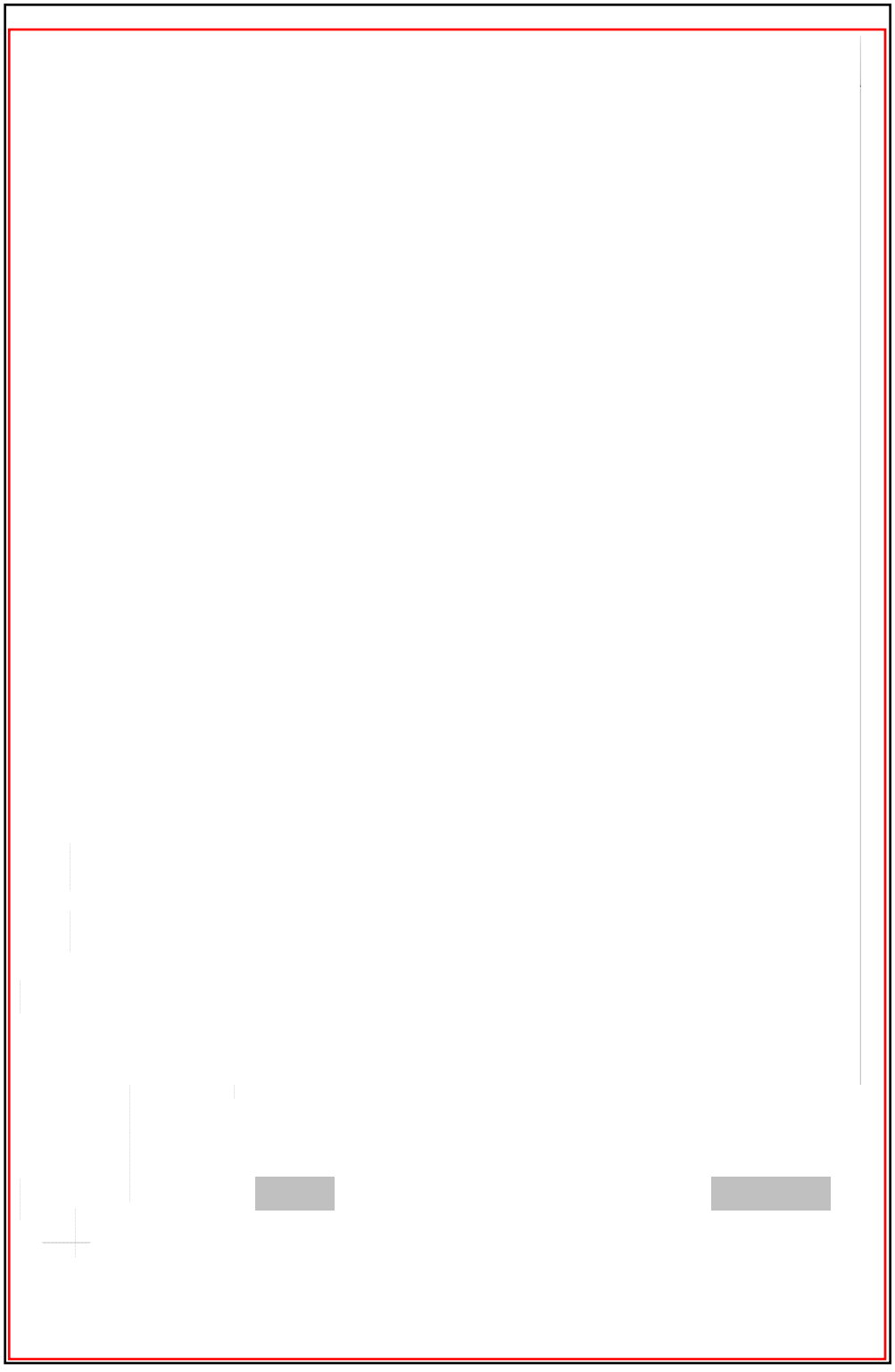
6.2 Preventive Maintenance

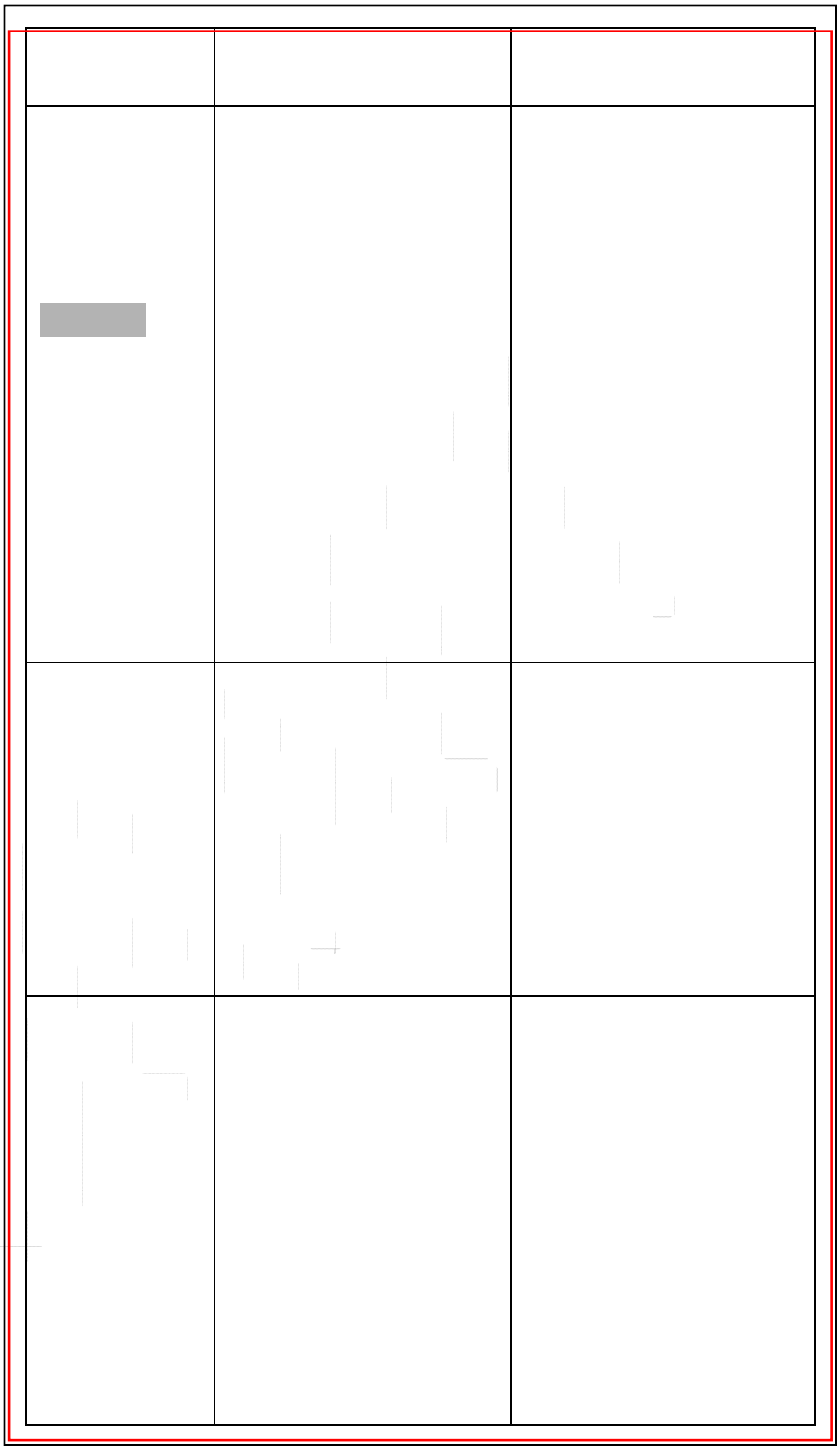
Call the Neuronetics service department to schedule an annual inspection and preventive maintenance visit.

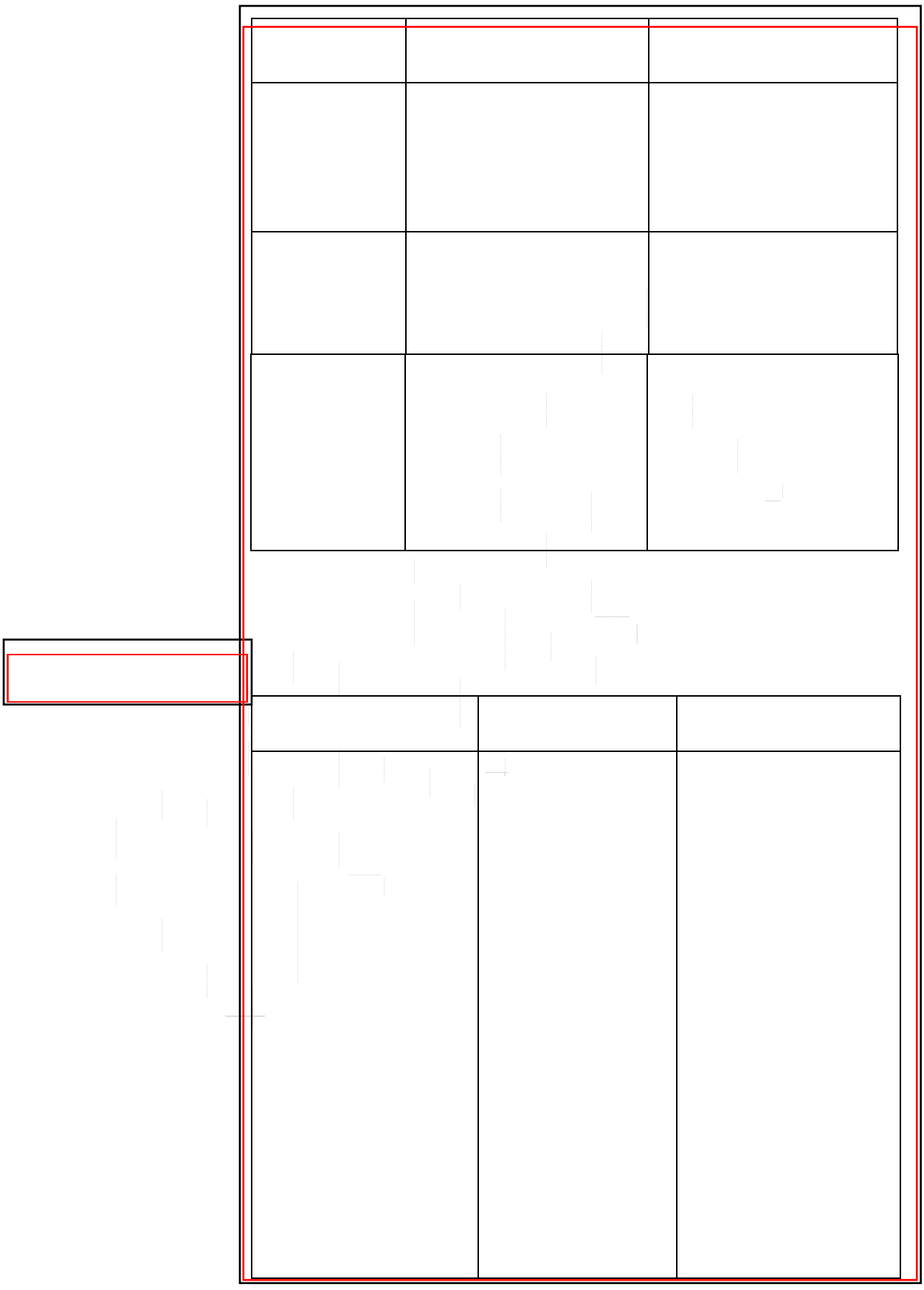
6.3 Adjusting System Alarms

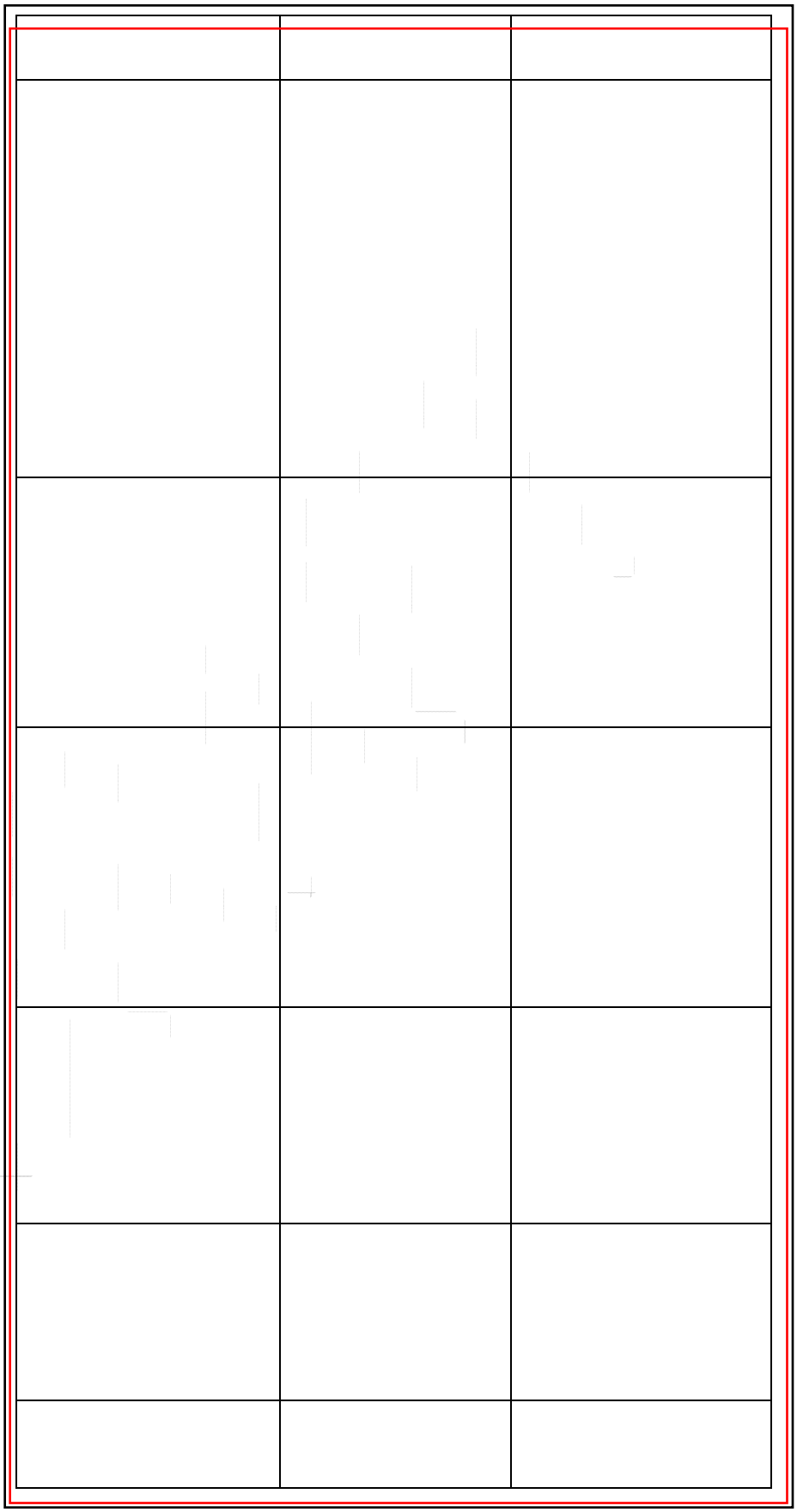
The NeuroStar TMS System is equipped with several audible alarms that alert you to conditions that require your attention. If these alarms are disturbing to the patient or distracting, you can silence them. If you silence alarms, the system will still display the alarm messages on the screen. Use the following steps to silence alarms.

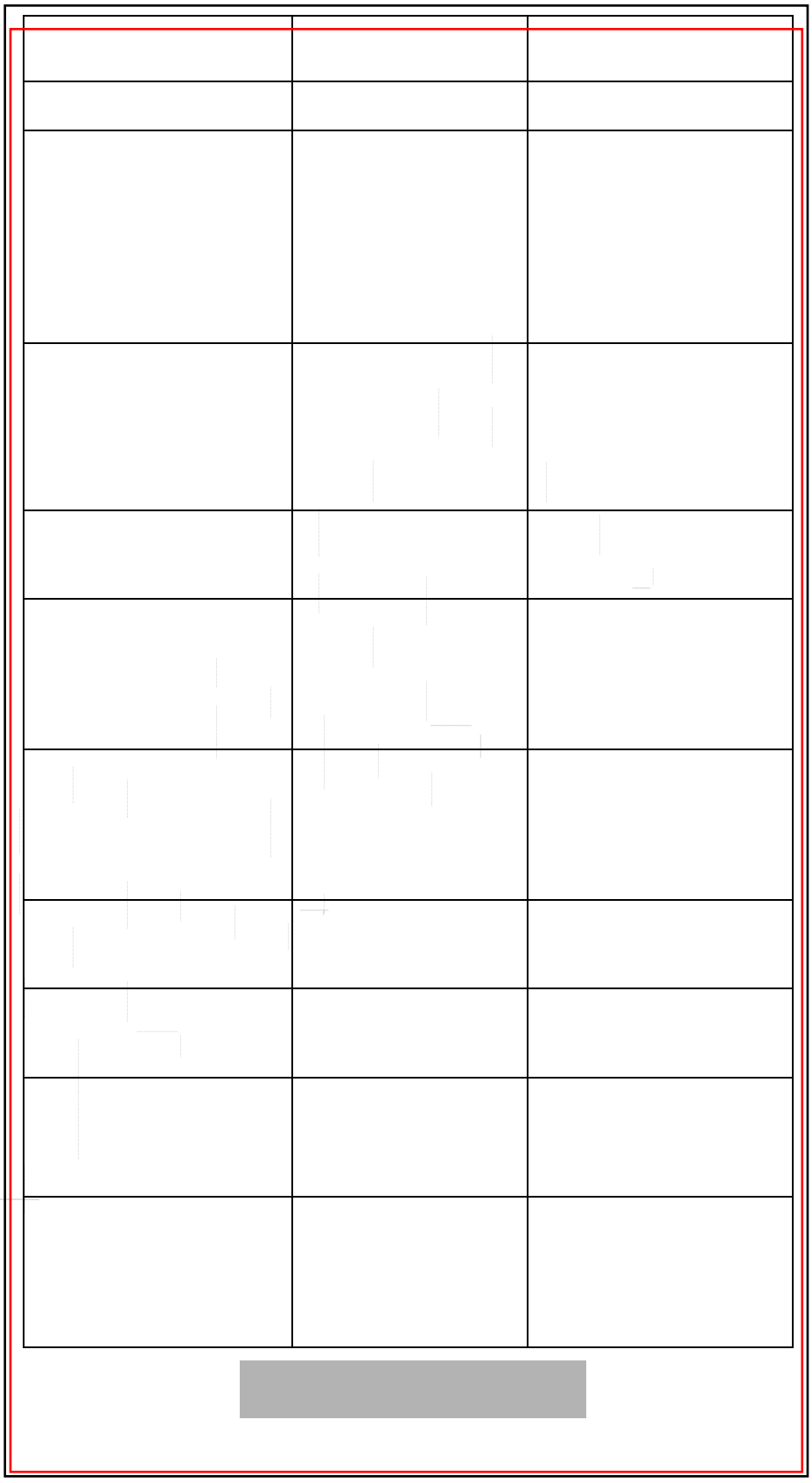


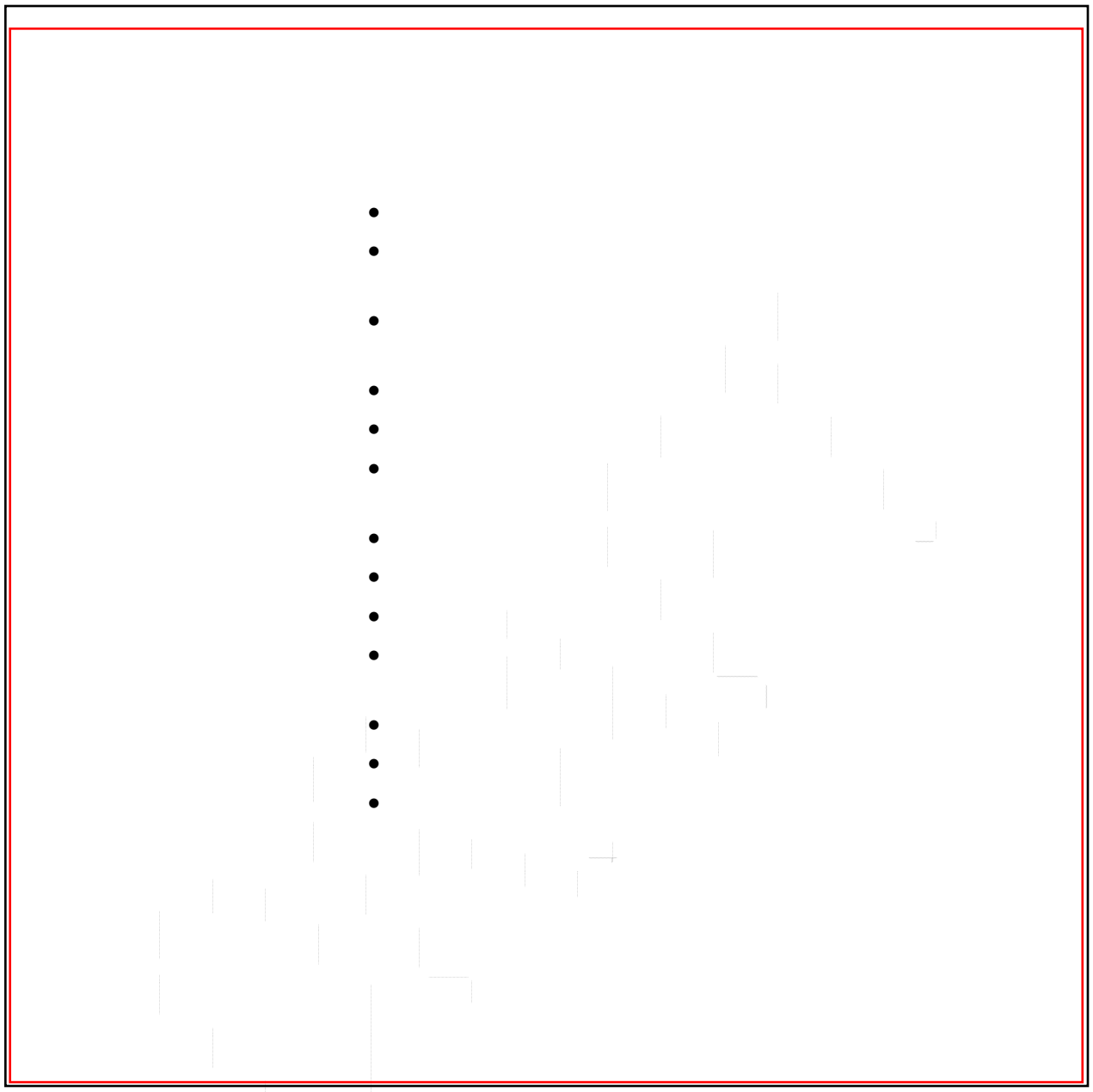


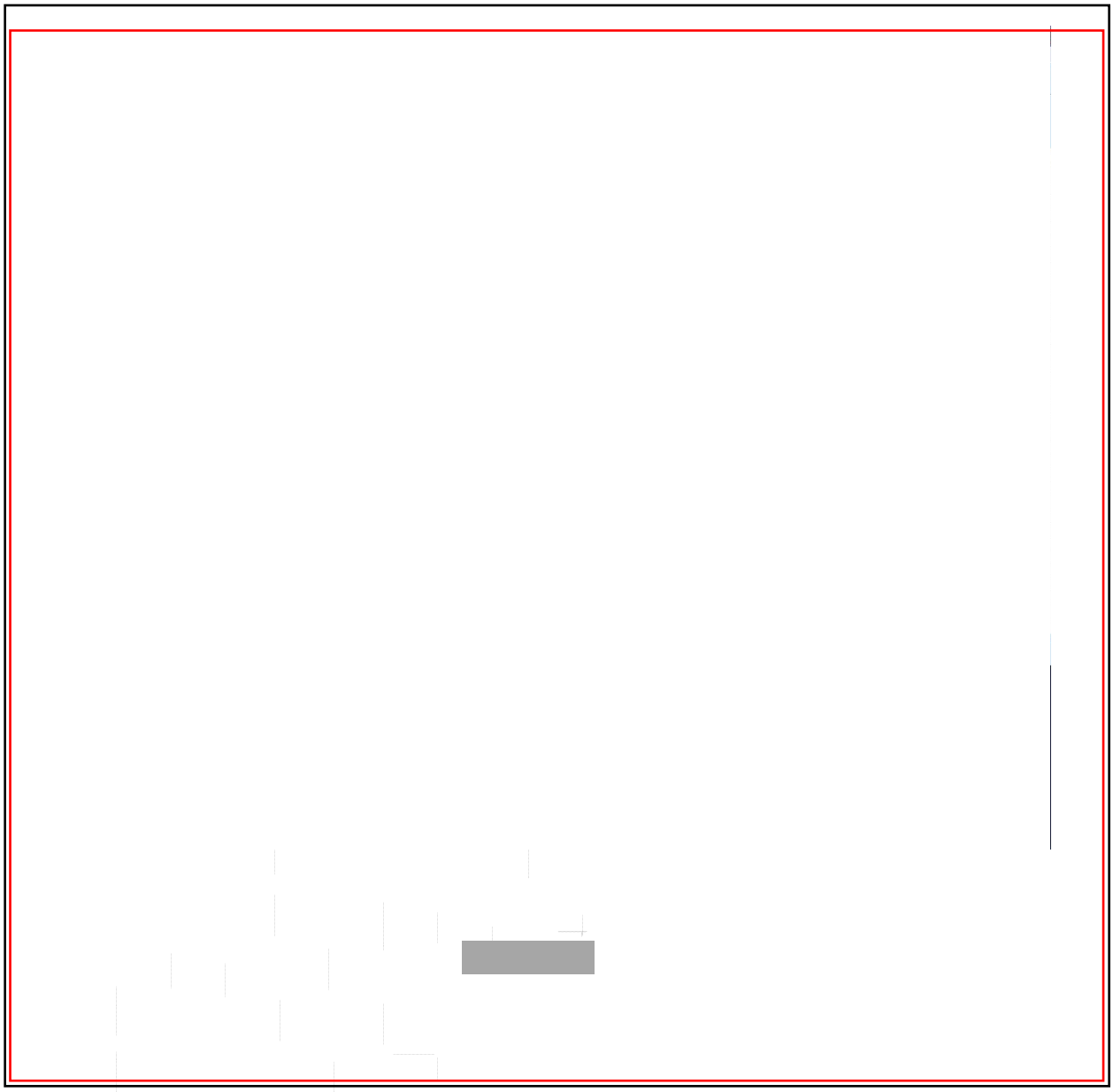


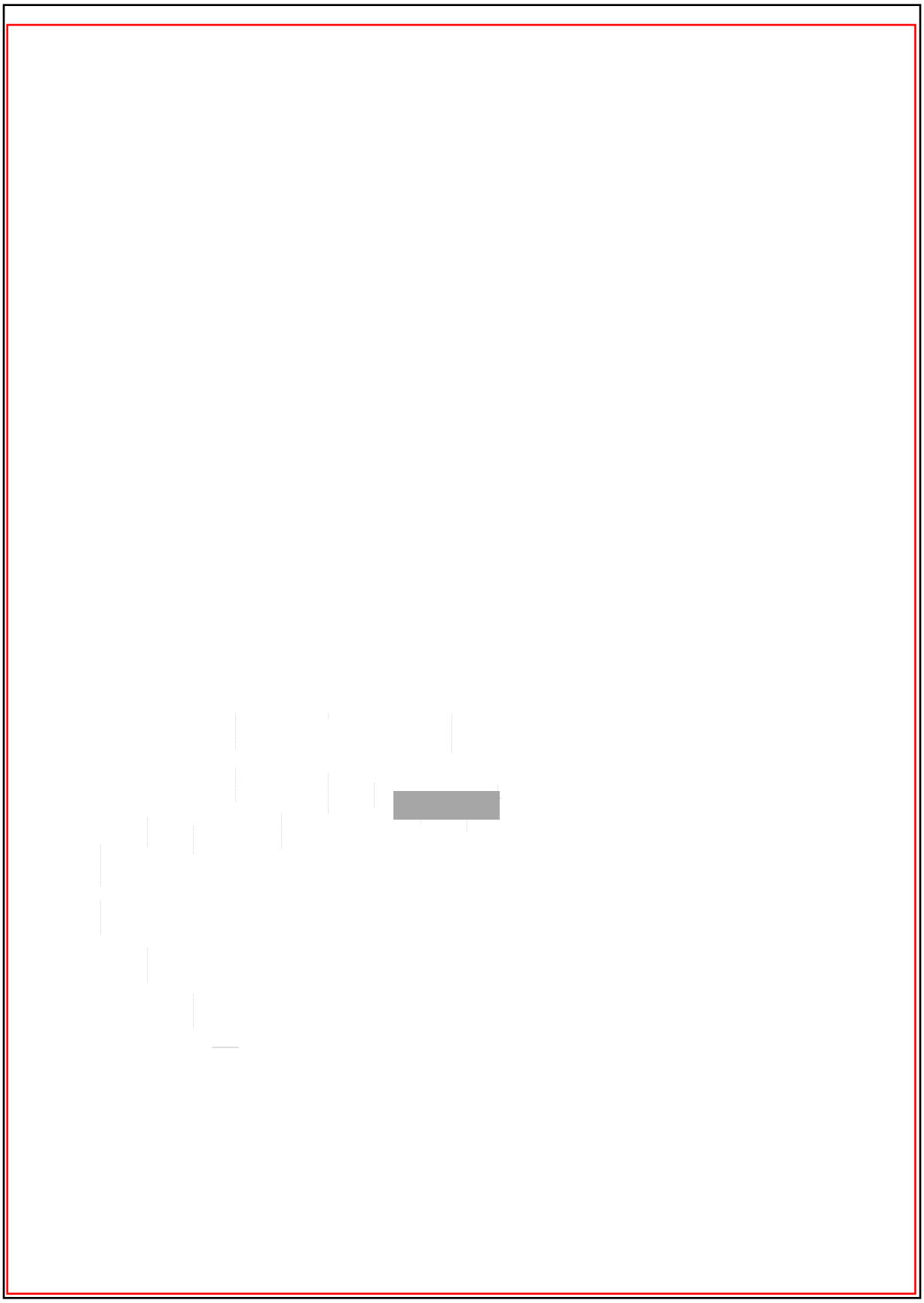


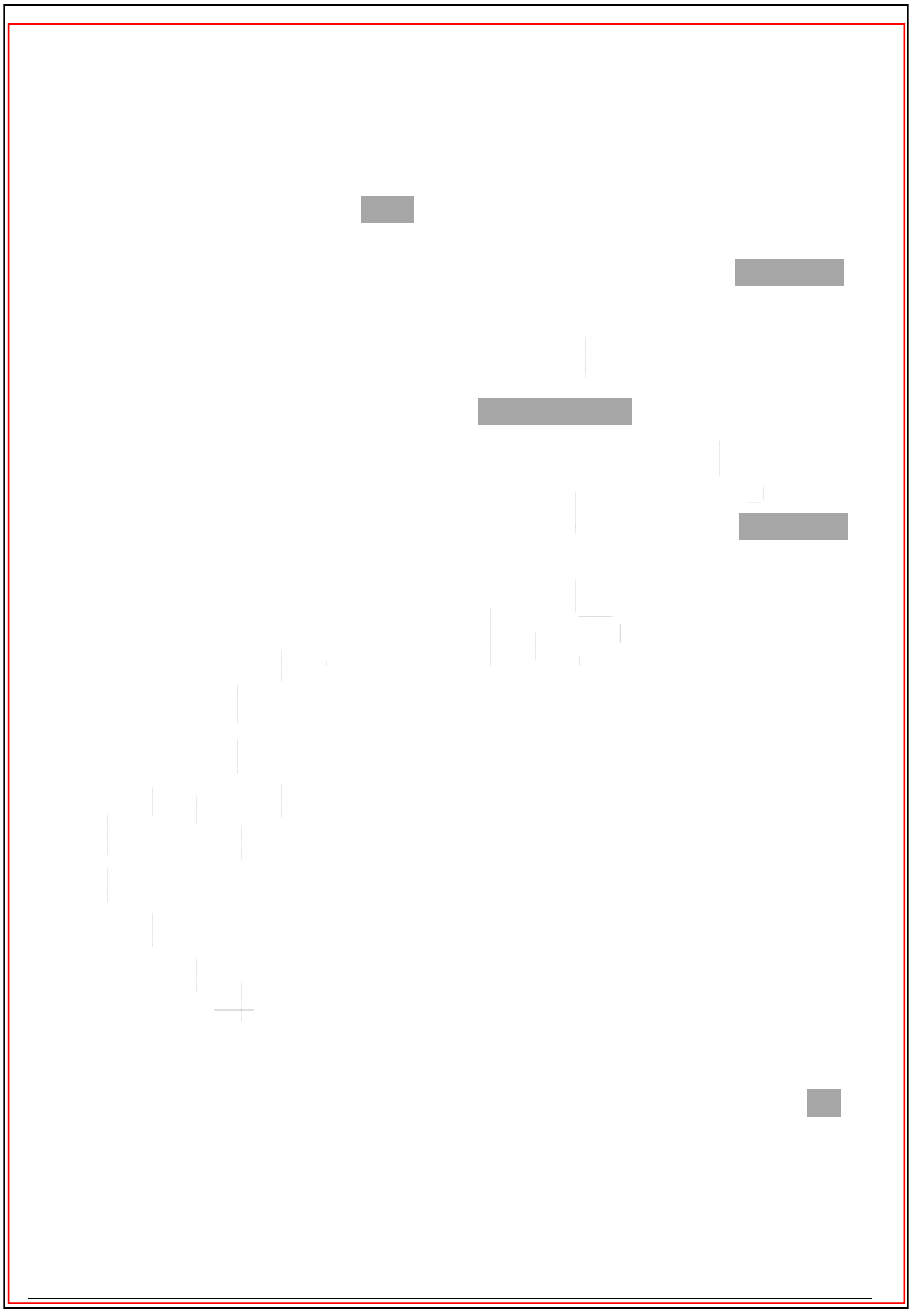


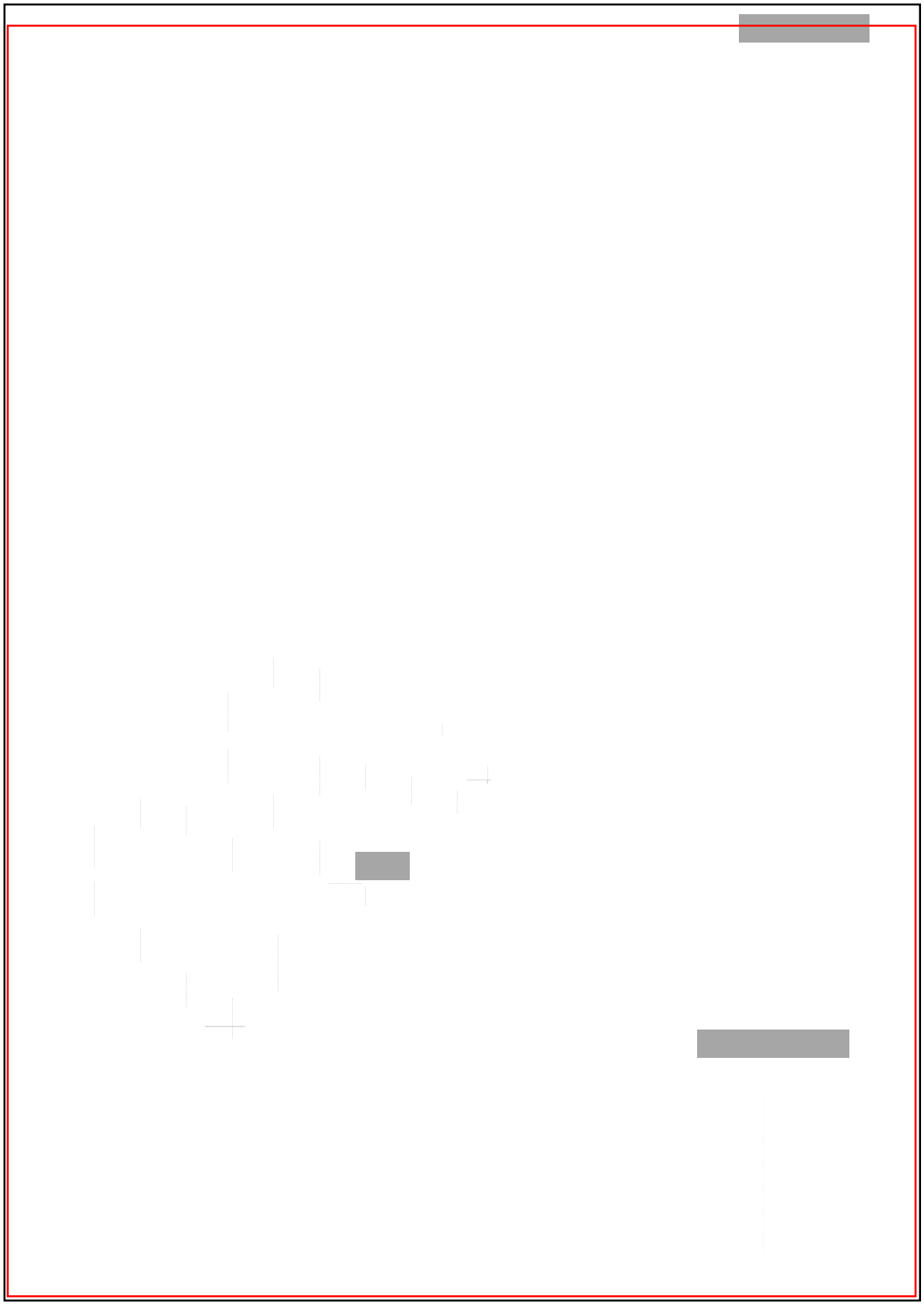


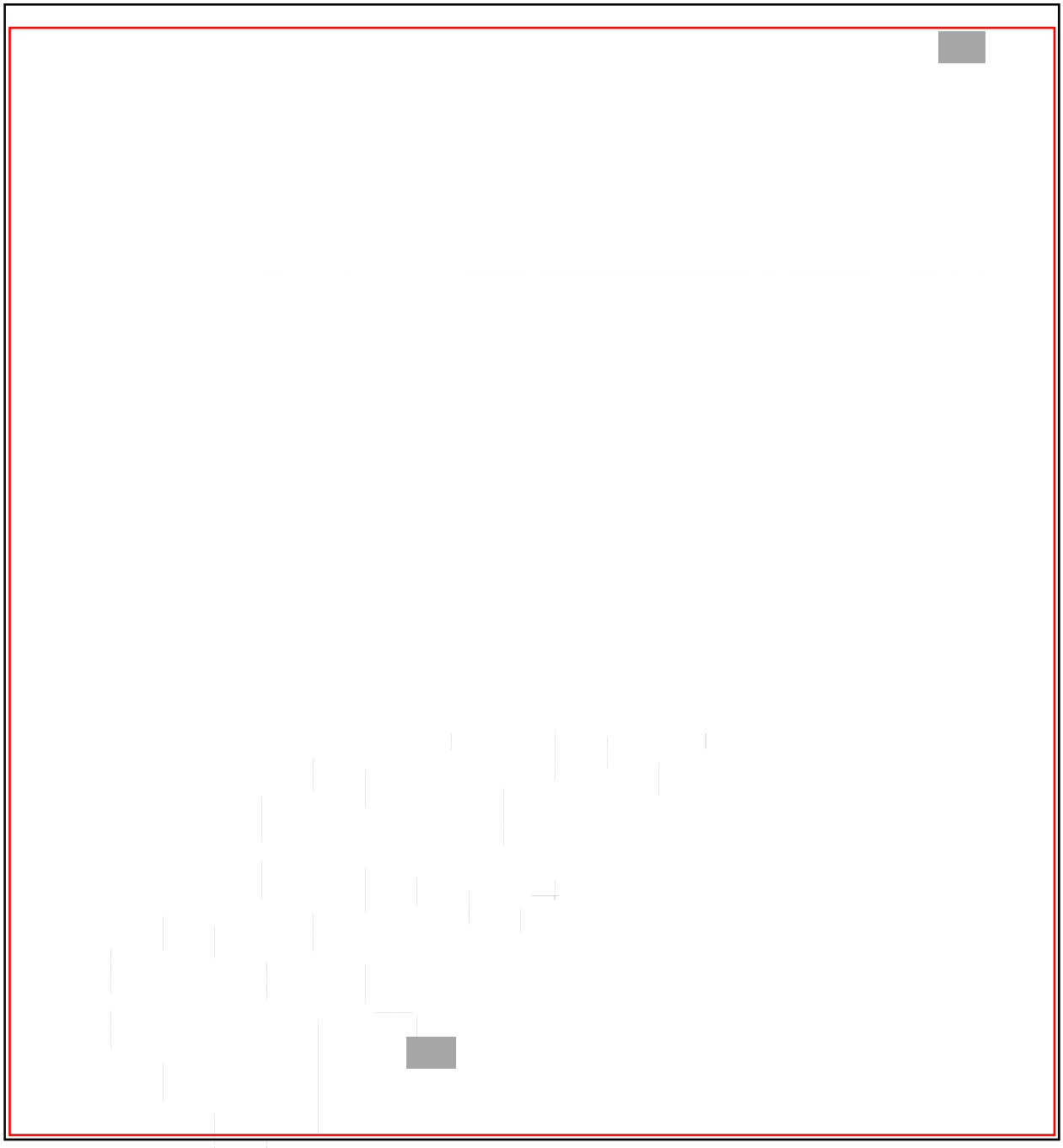


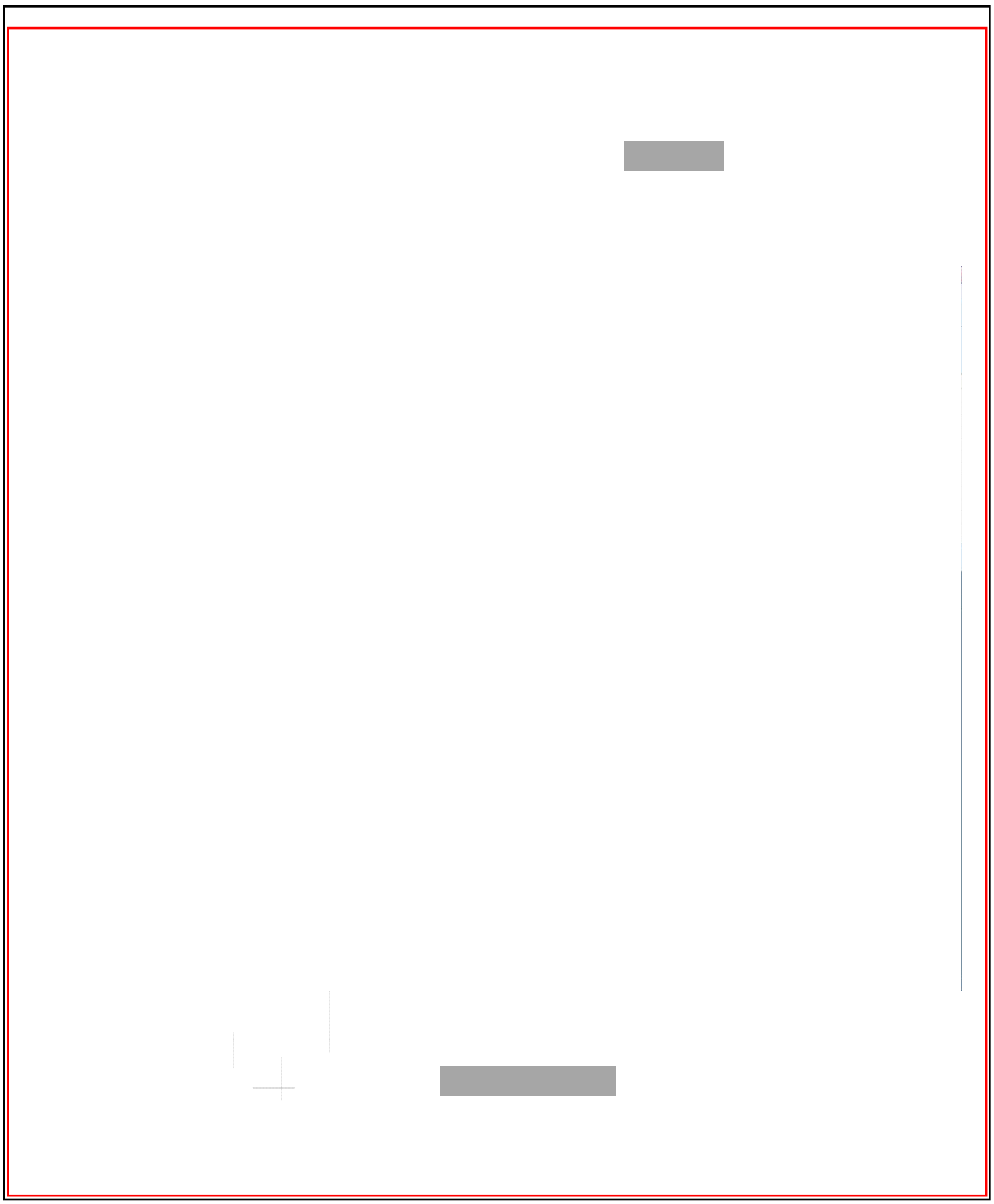


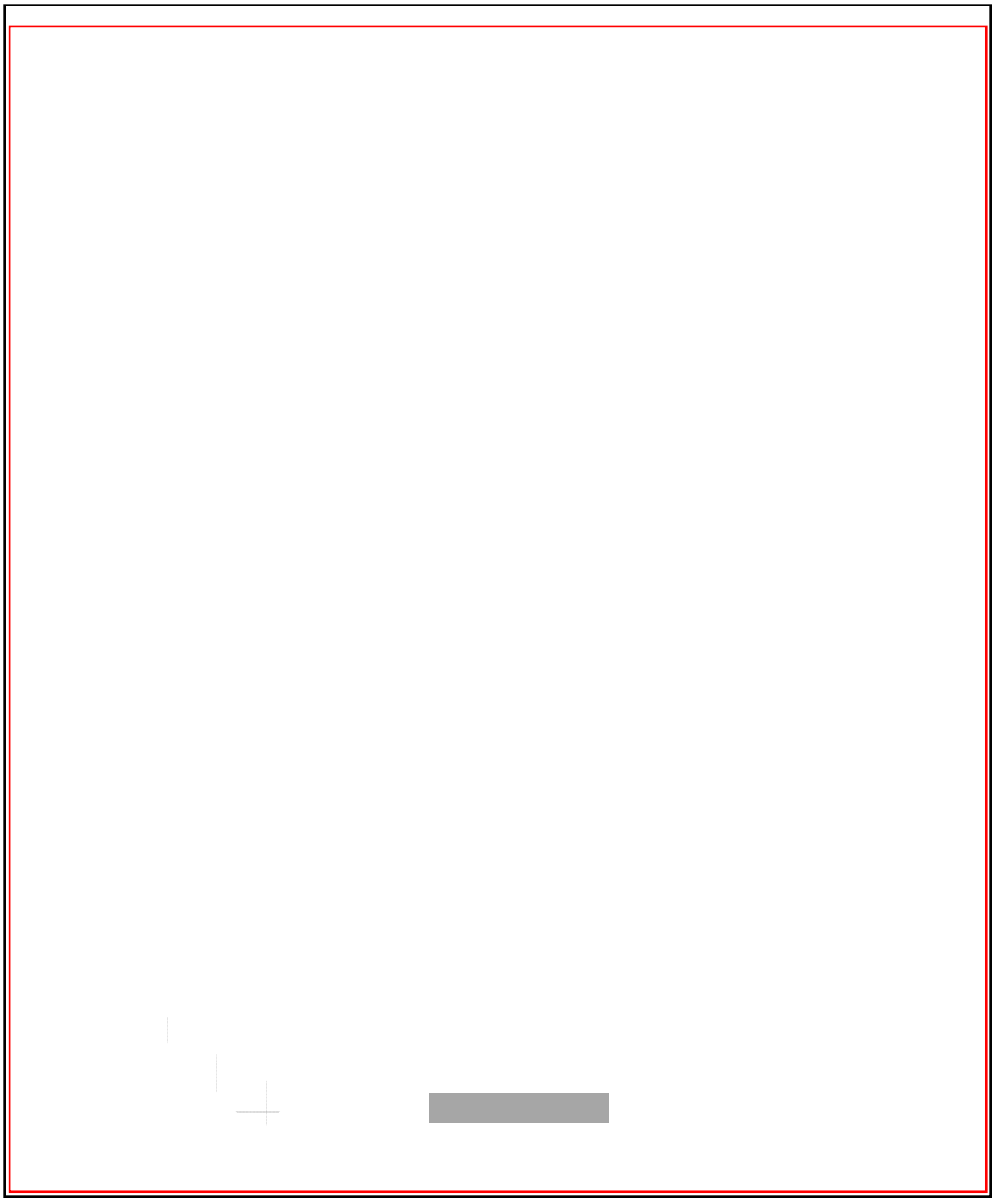


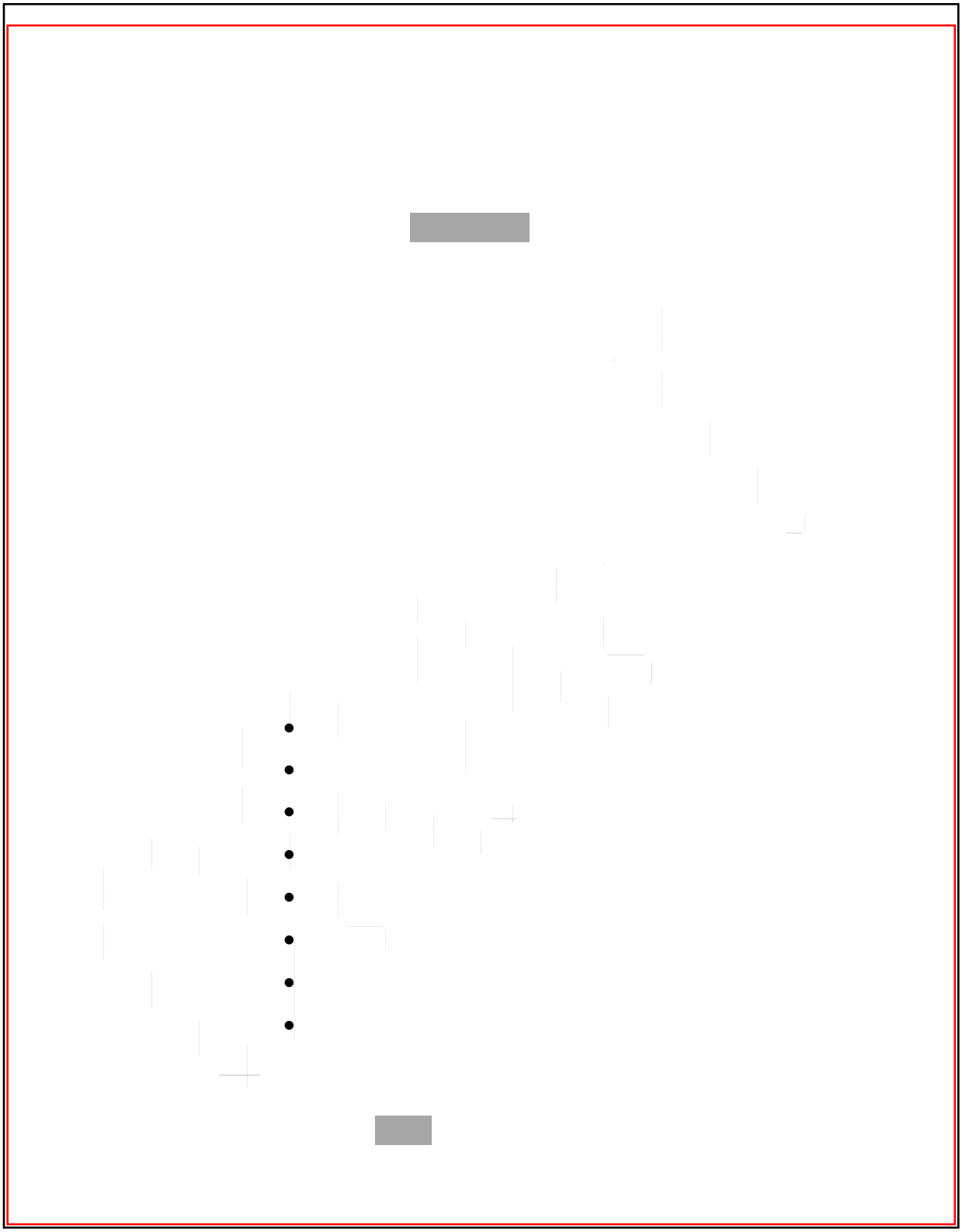


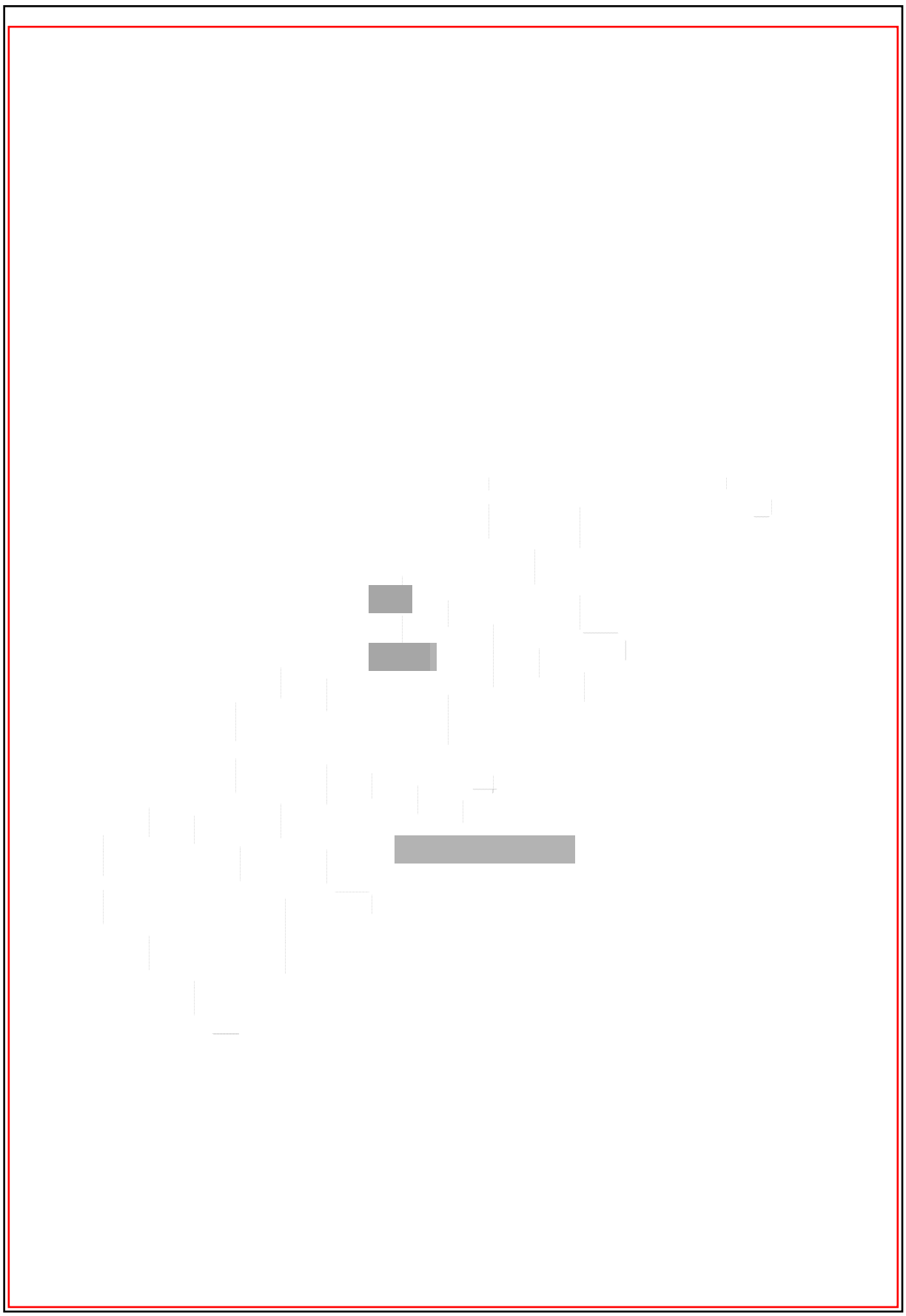


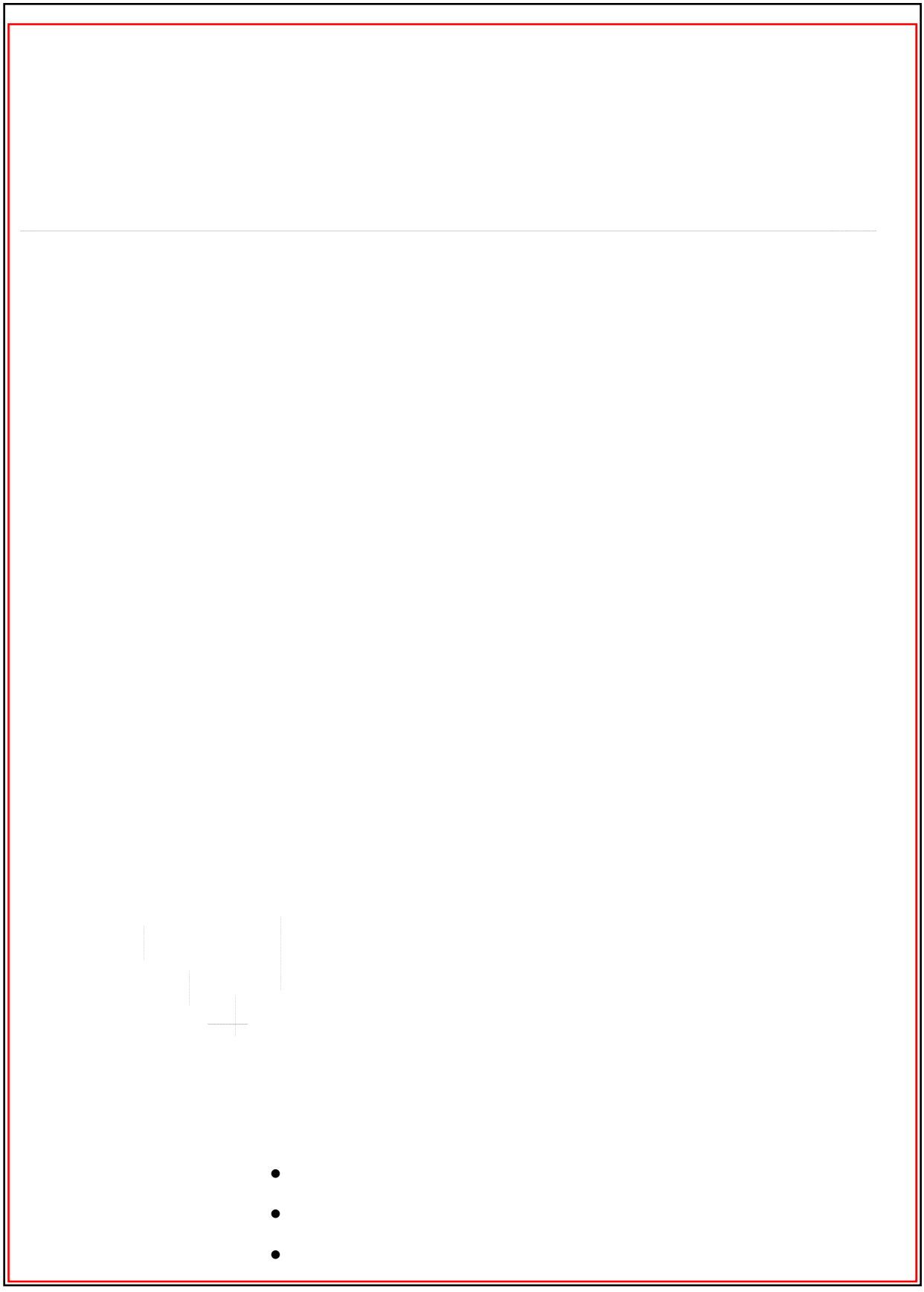


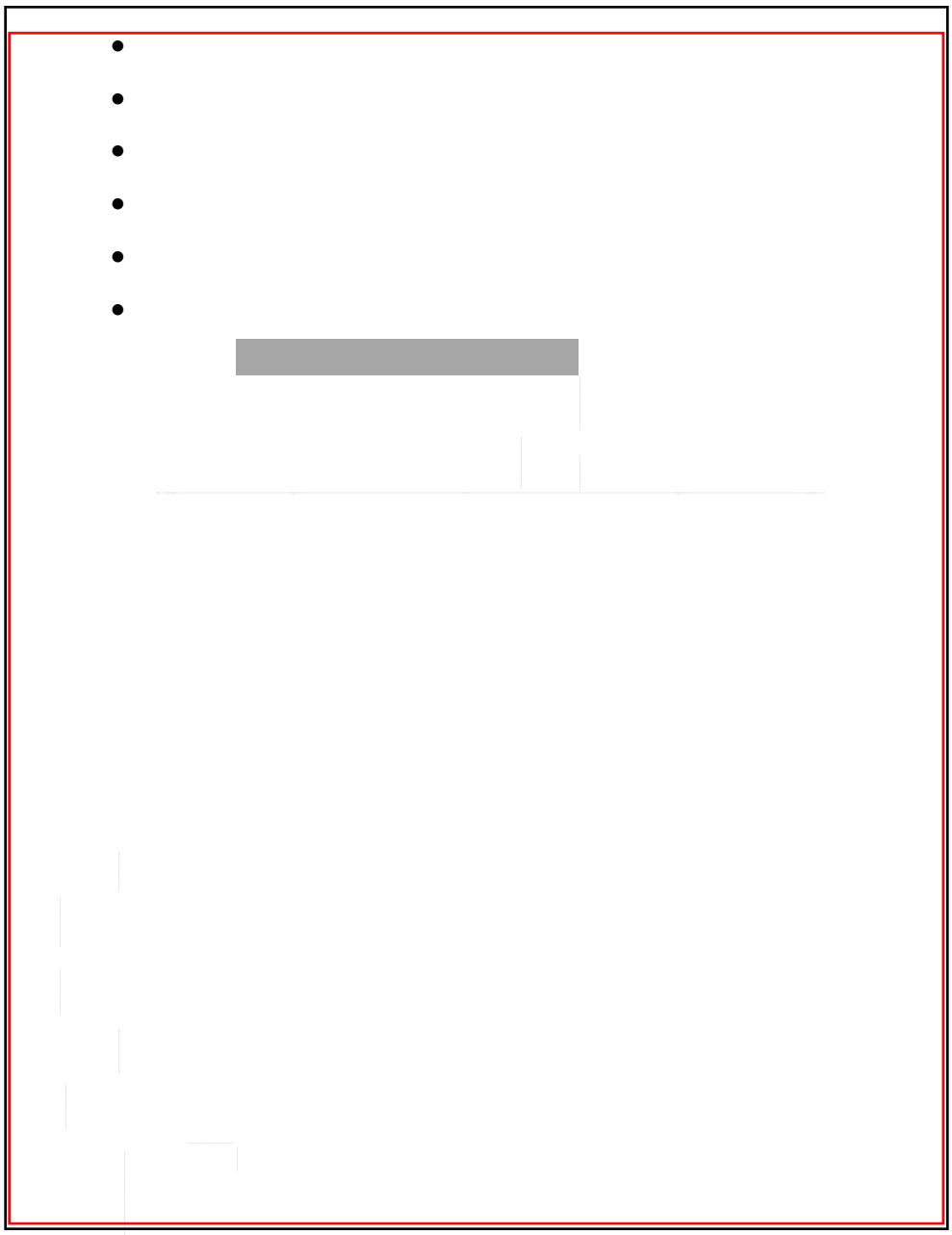


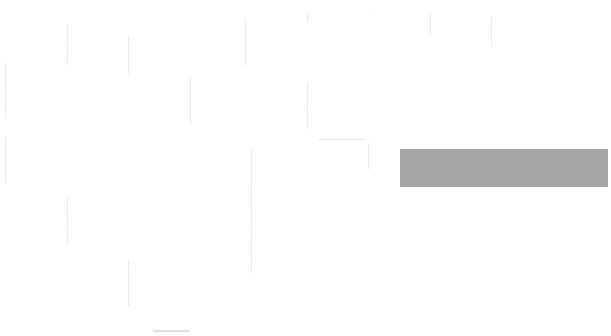


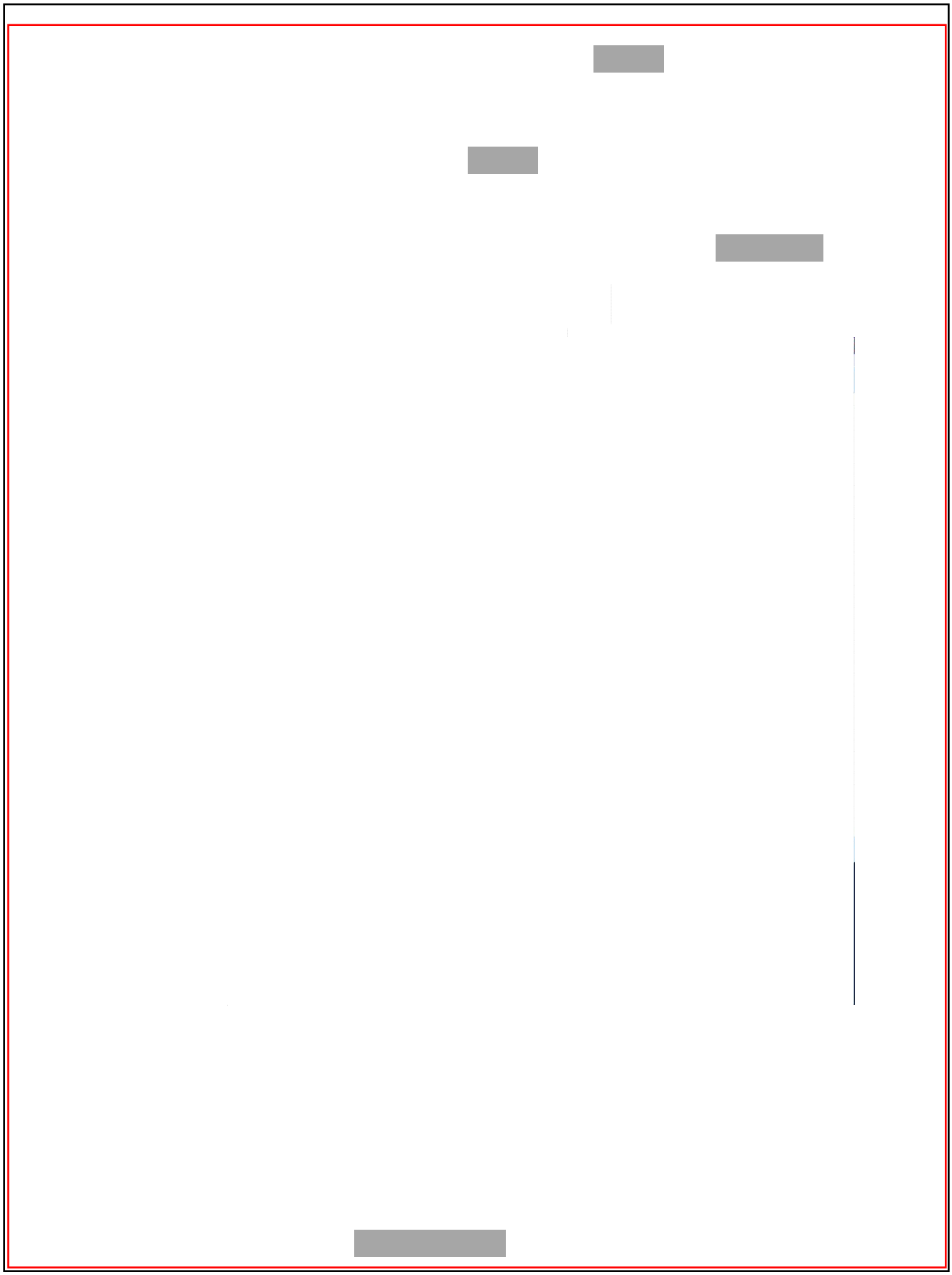


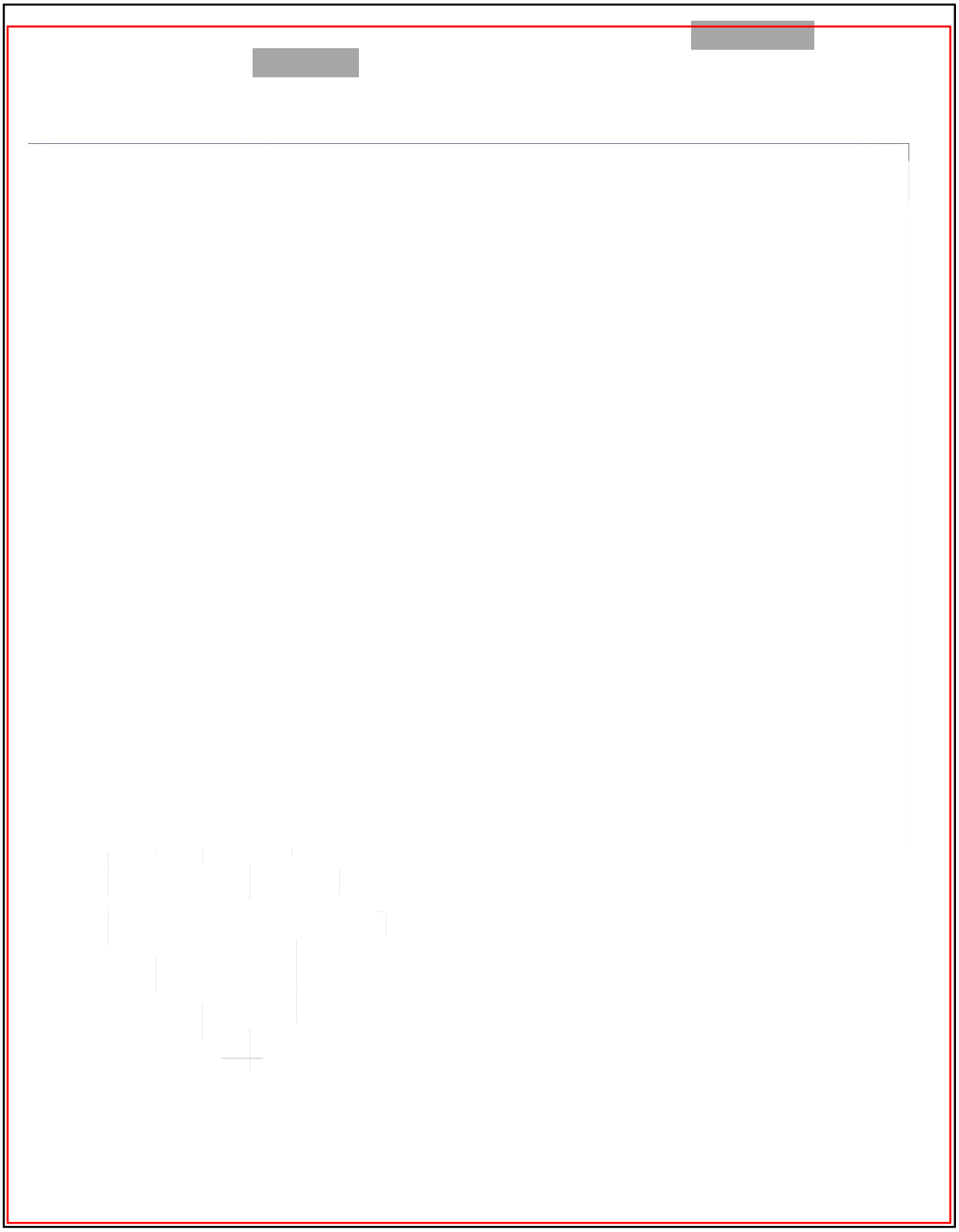


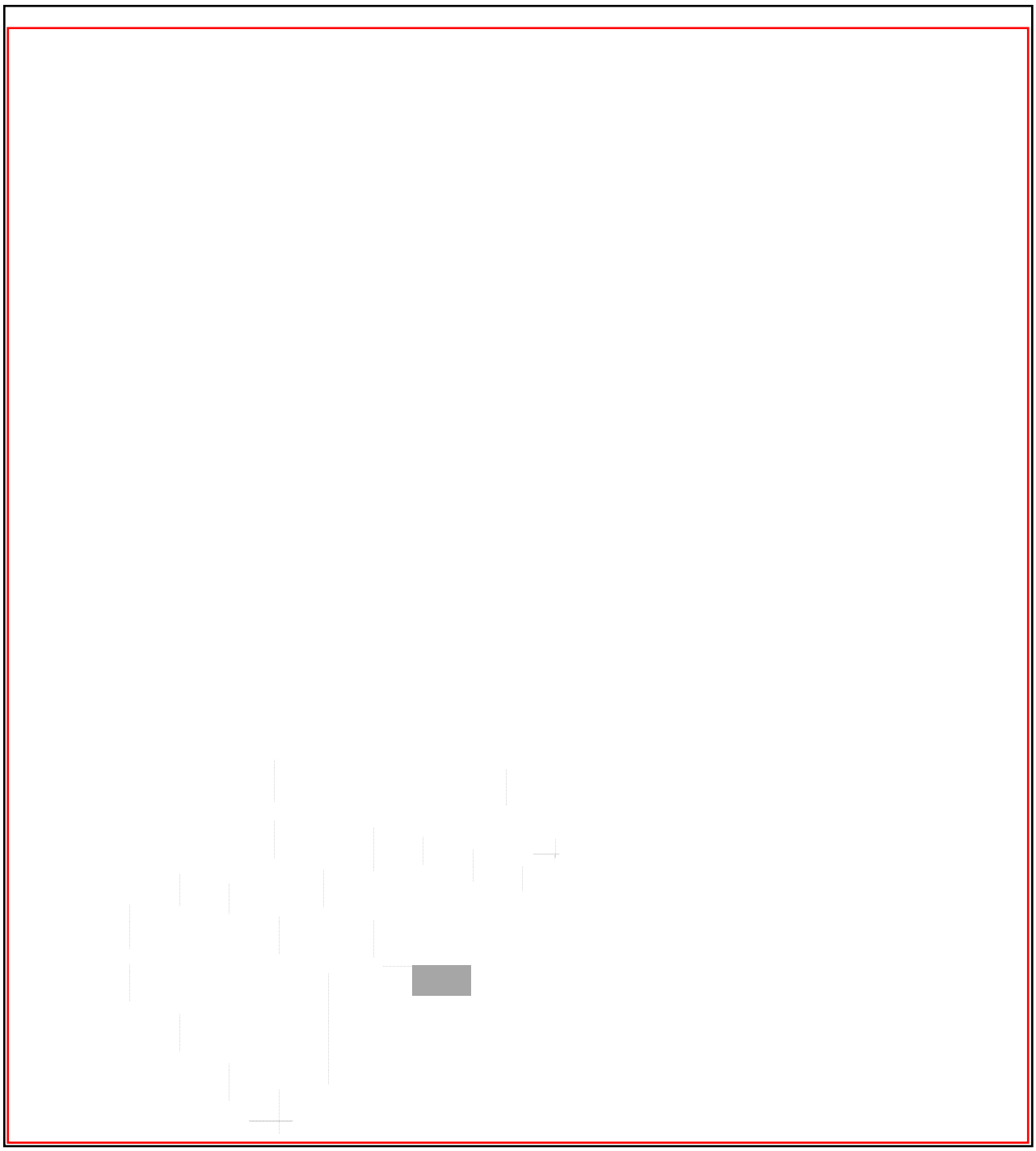


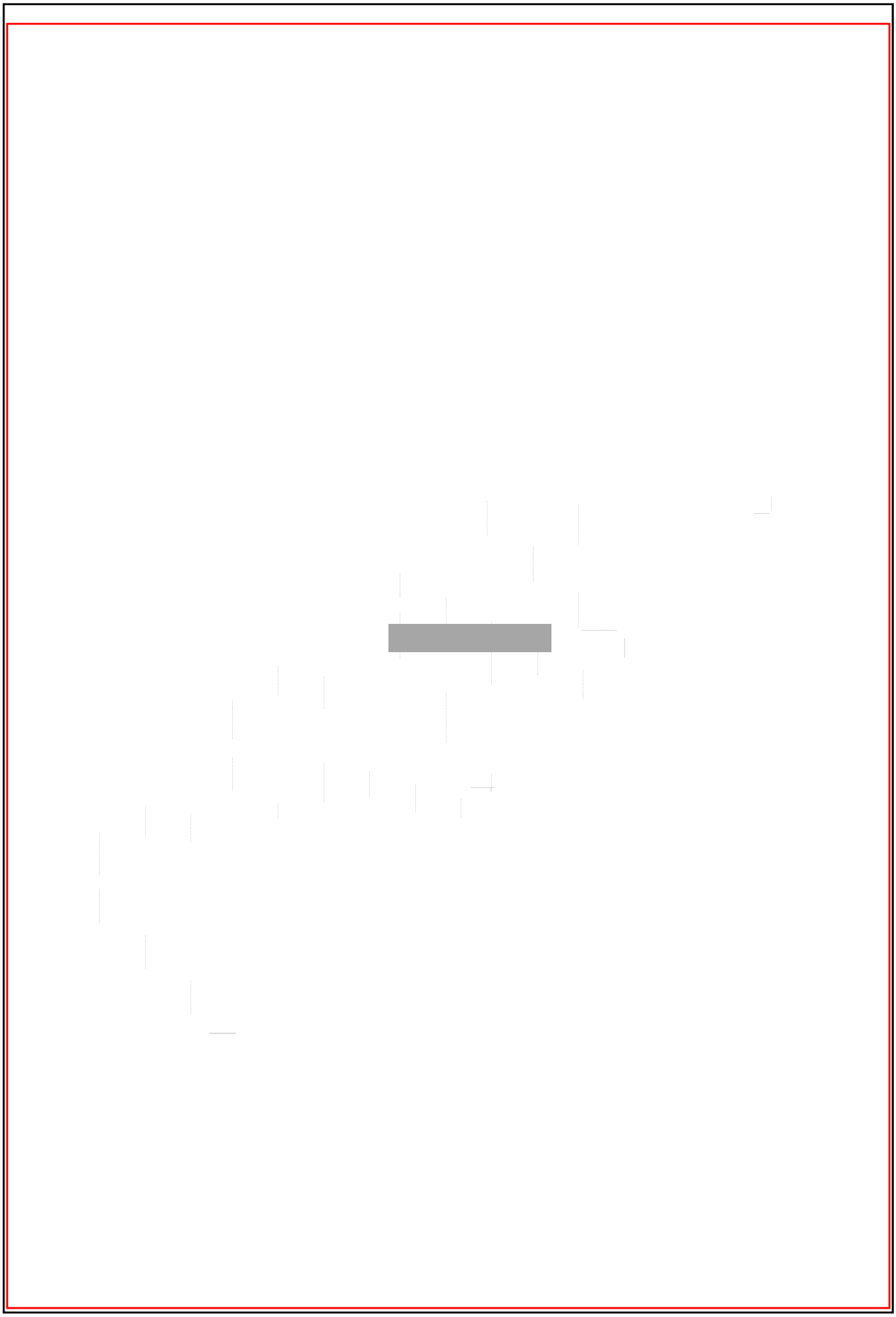


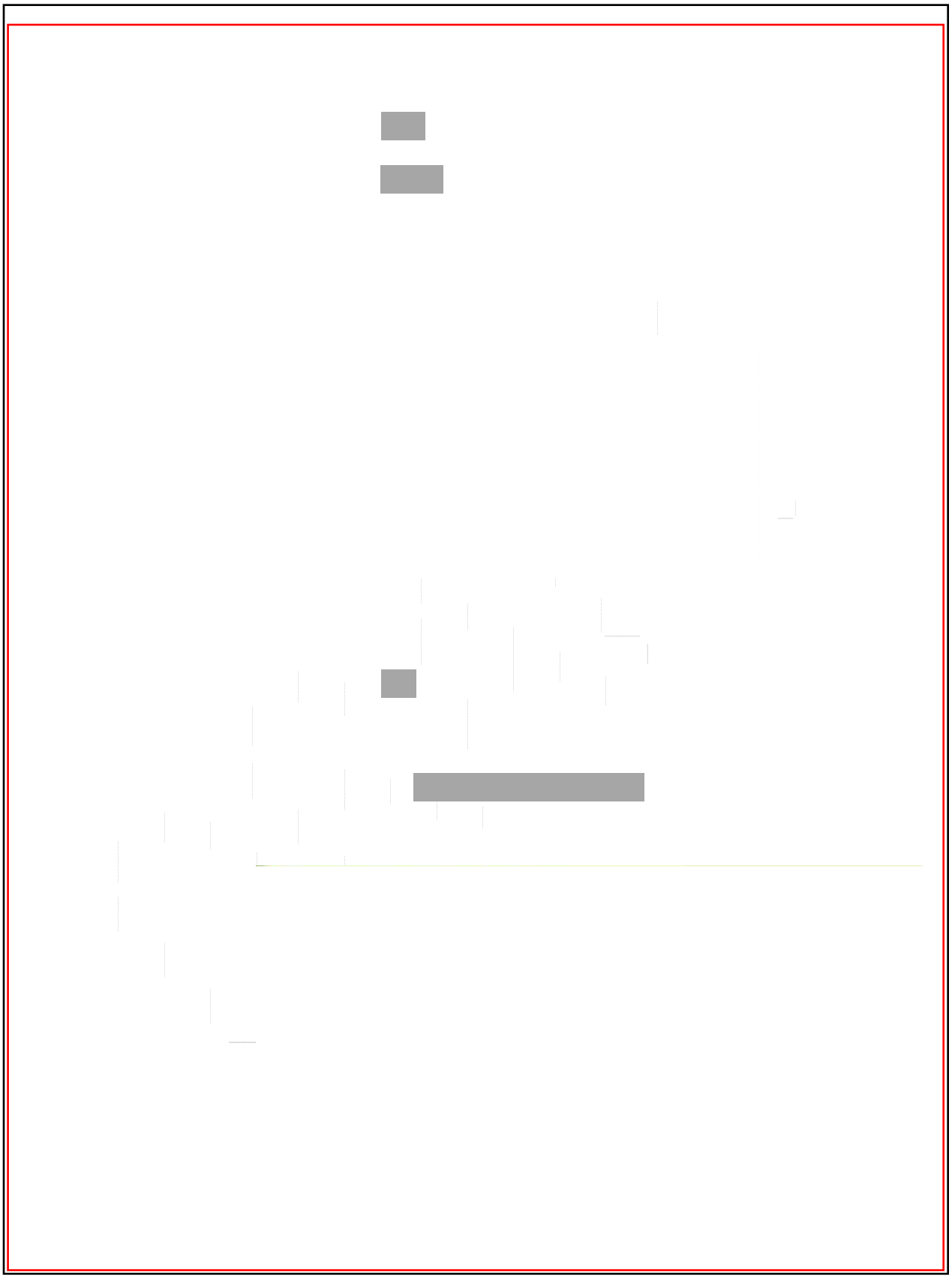


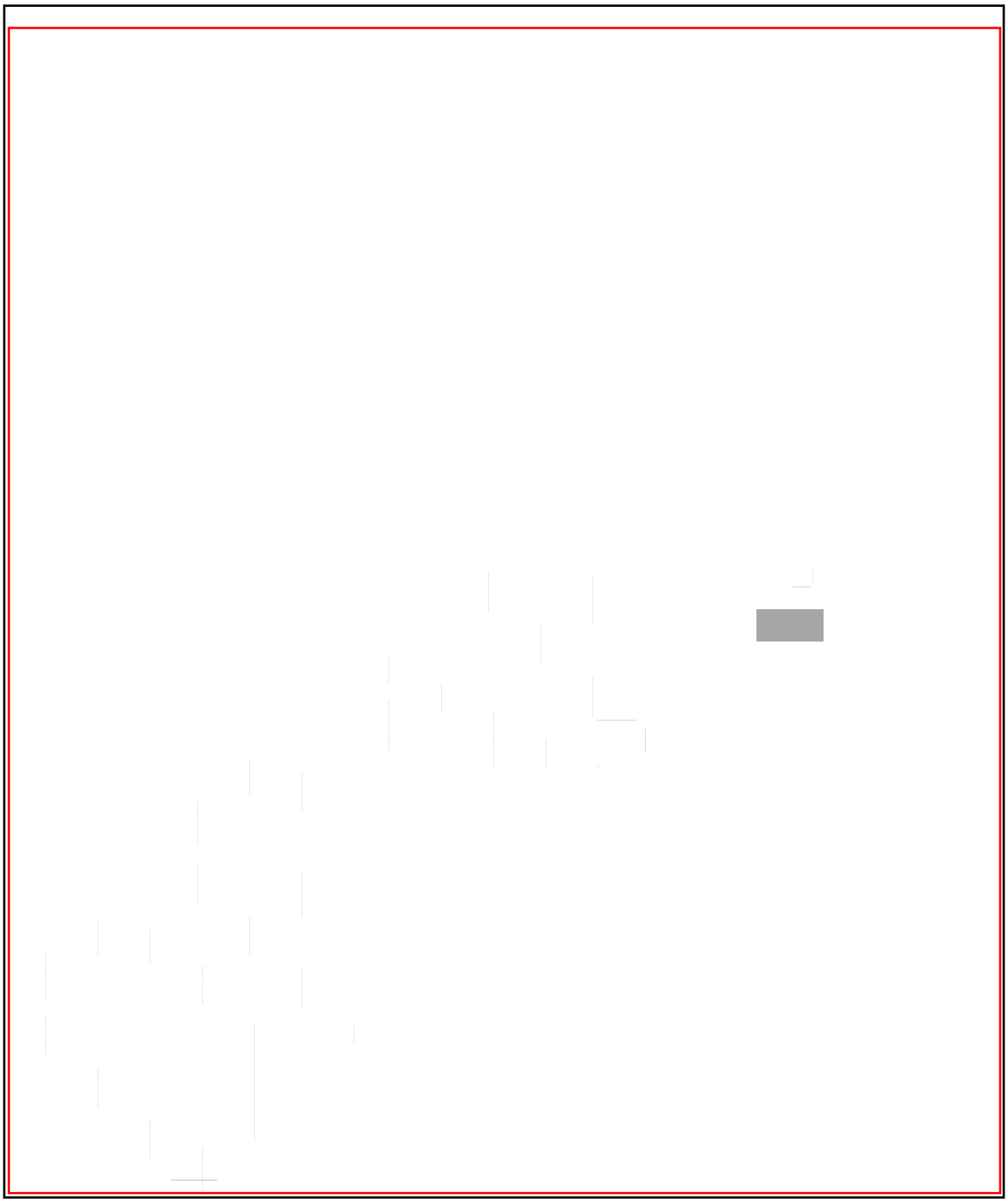


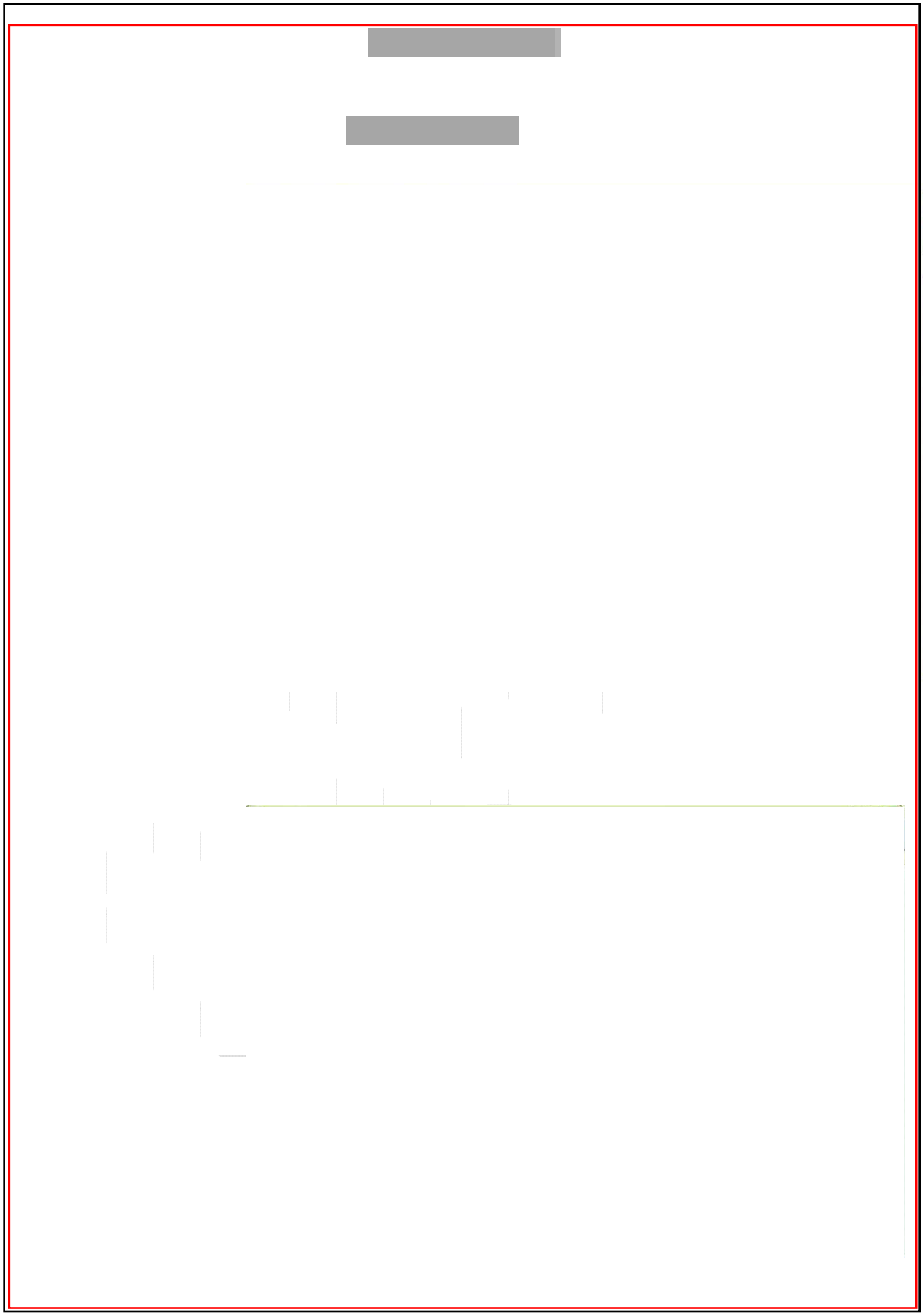


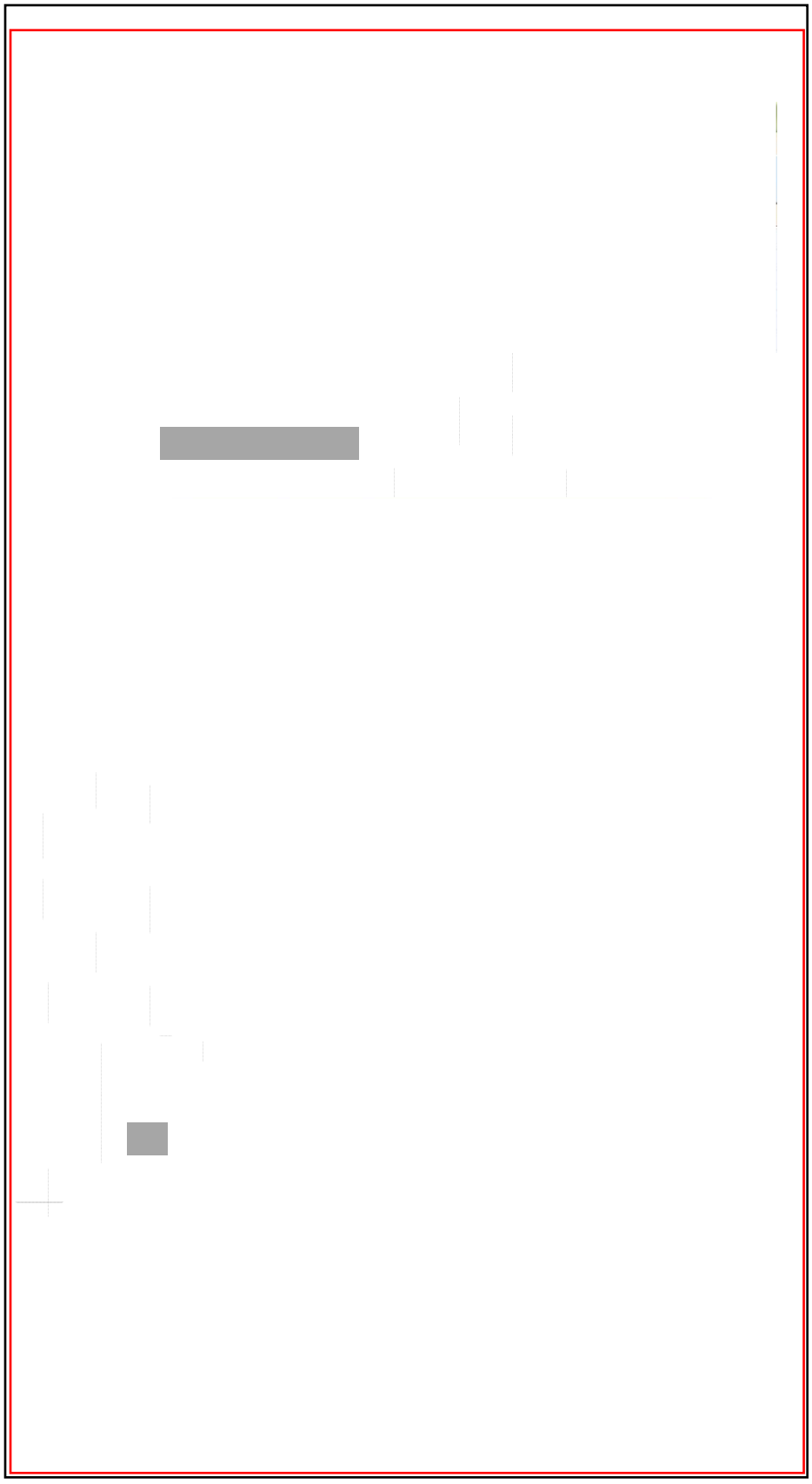












Appendix A - 1998 NINDS Consensus Guidelines

Anytime the user sets the pulse parameters that exceed the 1998 NINDS Consensus Guidelines, as specified in the table below, the system posts the “Parameters Exceed 1998 NINDS Consensus Guidelines” alarm.

The table below shows the 1998 NINDS Consensus Guidelines for maximum single train durations, in seconds, depending on %MT and PPS:

Maximum Duration of Single Trains
(seconds)

PPS	Intensity (% MT)												
	100	110	120	130	140	150	160	170	180	190	200	210	220
1	>1800	>1800	360	>50	>50	>50	>50	27	11	11	8	7	6
5	>10	>10	>10	>10	7.6	5.2	3.6	2.6	2.4	1.6	1.4	1.6	1.2
10	>5	>5	4.2	2.9	1.3	0.8	0.9	0.8	0.5	0.6	0.4	0.3	0.3
20	2.05	1.6	1.0	0.55	0.35	0.25	0.25	0.15	0.2	0.25	0.2	0.1	0.1
25	1.28	0.84	0.4	0.24	0.2	0.24	0.2	0.12	0.08	0.12	0.12	0.08	0.08

Note: Numbers preceded by > are the longest durations tested. No after discharge or spread of excitation has been encountered with single trains of rTMS at these combinations of stimulus frequency and intensity.

Table 1 Source: Reprinted from Wassermann EM: "Risk and Safety of Repetitive Transcranial Magnetic Stimulation: Report and Suggested Guidelines," from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. Electroencephalography and Clinical Neurophysiology 108(1):1-16, 1998. Reprinted with permission.

Appendix B – Neuronetics Clinical Studies

The clinical development program for the Neuronetics TMS System consisted of three integrated clinical protocols as displayed in Figure B-1.

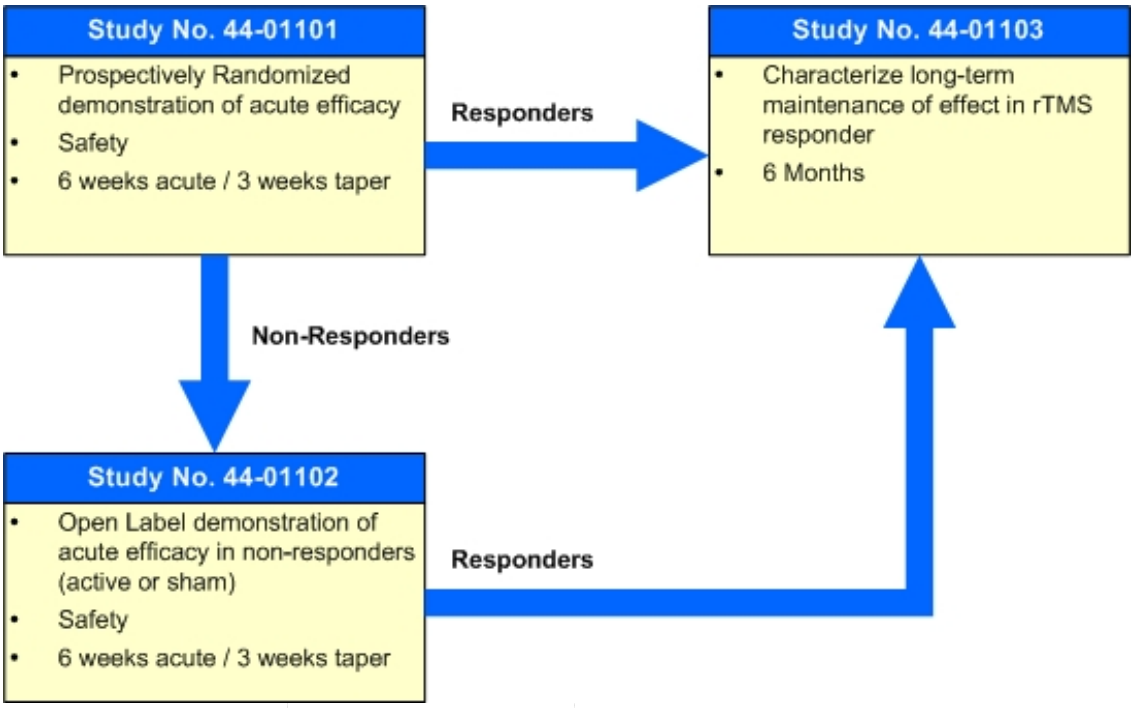


Figure B-1. Neuronetics' Clinical Studies and Patient Allocation

In brief, the efficacy of the Neuronetics TMS System was established in adult outpatients in a 9-week, randomized, sham-controlled clinical trial, Study 44-01101.

Patients who failed to receive benefit from their randomized assignment in Study 44-01101 were eligible to enter a 9-week, open-label cross-over study with the Neuronetics TMS System in Study 44-01102.

The maintenance of an acute clinical response to the Neuronetics TMS System in either Study 44-01101 or Study 44-01102 was established in a 24 week, open-label continuation clinical trial, Study 44-01103.

These studies show that transcranial magnetic stimulation (TMS) as delivered by the NeuroStar™ System is an effective, safe and well-tolerated antidepressant for the treatment for patients with major depressive disorder. The acute response to TMS treatment can be effectively maintained in a clinically meaningful manner during a follow up period of up to 24 weeks

B.1 Study 44-01101

Title: A Randomized, Parallel-Group, Sham-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of the Neuronetics Model 2100 CRS Repetitive Transcranial Magnetic Stimulation (rTMS) System in Patients with Major Depression.

Patients: Outpatients ages 18 to 70, meeting DSM-IV criteria for MDD, single episode or recurrent, with a current illness duration of 3 years or less and who had never previously been treated with TMS, were enrolled in Study 44-01101. The clinical diagnosis was confirmed by structured psychiatric interview. Patients were required to have a minimum symptom severity as reflected by a total score of at least 20 on the 17-item Hamilton Depression Rating Scale (HAMD17). In addition, patients were evaluated using the Antidepressant Treatment History Form (ATHF) and shown to have failed to receive benefit from at least 1 but no more than 4 adequate trials of an antidepressant in their current episode (ATHF Level 3 resistance rating). Patients who had failed to receive benefit from an adequate trial of electroconvulsive therapy at any point in their lifetime were excluded. Patients with psychiatric disorders other than MDD were also excluded. All patients were free of psychotropic medications for at least one week prior to and throughout the trial.

Design and Methods: A total of 325 patients were enrolled in Study 44-01101. This study design was comprised of three phases: a one week, no-treatment and drug washout lead-in phase, a six week acute treatment phase, and a 3 week taper phase. During the taper phase, treatment with the Neuronetics TMS System was tapered, while the patient was simultaneously tapered on to monotherapy with oral antidepressant medication. At any time after at least 4 weeks of participation in the acute phase of Study 44-01101, patients could be considered for enrollment in Study 44-01102 or 44-01103.

Patients were randomized to receive either active treatment or sham treatment. Randomization assignment was established prior to the start of the study, and was electronically recorded on sequentially assigned treatment cards that were used to control the operation of the Neuronetics TMS System in a blinded manner. This blinding method ensured identical appearance, placement and acoustic properties of the Neuronetics TMS System for both active and sham treatments. Efficacy outcome was assessed by study personnel not included in the treatment session itself as an additional means to ensure the study blind.

Treatment sessions were conducted in sequential five day series for the 6 week acute treatment phase. Six additional treatments were administered across the 3 week taper phase. The maximum number of treatments in was 36. Treatment parameters were standardized for each treatment session using a magnetic field intensity of 120% of the patient's observed motor threshold, at a repetition rate of ten magnetic pulses per second. Pulses were grouped in 30 second cycles with a stimulation on-time of 4 seconds, and an off-time of 26 seconds. A treatment session lasted for 37.5 minutes for a total number of 3000 magnetic pulses per session. Motor threshold was determined weekly by visual observation of thumb or finger movement using MT Assist®, which is a standardized mathematical algorithm that provides an iterated estimate of the motor threshold. The treatment location was over the left prefrontal cortex, determined by a standard convention of movement of the TMS coil 5 cm anterior to the motor threshold location along a left superior oblique angle.

The primary efficacy outcome was difference between active treatment and sham treatment using the total score of the Montgomery Asberg Depression Rating Scale (MADRS) at week 4 of the acute treatment phase. Secondary outcome measures included active versus sham

outcomes using the total score of the 24-item Hamilton Depression Rating Scale, and categorical outcomes such as 50% response rates and remission rates using both the HAMD and MADRS scores. Functional status and quality of life was measured using the Medical Outcomes Study 36-Item Short Form, and the Quality of Life Enjoyment and Satisfaction Questionnaire. Safety was assessed by adverse event reports, and by targeted safety evaluation of air-conduction auditory threshold. Cognitive function was assessed with the Mini Mental Status Examination, the Buschke Selective Reminding Test, and the Autobiographical Memory Inventory-Short Form.

Efficacy Results: Efficacy results for Study 44-01101 are summarized in Table B-2. Statistical significance at $p<0.05$ is shown highlighted.

Table B-2. A Priori-Defined Primary and Secondary Outcome Measures Observed in Study 44-01101. P Values for Contrasts Between Active TMS and Sham TMS Group for Intent-to Treat Study Population (All Analyses Conducted in LOCF Manner)

Primary Efficacy Outcome Measure	P value Week 4	P Value Week 6
MADRS Total Score	.057	.058
MADRS Total Score (baseline imbalance corrected)[1]	.038	.052
Secondary Efficacy Outcome Measures	**P value Week 4**	**P Value Week 6**
HAMD 24 Total Score	.012	.015
HAMD17 Total Score	.006	.005
MADRS Responder Rate	.045	.007
HAMD 24 Responder Rate	.030	.042
HAMD17 Responder Rate	.018	.015
SF-36 Item Questionnaire v1: Physical Functioning	.299	.229
SF-36 Item Questionnaire v1: Role Physical Score	.361	.221
SF-36 Item Questionnaire v1: Bodily Pain Score	.520	.301
SF-36 Item Questionnaire v1: General Health Score	.049	.047
SF-36 Item Questionnaire v1: Vitality Score	.179	.081
SF-36 Item Questionnaire v1: Social Functioning Score	.183	.386
SF-36 Item Questionnaire v1: Role Emotional Score	.105	.044
SF-36 Item Questionnaire v1: Mental Health Score	.006	.015
Q-LES-Q Total Score	.124	.035
MADRS Remission Rate	.633	.011
HAMD24 Remission Rate	.644	.012
HAMD17 Remission Rate	.705	.065
HAMD Anxiety/Somatization Factor Score	.025	.023
HAMD Core Depression Factor Score	.012	.008
HAMD Maier Factor Score	.003	.003

Primary Efficacy Outcome Measure	P value Week 4	P Value Week 6
HAMD Gibbons Factor Score	.007	.006
HAMD Retardation Factor Score	.007	.003
HAMD Sleep Factor Score	.211	.109
IDS-SR Total Score	.058	.053
Clinician Global Impressions-Severity (CGI-S) Total Score	.009	.012
Patient Global Impression-Improvement (PGI-I) Total Score	.181	.107

[1] *Recomputed analysis using a baseline cut-off for MADRS total score of 20 (see Section 13.1, Study Report 44-01101, Appendix 19)*

Efficacy Conclusions: TMS therapy delivered by the Neuronetics Model 2100 TMS System is statistically significantly superior to sham treatment at 4 and 6 weeks for key physician-rated depression measures (HAMD 17, HAMD24 and CGI-S) and for the MADRS total score when corrected for a statistically significant baseline score imbalance between active and sham groups.

Additionally, all three key depression measures (HAMD17, HAMD24 and MADRS) were statistically superior to sham treatment at 4 and 6 weeks for the clinically-meaningful categorical outcomes for >50% reduction in baseline score.

This data indicate that the TMS therapy delivered by the Neuronetics Model 2100 TMS System is effective in the treatment of major depressive disorder.

Durability of Effect: At the conclusion of the acute treatment phase, all remaining patients were entered into a continuation phase referred to at the *post-treatment taper phase*. During this portion of the study, all patients began a scheduled taper of their open-label, active TMS treatment across a 3-week schedule. At the same time, *all patients were initiated on open-label pharmacotherapy with a single antidepressant medication* selected from a protocol-defined list.

Categorical responder and remission rates for the primary disease-specific efficacy outcome measures (the MADRS, the HAMD24 and the HAMD17) were collected for all patients continuing into the post-treatment taper phase. These results showed that:

- The clinical effect of active TMS is sustained during transition to single-drug antidepressant monotherapy. This indicates that patients may be appropriately transitioned to clinically relevant continuation treatment without loss of clinical benefit achieved in the acute treatment phase.

Safety Results: The safety of TMS treatment using the Neuronetics TMS System was evaluated by the collection and evaluation of serious adverse events, spontaneous adverse events, cognitive function testing, auditory threshold testing and suicidal ideation.

Table B-3 summarizes adverse events by MedDRA-preferred term that occurred at an incidence of $\geq$ 2% on active and were greater than the incidence on sham.

Table B-3. Summary of MedDRA Preferred Term Adverse Events Occurring with an Incidence on Active TMS of > 2% and Greater Than the Incidence on Sham TMS

Body System (-) Preferred Term	Sham (N=158) N (%)	Active (N=165) N (%)
Ear and labyrinth disorders		
- Ear pain	1 (0.6)	4 (2.4)
- Tinnitus	2 (1.3)	7 (4.2)
Eye disorders		
- Eye pain	3 (1.9)	10 (6.1)
- Lacrimation increased	1 (0.6)	7 (4.2)
- Visual disturbance	2 (1.3)	4 (2.4)
Gastrointestinal disorders		
- Diarrhoea	6 (3.8)	8 (4.8)
- Nausea	10 (6.3)	17 (10.3)
- Toothache	1 (0.6)	12 (7.3)
- Vomiting	3 (1.9)	7 (4.2)
General disorders and site administration conditions		
- Application site discomfort	2 (1.3)	18 (10.9)
- Application site pain	6 (3.8)	59 (35.8)
- Facial pain	5 (3.2)	11 (6.7)
- Pain	3 (1.9)	7 (4.2)
- Pyrexia	1 (0.6)	4 (2.4)
Injury, poisoning and procedural complications		
- Overdose*	0	4 (2.4)
Musculoskeletal and connective tissue disorders		
- Arthralgia	5 (3.2)	10 (6.1)
- Muscle twitching	5 (3.2)	34 (20.6)
- Musculoskeletal stiffness	4 (2.5)	5 (3.0)
- Neck pain	4 (2.5)	8 (4.8)
Nervous system disorders		
- Dyskinesia	2 (1.3)	5 (3.0)
- Headache	87 (55.1)	96 (58.2)
- Hypoaesthesia	2 (1.3)	5 (3.0)
- Paraesthesia	4 (2.5)	6 (3.6)
- Tension headache	2 (1.3)	4 (2.4)
Psychiatric disorders		
- Agitation	3 (1.9)	4 (2.4)
- Anxiety	18 (11.4)	19 (11.5)
Reproductive system and breast disorders		
- Dysmenorrhoea	2 (1.3)	5 (3.0)
Respiratory, thoracic and mediastinal disorders		
- Cough	2 (1.3)	4 (2.4)
- Dyspnoea	1 (0.6)	6 (3.6)
Skin and subcutaneous tissue disorders		
- Pain of skin	1 (0.6)	14 (8.5)

Notes: * Overdose refers to events associated with inadvertent smart card operator error resulting in > 75 trains of active or sham TMS delivered to the patient on a single calendar day. Per protocol procedure, all of these events were considered as adverse events to be reported in the time frame and manner of serious adverse events.

- There were no deaths or seizures reported in Study 44-01101.
- The most common adverse events experienced by patients were headache (58.2% active TMS treatment vs. 55.1% sham TMS treatment) and application site pain (35.8% active TMS treatment vs. 3.8% sham TMS treatment). Both headache and application site pain lessened with time over the TMS treatment course, with application site pain substantially diminished within one week of treatment commencement.
- There was no evidence of clinically significant cognitive function testing change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System
- There was no evidence of clinically significant auditory threshold change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System (with use of earplugs during TMS treatment).
- There was no evidence that active TMS treatment was associated with worsening of suicidal ideation or emergent suicidal ideation during the acute treatment phase.

Overall Safety and Efficacy Conclusions: Study 44-01101 established that TMS therapy delivered by the Neuronetics TMS System is *statistically significantly superior to sham treatment at 4 and 6 weeks for key physician-rated depression measures* (HAMD 17, HAMD24 and CGI-S) and for the MADRS total score when corrected for baseline imbalance.

All three key depression measures (HAMD17, HAMD24 and MADRS) were *statistically superior to sham treatment at 4 and 6 week for the clinically-meaningful categorical outcomes for >50% reduction in baseline score*.

The safety was shown by the collection and evaluation of serious adverse events, spontaneous adverse events, cognitive function testing, auditory threshold testing and suicidal ideation.

The data indicates that TMS therapy delivered by the Neuronetics TMS System is safe and effective in the treatment of major depressive disorder.

B.2 Study 44-01102

Title: A 9-week, Uncontrolled, Open-Label Study to Evaluate the Efficacy and Safety of the Neuronetics Model 2100 Repetitive Transcranial Magnetic Stimulation (rTMS) System in the Treatment of Patients with Major Depression Previously Non-Responsive to Active or Sham rTMS Treatment.

Patients: See Study 44-01101.

Design and Methods: A total of 166 patients were enrolled in Study 44-01102. Patients who participated in Study 44-01101 for at least 4 weeks of acute phase treatment and who failed to receive benefit from their randomized treatment assignment in that study, and who also showed less than a 25% decline in their HAMD17 total score at exit compared to their baseline score, were eligible for enrollment into Study 44-01102. Treatment assignment from Study 44-01101 was not unblinded at the time of enrollment into Study 44-01102. Study 44-01102 was an open-label, uncontrolled clinical trial otherwise identical in design and treatment sequence to Study 44-01101.

Efficacy Results: Efficacy results for Study 44-01102 are summarized below for clinician-rated outcome measures as shown in Table B-4 . The table shows the mean change in total efficacy assessment scores, and responder and remission rates for patients who were randomized in Study 44-01101 to either active TMS or to sham TMS and were subsequently treated with open-label TMS in Study 44-01102.

Table B-4. Open-Label TMS Study 44-01102: A Priori-Defined Outcome Measures

Efficacy Outcome Measures	Week 4 Study 101 Active Non-Responder	Week 6 Study 101 Active Non-Responder	Week 4 Study 101 Sham Non-Responder	Week 6 Study 101 Sham Non-Responder
MADRS Total Score Mean Change[1]	-10.5	-12.5	-11.9	-17.0
HAMD 24 Total Score Mean Change[1]	-9.0	-11.1	-11.0	-14.5
HAMD17 Total Score Mean Change[1]	-6.4	-8.2	-8.2	-10.8
MADRS Responder Rate (%)[2]	20.5	26.0	25.0	42.4
HAMD 24 Responder Rate (%)	21.9	31.5	28.2	42.4
HAMD17 Responder Rate (%)	21.9	30.1	27.1	37.6
MADRS Remission Rate (%)[3]	5.5	11.0	5.9	20.0
HAMD24 Remission Rate (%)[4]	9.5	16.4	12.9	27.1
HAMD17 Remission Rate (%)[5]	6.8	15.1	10.6	21.2

[1] Change in total score mean change from baseline at entry to Study 44-01102
[2] Responder is >50% change from baseline score at entry to Study 44-01102
[3] MADRS Remission is defined as MADRS total score <10
[4] HAMD24 Remission is defined as HAMD24 total score <11
[5] HAMD17 Remission is defined as HAMD17 total score <8

Efficacy Conclusions: Patients with major depression who have failed to receive adequate clinical benefit from medication therapy show a clinically meaningful response to open-label treatment with the Neuronetics TMS System.

After failure to receive benefit from their randomized treatment assignment in study 44-01101, patients previously assigned to sham TMS show a consistent and numerically superior clinical benefit with open-label TMS treatment in comparison with patients previously assigned to active TMS.

A clinically meaningful proportion of patients who failed to receive clinical benefit after at least 4 weeks of active TMS, respond successfully to an extended duration of active treatment with TMS.

Durability of Effect: As in Study 44-01101, at the conclusion of the acute treatment phase, all remaining patients were entered into a continuation phase referred to at the *post-treatment taper phase* where they began a scheduled taper of their open-label, active TMS treatment across a 3-week schedule with *initiation onto open-label pharmacotherapy*. The results showed:

- Patients previously allocated to sham TMS treatment in study 44-01101 consistently showed a greater clinical benefit during this continuation period in Study 44-01102 as compared to those patients previously allocated to active TMS treatment.

Safety Results: The safety of TMS treatment using the Neuronetics TMS System was evaluated by the collection and evaluation of serious adverse events, spontaneous adverse events, cognitive function testing, auditory threshold testing and emergent suicidal ideation.

- There were no deaths or seizures reported in this study
- Adverse events and their temporal relationship in study 44-01102 were similar to that reported in study 44-01101.
- Application site pain was observed in both treatment groups, but the incidence was greater in the patient group that had previously been allocated to sham TMS treatment prior to entry into study 44-01102, suggesting that the prior exposure assisted in accommodation to this effect.
- For both headache and application site pain, the greatest incidence was observed during the first week of treatment with a substantial reduction in incidence after the first week of treatment, consistent with a rapid accommodation to these commonly experienced events. This accommodation effect was more pronounced for application site pain.
- There was no evidence of clinically significant cognitive function testing change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System
- There was no evidence of clinically significant auditory threshold change at either 4 weeks or 6 weeks associated with acute treatment with the Neuronetics TMS System.
- There was no evidence that active TMS treatment was associated with worsening of suicidal ideation or emergent suicidal ideation during the acute treatment phase.

B.3 Study 44-01103

Title: A 6-month, Open-Label Maintenance Study of Patients with Major Depression Previously Responsive to rTMS Treatment with the Neuronetics Model 2100 CRS Repetitive Transcranial Magnetic Stimulation (rTMS) System.

Patients: See Study 44-01101

Design and Methods: At total of 136 patients were enrolled in Study 44-01103. This study was an open-label, uncontrolled clinical trial providing 24 weeks of continuation oral antidepressant monotherapy to patients who showed a 25% or greater improvement in their HAMD17 total score at the end of participation in either Study 44-01101 or Study 44-01102, compared to their baseline HAMD17 score in those studies.

During the course of Study 44-01103, patients were permitted to adjust their monotherapy antidepressant medication schedule as clinically indicated, but were not permitted to switch or combine antidepressant regimens. In the event that a patient's clinical symptoms deteriorated as determined by change in the Clinical Global Impressions – Severity of Illness score, observed on at least two sequential study visits, then open-label TMS treatment was reintroduced in conjunction with continuation pharmacotherapy, for up to 24 sessions across six weeks. Treatment with the Neuronetics TMS System was discontinued if symptom resolution occurred. Patients were discontinued from this study if they experienced a recurrence of DSM-IV defined MDD or if they failed to receive benefit from a full course of reintroduction of treatment with the Neuronetics TMS System. Efficacy and safety outcomes were assessed using the same measurement instruments as in Study 44-01101.

Interim Efficacy Results: The data reported for Study 44-01103 are interim in nature at this writing. These data demonstrate that the durability of the acute treatment response to active TMS is maintained over the first four weeks of TMS-free treatment expressed in terms of the incidence of illness relapse. Using the protocol-defined definition of discontinuation for all cause during this time interval, the cumulative incidence of relapse is 2.3%.

An alternative definition was also applied in an exploratory manner over this same time interval, based on a definition of change in HAMD24 score derived (a relapse definition commonly used in the ECT literature). Based on this definition, the cumulative incidence of relapse across the first 4 weeks of TMS-free treatment is 9.1%.

Efficacy results for patients who were responders in the active treatment group in Study 44-01101 and continued directly into Study 44-01103 (Group 1) are summarized in Table 10.7 and show mean score change and remission rates for MADRS, HAMD 24 and HAMD 17 item scores.

Table 5. A Priori-Defined Outcome Measures for Group 1[1]

Efficacy Outcome Measures	Week 1	Week 2	Week 3	Week 4
MADRS Total Score Mean Change[2]	-20.1	-21.4	-20.3	-21.2
HAMD24 Total Score Mean Change[2]	-18.0	-19.0	-18.4	-19.6
HAMD17 Total Score Mean Change[2]	-14.0	-14.4	-13.9	-14.6
MADRS Remission Rate (%)[3]	50	59.1	52.7	45.5
HAMD24 Remission Rate (%)[4]	47.7	54.5	47.7	43.2
HAMD17 Remission Rate (%)[5]	50	56.8	43.2	43.2

[1] Group 1 are patients who were responders in the active treatment group in Study 44-01101

[2] Baseline is defined as baseline of Study 44-01101
[3] MADRS Remission is defined as MADRS total score <10
[4] HAMD24 Remission is defined as HAMD24 total score <11
[5] HAMD17 Remission is defined as HAMD17 total score <8

Overall, 38.2% of all patients in study 44-01103 have experienced at least one cycle of TMS reintroduction during the 6 month duration of the study. Most treatments occur subsequent to the first month, with the median time to reintroduction ranging from 6.5 to 11 weeks after enrollment in study 44-01103. These results suggest that symptomatic change sufficient to require TMS reintroduction occurs in less than half of the patients entering study 44-01103 overall, and that the time to reintroduction is not immediate, but occurs after approximately 1-3 months.

Interim Efficacy Conclusions: In patients who have shown an acute response to active treatment with the Neuronetics TMS System, the rate of protocol-defined relapse over a 4 week period of observation is 2.3% (9.1% using a literature-based alternative definition of relapse derived from the HAMD24 total score).

The acute response to active TMS treatment can be effectively maintained in patients treated with antidepressant medication monotherapy during a 4 week period of follow up after their last TMS treatment, as shown by the pattern of symptom change over that period:

- The mean change from baseline score prior to treatment shows a large, stable, and clinically meaningful reduction in total symptom burden over a 4 week period of maintenance treatment
- A majority of patients maintain a criterion score of remission as measured by either the MADRS, HAMD24 or the HAMD17 that is stable over a 4 week period of maintenance treatment

Depending upon their treatment path prior to entry into study 44-01103, the percentage of subjects who experienced symptomatic worsening and were provided with *reintroduction of active TMS* treatment for at least one cycle observed at this interim report across 24 weeks ranged from 33.3% to 47.8%**.**

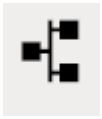
Safety Results: The safety of TMS treatment using the Neuronetics TMS System was evaluated by the collection and evaluation of serious adverse events and spontaneous adverse events for this interim report.

- There were no deaths, seizures or suicides.
- Patients who showed an acute response to TMS treatment during either controlled or open-label treatment with the Neuronetics TMS System show a pattern of adverse events during 24 week maintenance treatment with antidepressants that is consistent with the expected profile of adverse events with medication use and with the expected profile of adverse events seen in Neuronetics' studies 44-01101 and 44-01102.

Overall Safety and Efficacy Conclusions: A majority of patients who experienced symptomatic response to acute TMS treatment in study 44-01101 showed a clinically meaningful and stable pattern of symptomatic response during *4 weeks* of maintenance antidepressant pharmacotherapy alone. Active TMS was safe and well tolerated when administered in an adjunctive manner with antidepressant pharmacotherapy.

Appendix C – Symbols

Symbol	Meaning
	Attention: Consult Accompanying Documents
	Off (Power: disconnection from the Mains)
	On (Power connection to the Mains)
	Type BF Equipment
	Dangerous Voltage
	AC Power Input
	Quantity of Contents
	For Single Use Only. Do Not Reuse.
	Storage Temperature Range
	Latex-Free
	Electrostatic Sensitive Device
	Reset

Symbol	Meaning
	USB Port
	Network Connection
	Electromagnetic interference may occur in the vicinity of equipment.

Appendix D – Abbreviations, Terms, and Definitions

Highlighted terms refer to the main NeuroStar TMS System components.

Term	Meaning
Alignment Guide	A mechanical system that the clinician uses to register a patient's anatomical landmarks to help identify the coordinates and replicate the motor threshold and treatment positions on the patient's head.
A/P	Anterior/Posterior (used in locating the patient's MT).
APB	Abductor pollicis brevis, the muscle used in the so-called method of limits using either observation of twitch in the right APB muscle (thumb).
Brake	"Release to lock" type device placed on the coil assembly to hold the coil in place.
Coil	Electromagnet that is connected to the mobile console and gantry and placed against the side of the patient's head for therapy delivery during a treatment session.
Contact Sensing	Sensor and software used to detect contact between the coil and the patient's head.
Cushion Set	Set of cushions to help enhance the comfort and positioning of the patient in the desired posture for the duration of the treatment.
Display	Touch screen and LCD combination that provides the user interface for the NeuroStar TMS system. This is also the main user input device.
EMC	Electromagnetic Compatibility
EMG	Electro-myograph. An electronic measuring device that senses neurologically evoked potential with electrodes placed on the skin in the area of interest. EMG could be used to sense a thumb twitch when performing motor threshold determination.
Field Sensing	Capability of detecting the magnetic field strength of the coil during a test pulse sequence.
FRU	Field Replaceable Unit. The highest level of unit to which a malfunctioning component is integrated
Gantry	A retractable mechanical arm that helps to suspend the coil in space for positioning on a patient's head. It supports various degrees of motion to navigate the coil in free space and to move to a desirable location for determining MT and for delivering treatments. It supports the weight of the coil while permitting easy placement with the Alignment Guide.
Halo	Adjustable mechanical device to which the coil is attached. It is used to position the coil properly against the patient's head, and it includes a manual brake so the resistance can be adjusted by the operator.

Term	Meaning
Head Cushion	Soft, pliable cushion on the Head Support that provides comfort for the patient's head.
Head Cushion Liner	A disposable, single-use, hygienic paper sheet that is applied to the Head Cushion.
Head Support Unit	Frame and cushion attached to the treatment chair to support the patient's head during a treatment session and to assist in coil positioning.
HIPAA	Health Insurance Portability and Accountability Act, a Federal law that covers healthcare-related data processing identifiers and transactions, and that mandates security and privacy in data processing and communication.
Interval	The period of time between pulse trains (seconds).
Lumbar Cushion	Part of the treatment chair that consists of an adjustable cushion that supports the lumbar region of the patient's back during treatment.
LSOA	Left Superior Oblique Angle. The angle formed by tilting a mid-sagittal plane around an A/P axis (used in locating the patient's MT Position).
Mast	The vertical pole portion of the gantry.
MDD	Major Depressive Disorder
MEP	Motor Evoked Potential
Mobile Console	System component that contains the system electronics and controls and supports the gantry and display arm.
MT	Motor Threshold.
MT Assist®	A patented computer program that enables the NeuroStar TMS System user to pinpoint a patient's MT location and MT level.
MTL	Motor Threshold Level. The minimum value of an electromagnetic pulse output needed to stimulate a patient's motor strip to cause a thumb twitch.
NINDS	National Institute for Neurological Disorders and Stroke
PC	Personal Computer
PDMS	Practice Data Management System, the optional NeuroStar TMS System patient management and reporting software that runs on a separate personal computer and communicates with the NeuroStar TMS System mobile console through a wireless connection.
Power Module	Hardware that contains the power supply, power storage, discharge circuits, and the controlling logic.
Processor Module	Hardware that contains the computer and boards that control the user interface and that drive the NeuroStar TMS system.
Pulse Repetition Rate	Measurement that defines the number of magnetic pulses occurring in a second. The unit for this parameter is in Pulses Per Second (PPS)

Term	Meaning
Pulse Test	A preliminary NeuroStar TMS System test in which the system generates pulses of 1.2 and 2.1 SMT units. The system takes a reading for each set. If the system fails to generate these pulses, it displays a failure message and prevents the user from performing treatments or MT.
Pulse Train	The group of NeuroStar TMS System electromagnetic pulses occurring during treatment stimulation time.
Save MT	MT Assist® software option that enables the user to store in the system the MT level for a patient.
SenStar™	A single-use disposable integrated flexible circuit that must be attached to the coil prior to treatment to facilitate contact sensing and magnetic field detection and to decrease the magnetic field at the scalp surface to enhance tolerability during treatment
SI	Superior/Inferior
Side Pad	Soft, pliable cushion that offers counter forces to the coil to hold the head in the desired position.
Simple View	MT Assist® program screen that lists the patient's MT level, the MT search pass number, and a progress bar for the current search. (See also, Tabular view.)
SMT	Standard Motor Threshold
SMT Unit	The amount of voltage required to stimulate the neurons in a person's brain 2 cm below the scalp. A measurement unit used to specify a stimulator output level.
Stimulation Time ("Stim Time")	The length of a pulse train (seconds).
System Processor Board	Hardware containing the main processor and other PC components.
System Software	The main software residing in the processor module and running on the NeuroStar TMS System processor board.
Tabular View	MT Assist® application screen that lists for each pass in table format the MT level, the MT Assist® pass number, and a yes/no field for the clinician to record the observation of the patient's thumb twitch. (See also, Simple view.)
Treatment Chair	Patient treatment platform in the form of a chair that seats the patient comfortably at a electro-mechanically adjustable heights and angles (between 45° and 90°) for treatment and includes the head support.
Treatment Coil	The active and fully functioning electromagnetic coil that is connected to the mobile console and placed against patient's scalp for treatment delivery during a TMS session.

Term	Meaning
TMS	Transcranial Magnetic Stimulation, a method of using very short pulses of magnetic energy to stimulate nerve cells in the brain. TMS will be used synonymously with Repetitive Transcranial Magnetic Stimulation, which refers to TMS with repetition rates greater than 1 pps.
Treatment Record	Electronic record containing the details of the patient's treatment sessions.
USB	Universal Serial Bus. Port used to connect external devices to the NeuroStar TMS System hardware.

Appendix E – Treatment Graph Interpretation

The NeuroStar TMS System software displays the treatment graph on the screen during a treatment session.
The treatment graph displayed for any operation has the following base characteristics:

- The X-axis represents time. There are three readable labels on the X-axis showing time remaining in minutes and seconds. There is a label below the Y-axis showing the total treatment time.
- The Y-axis represents the %MT with major labels on the Y-axis for 0%, 80%, 100%, 120%, and 140%.
- The trains on the treatment graph are represented by filled boxes. The number of filled boxes on the graph is the number of trains called for in the treatment parameters.
- The height of each box is scaled to represent the current machine output level setting based on the %MT.
- The width of each box is scaled to represent the Stimulation Time.
- The spacing between each box is scaled to represent the Interval Time.
- The first filled box is placed on the Y-axis, representing the fact that once the treatment begins, pulses occur immediately.
- There is a colorized contact sensor display history integrated in the treatment graph, showing green when the contact sensor is good and red when the contact sensor is poor.
- There is a vertical line indicator at the time there was a pause in treatment. The indicator for manual pauses is a light red color and labeled with a “P”. The indicator for an auto pause due to contact sensing off is a bright red and is labeled “AP.”
- There is a current time vertical line that increments every second. This vertical line is a sweeping cursor.

Appendix F – Electromagnetic Compatibility

Table F-1. Neuronetics Declaration: Electromagnetic Emissions

The NeuroStar TMS System is intended for use in the electromagnetic environment specified below. The NeuroStar TMS System user should ensure that the equipment is used in such an environment.		
Emissions Test	Compliance	Electromagnetic Environment - Guidance
RF Emissions CISPR 11	Group 2	The NeuroStar TMS System must emit electromagnetic energy in order to perform its intended function. Nearby electronic equipment may be affected.
RF Emissions CISPR 11	Class A	The NeuroStar TMS System is suitable for use in all establishments other than domestic and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes.
Harmonic Emissions IEC 61000-3-2	Not applicable	
Voltage Fluctuations/Flicker Emissions IEC 61000-3-3	Not applicable	

(EN 60601-1-2 Table 201)

Table F-2. Neuronetics Declaration – Electromagnetic Immunity

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
The NeuroStar TMS System is intended for use in the electromagnetic environment specified below. The customer or user of the NeuroStar TMs System should assure that it is used in such an environment.			
Immunity Test	IEC 60601 Test Level	Compliance Level	Electromagnetic Environment – Guidance
			Portable and mobile radio frequency communications equipment should be no closer to the NeuroStar TMS System, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter.
			Recommended Separation Distance
Conducted RF IEC	3 VRMS 150 kHz to	3V	$d = (1.17)\sqrt{P}$

Guidance and Manufacturer's Declaration – Electromagnetic Immunity			
61000-4-6	80 MHz		
Conducted RF IEC 61000-4-3	3 VRMS 80 MHz to 2.5 GHz	3V/m	$d = (1.17)\sqrt{P}$ 80 MHz to 800 MHz $d = (2.33)\sqrt{P}$ 800 MHz to 2.5 GHz where ***P*** is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and ***d*** is the recommended separation distance in meters (m). Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey,[a] should be less than the compliance level in each frequency range.[b] Interference may occur in the vicinity of equipment marked with the following symbol: 

NOTE 1 At 80 MHz and 800 MHz, the higher frequency range applies.

NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects, and people.

[a] Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast, and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the NeuroStar TMS System is used exceeds the applicable RF compliance level above, the NeuroStar TMs System should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as reorienting or relocating the NeuroStar TMS System.

[b] Over the frequency range of 150 kHz to 80 MHz, field strengths should be less than 3 V/m.

(EN 60601-1-2 Table 204)

Table F-3. Recommended Separation Distance between Portable and Mobile RF Communications Equipment and the NeuroStar TMS System for Equipment and Systems that are not Life-Supporting

Recommended Separation Distance between Portable and Mobile RF Communications Equipment and the NeuroStar TMS System

The NeuroStar TMS System is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or user of the NeuroStar TMs System can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the NeuroStar TMs System as recommended below, according to the maximum output power of the communications equipment.

Rated Maximum Output Power of Transmitter (W)	Separation Distance According to Frequency of Transmitter (m)		
	150 kHz to 80 MHz $d = (1.17)\sqrt{P}$	80 MHz to 800 MHz $d = (1.17)\sqrt{P}$	800 MHz to 2.5 GHz $d = (2.33)\sqrt{P}$
0.01	0.12	0.12	0.23
0.1	0.37	0.37	0.74
1	1.17	1.17	2.33
10	3.70	3.70	7.37
100	11.7	11.7	23.3

For transmitters rated at a maximum output power not listed above, the recommended separation distance *d* in meters (m) can be estimated using the equation applicable to the frequency of the transmitter, where *P* is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer.

NOTE 1 At 80 MHz and 800 MHZ, the separation distance for the higher frequency range applies.

NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structure, objects, and people.

(EN 60601-1-2 Table 206