Official Title: A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors.

NCT Number: NCT03094286

Document Dates: Protocol Amendment Version 4.1: 14 November 2018

A PHASE II EXPLORATORY STUDY OF DURVALUMAB (MEDI4736) IN HIV-1 PATIENTS WITH ADVANCED SOLID TUMORS

DURVAST: Durvalumab in solid tumors

Study Sponsor: Fundación GECP

EudraCT Number: 2016-004524-38

Sponsor code: GECP 16/04

[redacted]

Version 4.1

Protocol Signature Page

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DURVAST: Durvalumab in solid tumors

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Approved By

Signature

_____

[redacted]

Principal investigator

Signature

_____

[redacted]

Study coordinator

Signature

_____

[redacted]

Fundación GECP President

Principal Investigator Protocol Signature Page

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EudraCT Number: 2016-004524-38

Protocol version: v 4.1, 14th November 2018

As principal investigator of this site, I hereby confirm that:

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations.

I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by the Fundación GECP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial.

I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 25 years according to the new Royal Decree 1090/2015 approved in Spain.

Name of Principal Investigator:_____

Institution's name and place:_____

_____ _____

Signature Date

Investigational Drug Substance(s)	Durvalumab (Medi4736)
Version	4.1
Date	14th November 2018

A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors

Sponsor: Fundación GECP
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PROTOCOL SYNOPSIS

Clinical Protocol GECP16/04 (ESR 15-10869)

Study Title: Phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors
Protocol Number: GECP 16/04 [redacted]
Clinical Phase: II
Study Duration: Recruitment period will be 12 months First subject in: Q1, 2016 Last subject out: Q1, 2018 Survival follow-up will continue until 5 years after the last subject receives the last dose of durvalumab
Investigational Product(s) and Reference Therapy: Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration.
Research Hypothesis PD-1/ PD-L1 coinhibitory pathway plays a significant role in the regulation of the immune response in both chronic infectious diseases and cancer. Preclinical and animal data support the safety and promising activity of anti-PD-1 antibody in HIV-1 infection. Demonstrated anticancer activity and safety profile of durvalumab (MEDI4736) in cancer clinical trials. Unlikely drug interactions of durvalumab (MEDI4736) and antiretroviral treatments. We propose a phase II clinical study designed to assess the feasibility of durvalumab (MEDI4736) in HIV-1-infected individuals with solid tumors. Additionally we hope to obtain data that let us understand

the possible benefit of this treatment in cancer patients and HIV infection, exploring if activity of durvalumab (MEDI4736) could be higher in cancer that has been produced at least in part due to the chronic immunosupression. Simultaneously, it will allow us to investigate the effect of disrupting this immunoregulatory pathway might have in reversing cancer pathways and HIV-specific T-cell function during persistent chronic HIV infection in humans.

In this regard, our hypothesis is:

HIV patients with cancer have a similar outcome in terms of tolerability when treated with durvalumab (MEDI4736) monotherapy at the recommended dose than non HIV infected patients.

Objectives:

Primary Objectives:

To explore the feasibility of durvalumab (MEDI4736) monotherapy at the recommended dose of 1500mg every 4 weeks in solid tumors in HIV-1-infected patients.

Secondary Objective(s):

- To assess ORR (RECIST 1.1 and irRECIST) and duration of response.
- To evaluate the PFS rate at 6 months.
- To evaluate the OS rate at 12 months.

[redacted]

Study Design:

This is a multicenter, national, nonrandomized, open label trial, phase II trial in subjects with advanced solid tumors and HIV-1 infection. Twenty patients will receive durvalumab.

Patients have to be diagnosed of advanced (metastatic or locally advanced disease without cure options with surgery or radiotherapy) cancer of any of these types: lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastro-esophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity.

Adverse events (AEs) will be assessed throughout and evaluated using National Cancer Institute (NCI) Common Technology Criteria version of Adverse Events version 4.03 (CTCAE v 4.03).

Tumor measurements by PET-CT, CT scan or MRI will be performed every 8 weeks to determine response to treatment. Response will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and immune related response criteria (irRECIST).

Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. Treatment may continue past the initial determination of disease progression per RECIST1.1 if the subject`s performance status has remained stable, and if the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outline in the protocol.

Number of Centers: between 5 and 10

Number of Subjects: 20

Study Population:

The study will be performed in 20 HIV patients with a histological confirmed diagnosed of advanced solid tumors (lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastro-esophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity) for which no additional oncologic standard treatment is available, or for which the subject declines standard treatment.

Recruitment period will be 12 months.

Patients will continue their antiretroviral treatment during study time, following standard HIV-1 treatment recommendations.

Inclusion Criteria:

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
2. Age $\geq$ 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) 0-2
4. Life expectancy of $\geq$ 16 weeks

5. Adequate normal organ and marrow function as defined below:

- Haemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
- Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
- Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight(kg)x(140 – Age)}}{\text{72 x serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg) x (140 – Age) x0.85}}{\text{72 x serum creatinine (mg/dL)}}$$

6. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

7. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

8. Subjects with histologically or cytologically advanced/metatasic-documented lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity, refractory to standard treatment, intolerant of standard treatment, or for which no standard therapy exists or who refuse the standard treatment.

9. Subjects may be included irrespectively of number of previous lines of treatment for advanced disease.

10. Prior palliative radiotherapy must have been completed at least 2 weeks prior to start the study treatment (subjects may receive localized palliative radiotherapy while receiving study drug).

11. Documented HIV-1 infection

12. Undetectable viral load in the last analysis.

13. Subjects with brain metastases are eligible if they are asymptomatic, are treated or are neurological stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of < 10 mg daily prednisone or equivalent.

14. Subjects must be following an antiretroviral therapy at the moment of the inclusion.

Exclusion Criteria:

1. Involvement in the planning and/or conduct of the study. Previous enrollment in the present study.

2. Participation in another clinical study with an investigational product during the last 4 weeks.

3. Other untreated coexisting HIV related malignancies.

4. Any previous treatment with a PD1, PD-L1 or PD-L2 inhibitor, including durvalumab.

5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 28 days prior to the first dose of study drug.

6. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.

7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

8. Any unresolved toxicity (CTCAE grade 2) from previous anti-cancer therapy. *Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).*

9. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.

10. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

11. Any syndrome that requires systemic corticosteroid/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger (vitiligo, autoimmune thyroiditis, or type 1 diabetes mellitus are permitted to enroll)

12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

13. History of primary immunodeficiency.

14. History of allogeneic organ transplant.

15. History of hypersensitivity to durvalumab or any excipient.

16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B or C, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

17. Known history of active tuberculosis.

18. Any serious or uncontrolled medical disorder or active infection non HIV, that would impair the ability of the subject to receive the treatment of protocol therapy under treating physician criteria.

19. Subjects with previous malignances (except non melanoma skin cancer, and cancer in situ of: bladder, gastric, colon, cervical/dysplasia, melanoma, breast) are excluded unless a complete remission was achieved at least 5 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

21. Female subjects who are pregnant, breast-feeding, male, or female patients of reproductive potential who are not employing an effective method of birth control.

22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.

24. Subjects with uncontrolled seizures.

25. Patients with tumoral disease in the head and neck region, such as peritracheal or periesophageal lymph node involvement, with infiltration of structures of the digestive, aerea or vascular pathways that represent a risk of increased bleeding.

26. Patients with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding.

27. Patients with digestive bleeding.

Investigational Product(s), Dose and Mode of Administration:

Durvalumab, 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) if> 30 kg.
If patient is ≤30 kg, weight-based dosing, equivalent to 20 mg/kg Q4W, should be used (Appendix 2).

Study Assessments and Criteria for Evaluation:

Safety Assessments:

- Safety assessments will be based on adverse event reports, results of clinical laboratory tests, immune safety tests, physical examinations, vital sign measurements, ECOG performance status during the study and up to six months following the last study drug administration. It will be reported based on Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Efficacy Assessments:

-Tumor response evaluation will be classified according to RECIST 1.1 criteria and irRECIST criteria.

- Progression free survival at 6 months and overall survival at 12 months.

[redacted]

Statistical Methods and Data Analysis:

The primary endpoint of the study is the feasibility of durvalumab monotherapy at the recommended dose of 1500 mg every 4 weeks in solid tumors in HIV-1-infected patients.

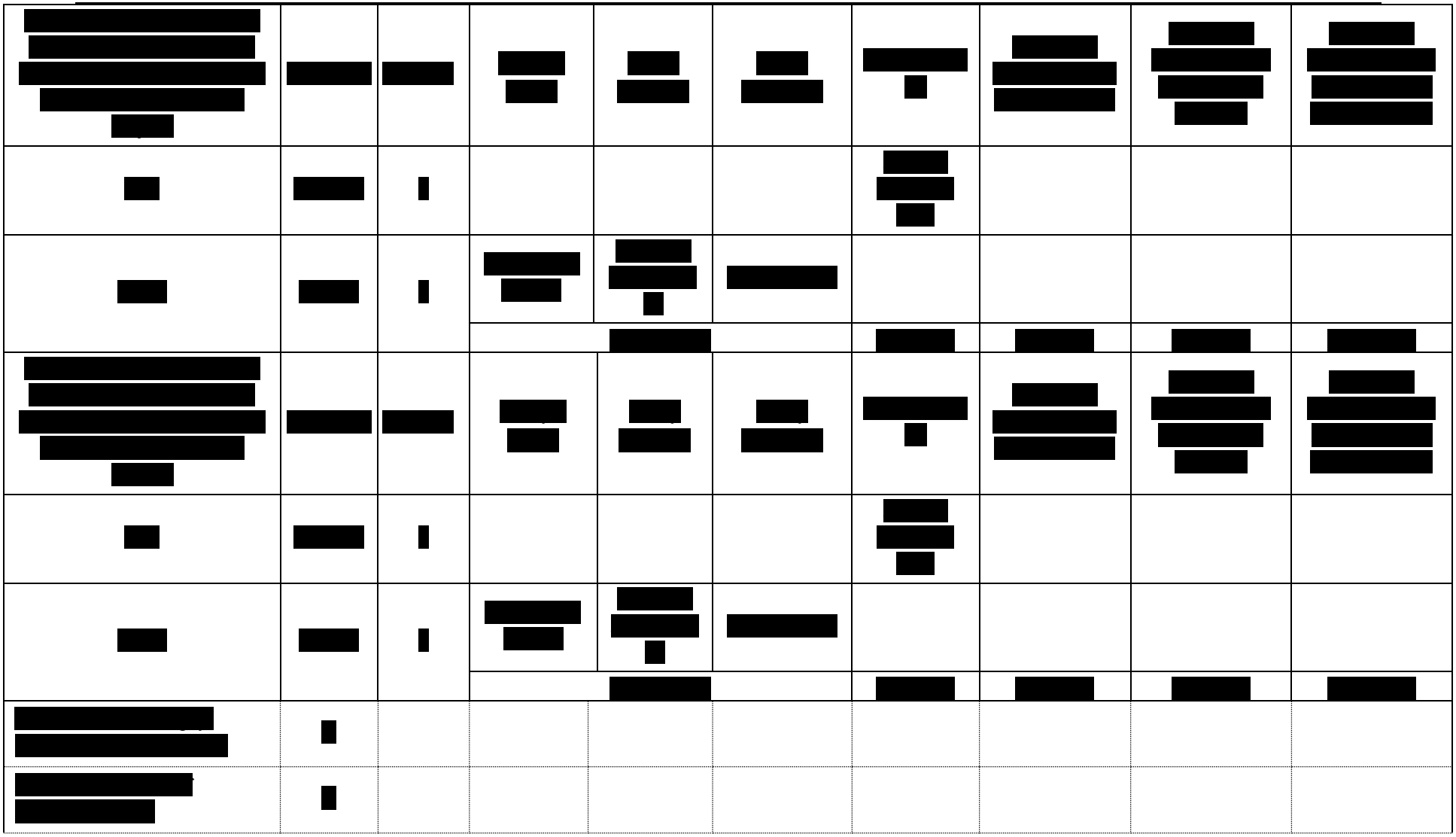
Feasibility will be defined based on the rate of patients that will complete at least 4 treatment cycles. One cycle is four weeks with infusions every four weeks. It is assumed that at least 50% of patients must be complete 4 cycles for considering feasible the treatment with durvalumab.

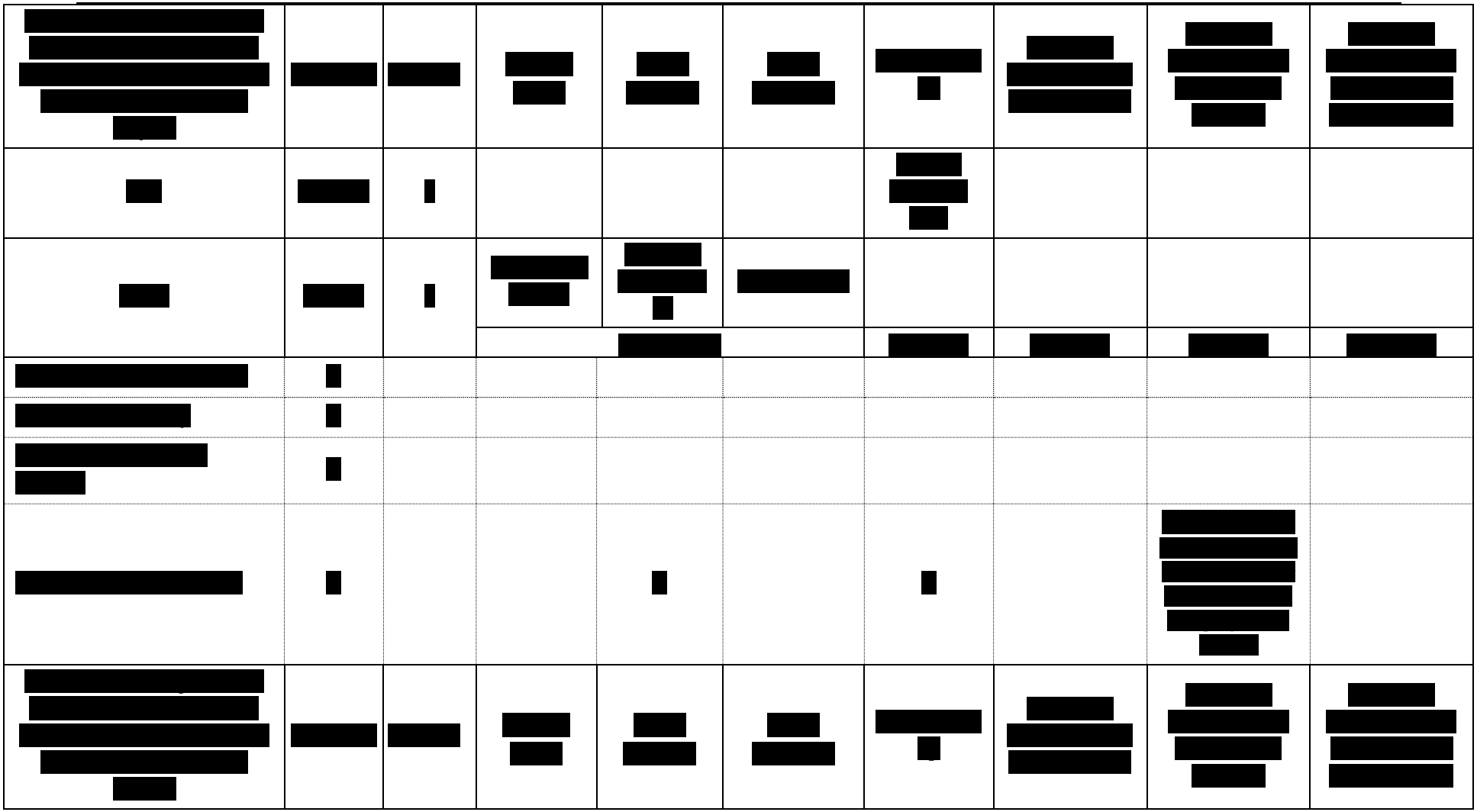
Kaplan Meier method will be used to estimate the survival function. Secondary measurements will be PFS rate at 6 months and OS rate at 12 months.

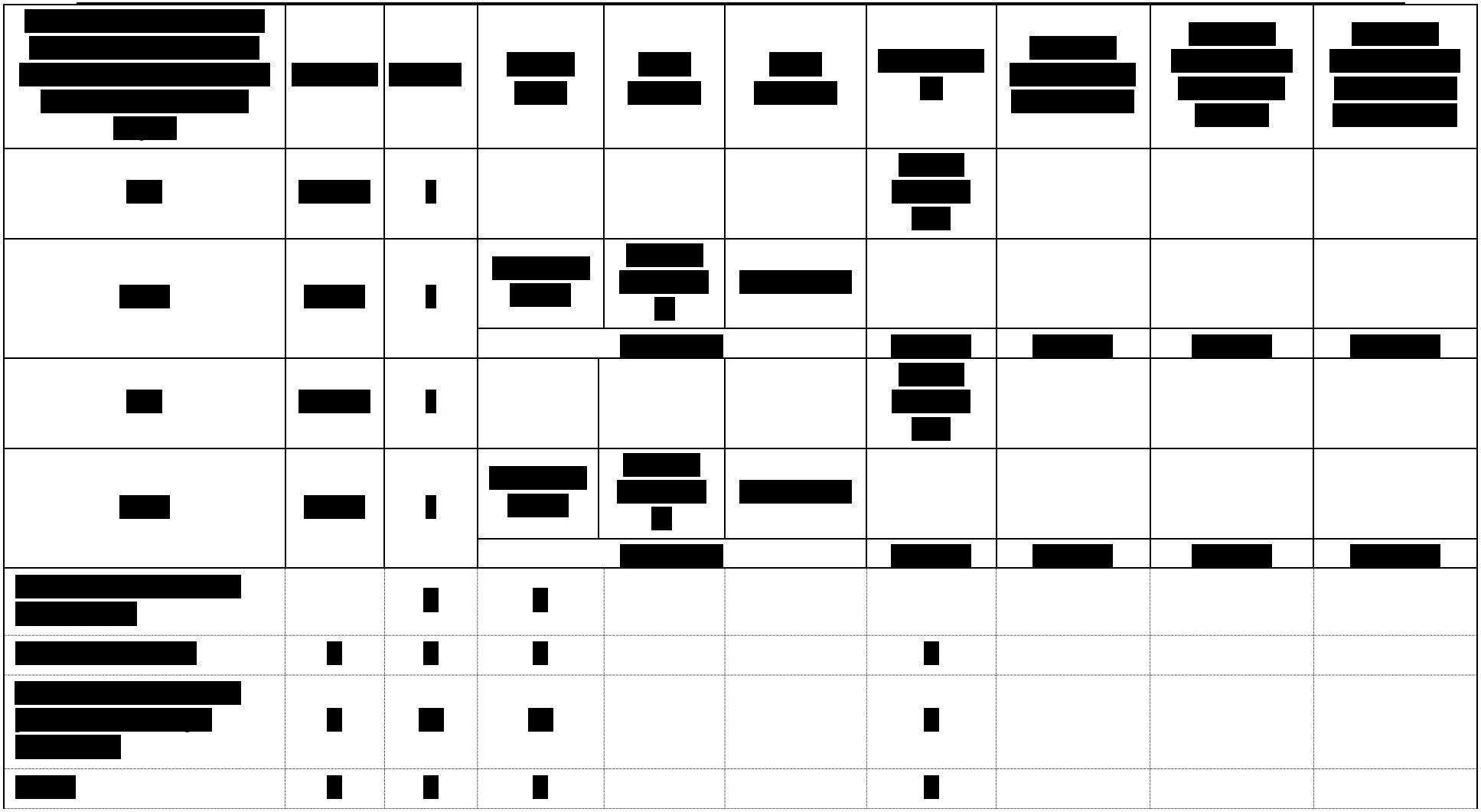
Sample Size Determination:

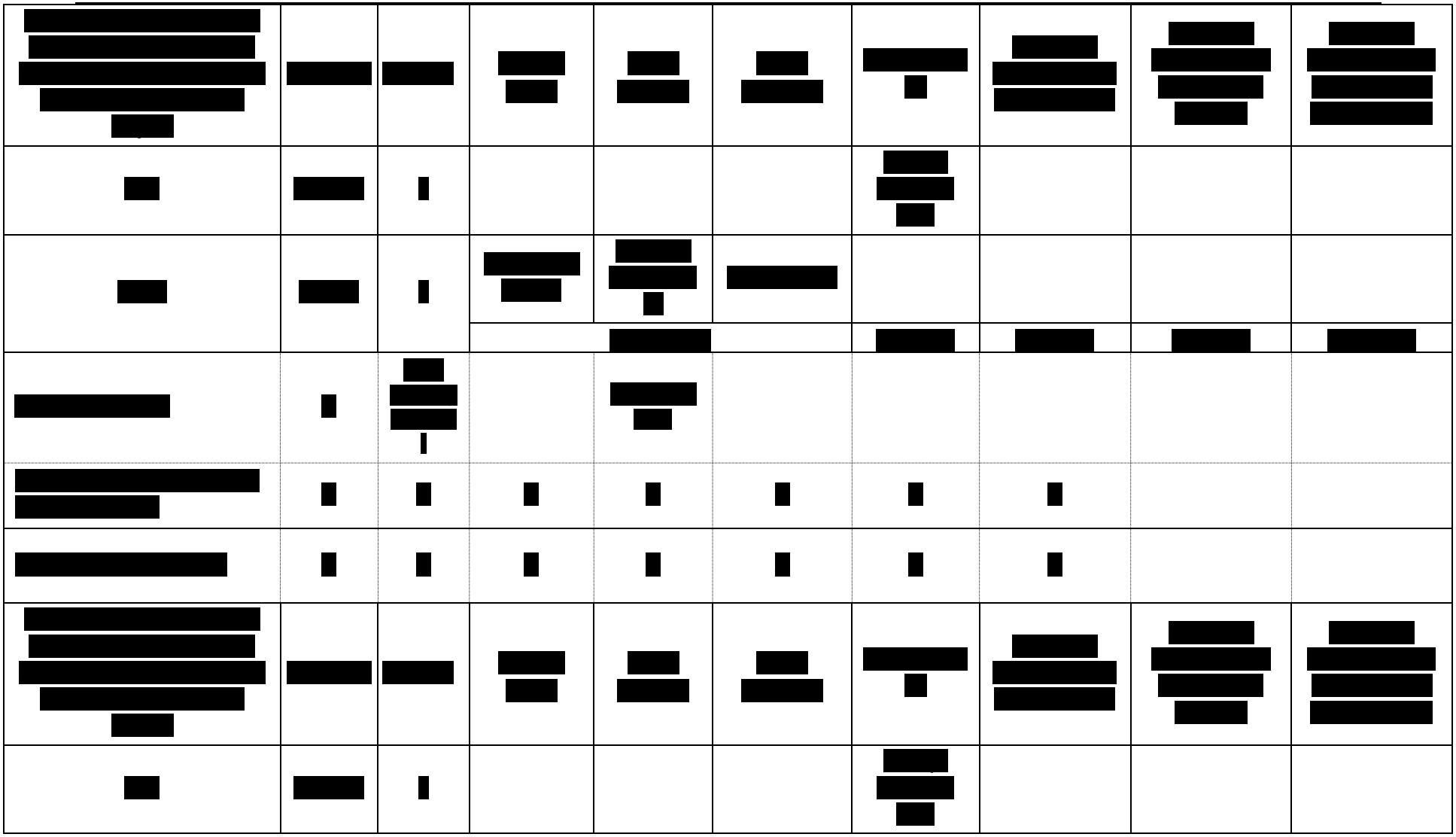
Sample size calculation for an estimated proportion of 50% with a level of confidence of 95% and a accuracy of 22%: 20 patients must be included in this study.

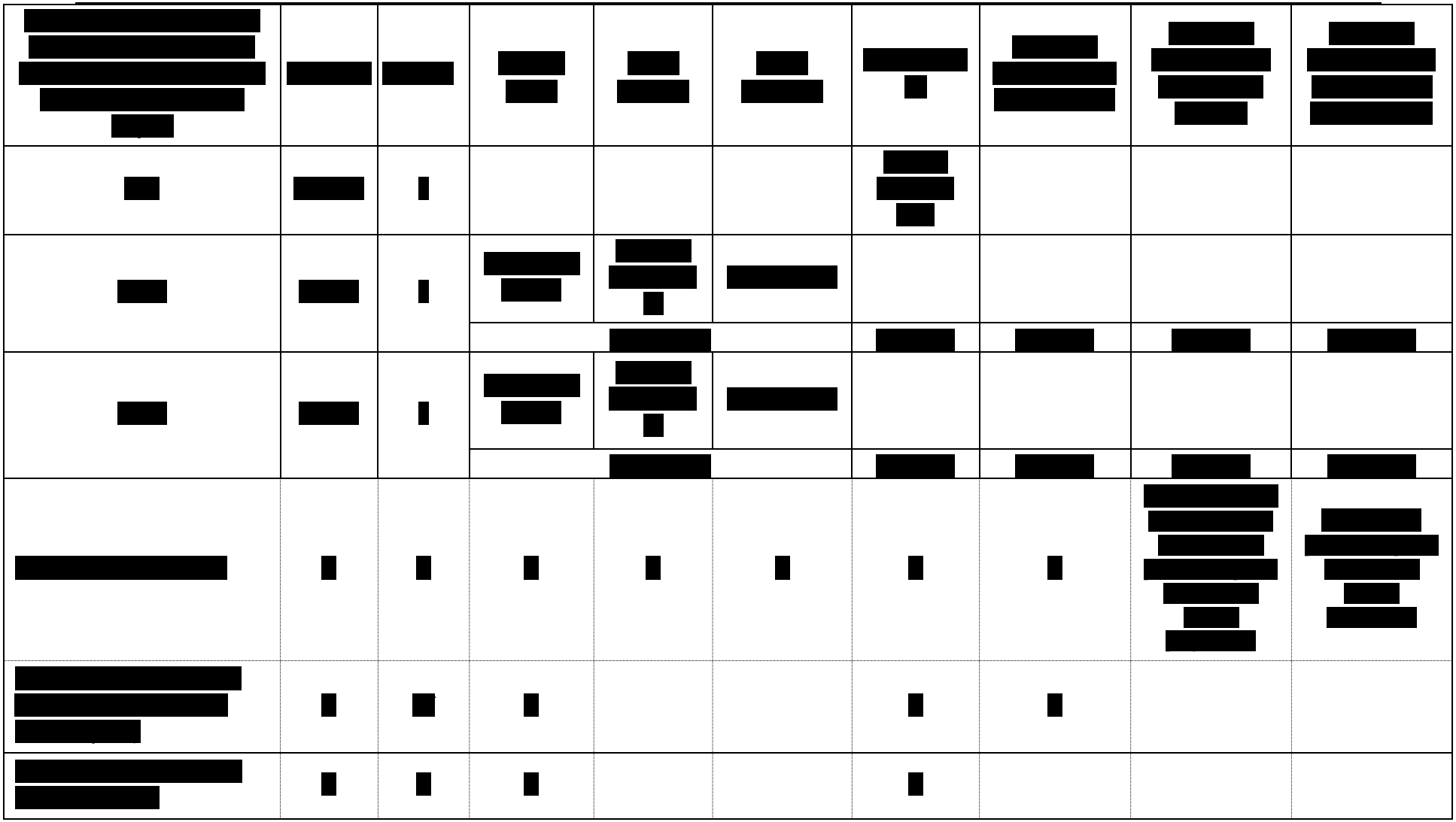
Table 1. SCHEDULE OF STUDY ASSESSMENTS

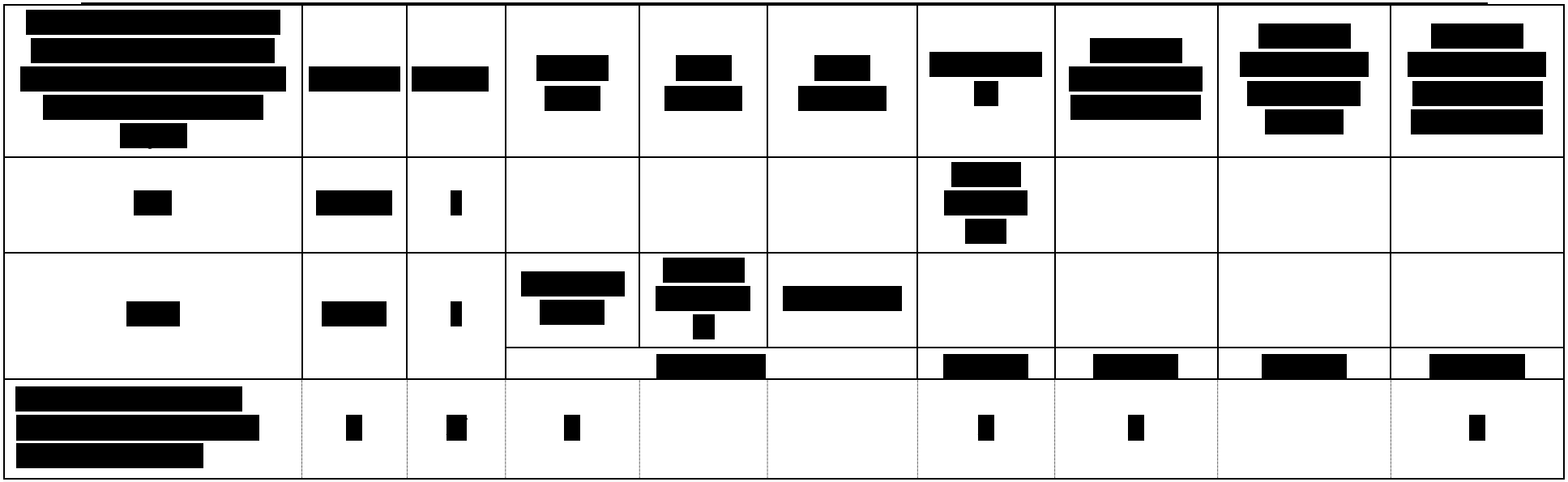


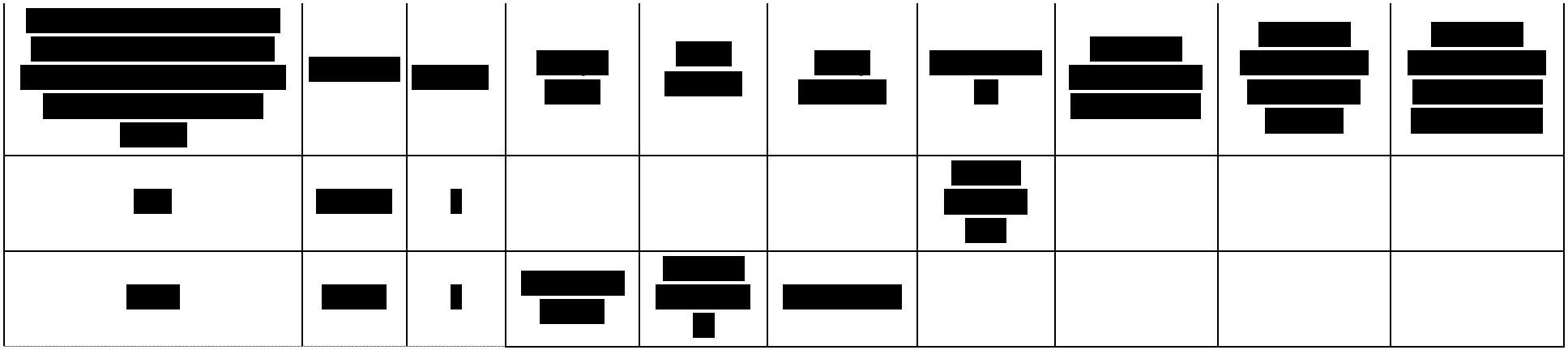












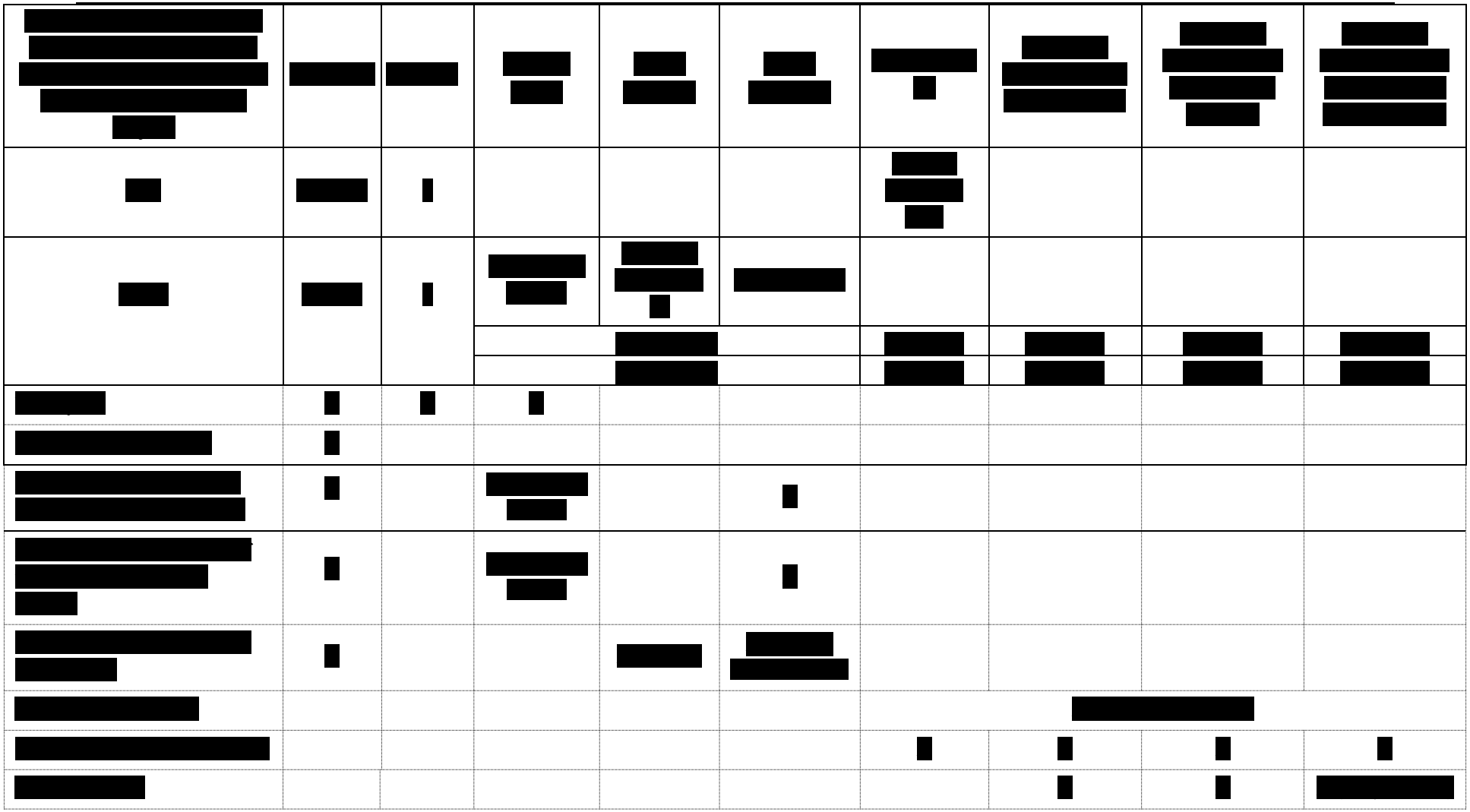


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TABLE OF CONTENTS PAGE

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8 [redacted]

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LIST OF TABLES

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	peak concentration
Cmax,ss	peak concentration at steady state

Abbreviation or special term	Explanation
Cmin	trough concentration
Cmin,ss	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded

Abbreviation or special term	Explanation
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry

Abbreviation or special term	Explanation
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response

Abbreviation or special term	Explanation
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks

Abbreviation or special term	Explanation
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
t½	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to peak concentration

Abbreviation or special term	Explanation
Tmax,ss	time to peak concentration at steady state
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization

1. INTRODUCTION

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1.4 Rationale for conducting this study

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions.

1.5 Benefit/risk and ethical assessment

The benefit-risk relationship has been carefully considered in the planning of the trial. Based on the nonclinical and clinical studies available to date, the conduct of the trial is considered justificable using the dose and dose regimen of the durvalumab as specified in this clinical trial protocol.

The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustificable.

The primary known risks of exposure to durvalumab include:

- Infusion-related reactions and
- irAEs

In addition, since durvalumab could induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of tumor lysis syndrome.

Clinical trials with antibodies that block PD-1/PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with response duration of 1 year or more for the majority of patients(22-30).

Given the suboptimal treatment options for patients with recurrent locally advanced or metastatic solid tumors in HIV-1 infected patients, and the safety profile of durvalumab, the risk-benefit ratio of treatment with durvalumab in the targeted trial population is considered positive.

This clinical trial protocol will be conducted in compliance with the clinical trial protocol, ICH GCP and the applicable national regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary objective(s)

To explore the feasibility of durvalumab (MEDI4736) monotherapy at the recommended dose of 1500 mg every 4 weeks in solid tumors in HIV-1-infected patients.

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions. The aim of this study is to explore the feasibility of durvalumab (MEDI4736) in HIV-1-infected patients who are diagnosed with a solid tumor (lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity) for which no additional oncologic standard treatment is available, or for which the subject declines standard treatment.

2.2 Secondary objective(s)

- To assess ORR (RECIST 1.1 and irRECIST) and duration of response

- To evaluate the PFS rate at 6 months
- To evaluate the OS rate at 12 months

Durvalumab (MEDI4736) has demonstrated activity in several cancer types in the general population. In this study, as secondary objective, we will analyze activity of the drug as activity in terms of Response rate according to RECIST1.1 criteria, and according to OS rate at 12 months and PFS at 6 months.
Several data indicate that anti PD-1/PD-L1 treatments in oncology could have activity in terms of OS with long responders, that it is not always correlated to classical endpoint of response rate or median survival.
In this trial given that patients will be included with different solid tumors, and different lines of treatment, activity of the drug is a secondary objective, in order to determine if activity looks similar to activity reported in solid tumors without HIV- infection.

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3. STUDY DESIGN

3.1 Overview of study design

This is a multicenter, national, non-randomized, phase II study in HIV-1 infected patients with advanced solid tumors.

Twenty evaluable patients will be included in the trial. Patients will be included irrespective of number the previous line of treatments.

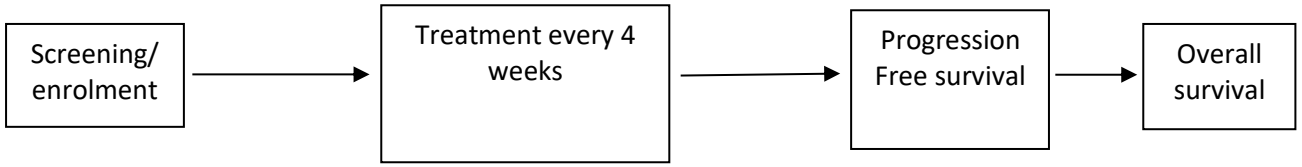
The clinical trial will be performed in 10 hospitals from the Spanish Lung Cancer Group in Spain with a competitive enrollment.

It is a single arm study. All patients included will received the treatment with durvalumab (MEDI4736). There is not placebo treated patients.

Patients must have stopped the previous treatments for cancer at least 30 days before starting study medication.

3.2 Study schema

Figure 1. Study flow chart



3.3 Study Oversight for Safety Evaluation

The whole trial may be discontinued prematurely in the event of any of the following situations:

- New information leading to unfavourable risk-benefit judgement of the trial drug, as inefficacy of the drug for this population, significant previously unknown adverse reactions or unfavourable safety findings.
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.

4. SUBJECT SELECTION

Only persons meeting the inclusion criteria and no exclusion criteria may be enrolled into the trial. Prior to performing any trial assessments not part of the routine medical care, the investigator will ensure that the subjects have provided written informed consent.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
2. Age $\geq$ 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) 0-2.
4. Life expectancy of $\geq$16 weeks.
5. Adequate normal organ and marrow function as defined below:
   - Haemoglobin $\geq$ 9.0 g/dL
   - Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L ($\geq$ 1500 per mm^3)
   - Platelet count $\geq$ 100 x 10^9/L ($\geq$100,000 per mm^3)
   - Serum bilirubin $\leq$ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent

hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN

- Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

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Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

6. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

7. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

8. Subjects with histologically or cytologically-documented advanced/metastasic lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity, refractory to standard treatment, intolerant of standard treatment, or for which no standard therapy exists or who refuse the standard treatment.

9. Subjects may be included irrespectively of number of previous lines of treatment for advanced disease.

10. Prior palliative radiotherapy must have been completed at least 2 weeks prior to start the study treatment (subjects may receive localized palliative radiotherapy while receiving study drug).

11. Documented HIV-1 infection

12. Undetectable viral load in the last analysis.

13. Subjects with brain metastases are eligible if they are asymptomatic, are treated or are neurological stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of < 10 mg daily prednisone or equivalent.

14. Subjects must be following an antiretroviral therapy at the moment of the inclusion.

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study. Previous enrollment in the present study.

2. Participation in another clinical study with an investigational product during the last 4 weeks.

3. Other untreated coexisting HIV related malignancies.

4. Any previous treatment with a PD1, PD-L1 or PD-L2 inhibitor, including durvalumab.

5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 28 days prior to the first dose of study drug.

6. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.

7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

8. Any unresolved toxicity (CTCAE grade 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).

9. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.

10. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

11. Any syndrome that requires systemic corticosteroid/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger (vitiligo, autoimmune thyroiditis, or type 1 diabetes mellitus are permitted to enroll).

12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

13. History of primary immunodeficiency.

14. History of allogeneic organ transplant.

15. History of hypersensitivity to durvalumabor any excipient.

16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B or C, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

17. Known history of active tuberculosis.

18. Any serious or uncontrolled medical disorder or active infection non HIV, that would impair the ability of the subject to receive the treatment of protocol therapy under treating physician criteria.

19. Subjects with previous malignances (except non melanoma skin cancer, and cancer in situ of: bladder, gastric, colon, cervical/dysplasia, melanoma, breast) are excluded unless a complete remission was achieved at least 5 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.

21. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.

22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.

24. Subjects with uncontrolled seizures.

25. Patients with tumoral disease in the head and neck region, such as peritracheal or periesophageal lymph node involvement, with infiltration of structures of the digestive, aerea or vascular pathways that represent a risk of increased bleeding.

26. Patients with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding.

27. Patients with digestive bleeding.

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of investigational product

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up.

2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.

3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute asafety risk.

4. Pregnancy or intent to become pregnant.

5. Any AE that meets criteria for discontinuation as defined in Appendix 1, Section 10.1.3

6. Adverse event related to durvalumab of any Grade>3 ADRs or repetitive Grade 3 ADRs with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 10.1.3, Appendix 1

7. Grade ≥ 3 infusion reaction.

8. Subject non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.

9. Initiation of alternative anticancer therapy including another investigational agent.

10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified ashaving permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for [redacted], unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

4.4 Replacement of subjects

Subjects withdrawn from the study will not be replaced.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab

The sponsor will supply durvalumab to the site's pharmacies as a 500-mg vial solution for infusion after dilution.

5.1.1 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

The trial medication and its packaging will be labeled in accordance with annex 13 of EU Guidelines to Good Manufacturing Practice.

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[redacted]	[redacted]

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[redacted]

5.1.5 Accountability and dispensation

The investigator is responsible for ensuring accountability for trial drug, including reconciliation of drugs and maintenance of drug records.

[redacted]

[redacted]

6. TREATMENT PLAN

6.1 Subject enrollment

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject`s routine medical care, the investigator will ensure that the subject or his/her legal representative, has provided written informed consent following the procedure.

6.1.1 Procedures for handling subjects incorrectly enrolled

Subjects who are incorrectly enrolled or initiated on treatment should be withdrawn from the study.

[redacted]

[redacted]

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

Contraception

Females of childbearing potential who are sexually active with a non sterilised male partner must use effective contraception from screening, and must agree to continue using such precautions for at least 90 days following the last infusion of durvalumab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Subjects must use acceptable methods of effective contraception as described in Table 2.
- Non-sterilised males who are sexually active with a female partner of childbearing potential must use acceptable methods of effective contraception (see Table 2) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 2. Effective methods of contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Combined pill
		Minipill
		Patch

[a] This is also considered a hormonal method.

Blood donation

As patients are HIV infected, they do not donate blood while participating in this study neither after its finalization.

[redacted]

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8. STUDY PROCEDURES

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10. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

10.1.1 Safety Parameters

10.1.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or non treatment emergent. A non treatment-emergent AE is any new sign or symptom,

disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or non serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

10.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

[redacted]

[redacted]

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.

The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below:

Grade 1 (mild) An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

Investigators must systematically assess the causal relationship of AEs to the trial treatment using the following definitions. Decisive factors for the assessment of causal relationship of an AE to trial treatment include, but may not be limited to, temporal relationship between the AE and treatment administration, known side effects of trial treatment, medical history, concomitant medication, course of the underlying disease, trial procedures.

Not related: Not reasonably related to the trial. The AE could not medically (pharmacologically / clinically) be attributed to the trial treatment in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the trial treatment The AE could medically (pharmacologically / clinically) be attributed to the trial treatment.

TEAEs defined as possibly related to trial treatment will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to treatment. Treatment emergent AEs are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. Any AEs with an onset or worsening date after the on-treatment period will be reported separately.

All premature terminations will be summarized by primary reason for treatment discontinuation/withdrawal.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded in the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

In cases of surgical or diagnostic procedures, the condition / illness leading to such a procedure is considered as the AE rather than the procedure itself.

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or

neutropenia, is considered serious only if the condition meets one of the serious criteria described below. If death occurs, the primary cause of death (or event leading to death) should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might be reported as an SAE.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab (yes or no)
- Action taken with regard to durvalumab
- Outcome

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to<<criteria>>
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab).

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

10.3.2 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The Sponsor is responsible for informing the Regulatory Authorities of the SAE as per local requirements.

The sponsor must inform local Health Authorities, via a CIOMS form, of any serious or unexpected adverse events that occur, and will concurrently forward all such reports to AstraZeneca. A copy of the CIOMS report must be faxed to AstraZeneca at the time the event is reported to local Health Authorities. It is the responsibility of the sponsor to compile all necessary information and ensure that the local Health Authorities receives a report according to the local reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the CIOMS form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The EudraCT Number
- The sponsor's name and address
- The trial name/title and ESR reference number (ESR-##-#####)

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

***** [redacted]

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the local Health Authorities.

Serious adverse events that do not require expedited reporting to local Health Authorities still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.3.3 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

[redacted]

[redacted]

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10.3.7 Pregnancy

10.3.8 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

10.3.9 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the Ethics Committees (ECs) prior to use.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

The screening analysis set includes all subjects who signed the ICF.

ITT Analysis set: the ITT analysis set will include all subjects who were included into the trials.

Per-protocol analysis set will include all ITT subjects who do not have major protocol violations.

[redacted]

11.2 Methods of statistical analyses

In general descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Count missing observations will be included in the denominator and presented in a separate category.

[redacted]

[redacted]

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[redacted]

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

12.2 Ethics and regulatory review

The Investigator is responsible for the conduct of the trial at his site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their own origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In particular the investigator must ensure that only patients who have their informed consent are included in the trial.

12.3 Informed consent

An unconditional prerequisite for a subject´s participation in the trial is his/her written informed consent. The subject´s written consent to participate in the trial must be given before any trial-related activities are carried out. [redacted]

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (IHC Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his /her designate will inform the subject

verbally of all aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

The ICF must be signed and personally dated by the Investigator and the subject.

The signed and dated declaration of informed consent will remain at the Investigator´s site, and must be safely archived. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

A unique subject number will be assigned to each subject at inclusion by IVRS system, immediately after informed consent has been obtained. This number will serve as the subject`s identifier in the trial as well as in the clinical trial database. The subject`s data will be stored under this number. Only the investigator will be able to link the subject`s identity with the subject`trial data via an identification list kept at the site. The medical data that are reviewed at the site during the source data verification by the Clinical Trial Monitor, audits, and Health Authority inspections will be kept strictly confidential.

Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

12.4 Changes to the protocol and informed consent form

Any change in the approved protocol will require a Protocol amendment. The Investigator must not make any change in the study without favorable opinion from the Ethics Committee and authorization from the Health Authorities, except as necessary to eliminate an impending and obvious risk for the subjects except when necessary to remove an apparent, immediate hazard to subjects. Protocol changes introduced to eliminate an impending and obvious risk may be implemented immediately, but must subsequently be documented in an amendment, reported to the Ethics Committee and be submitted to the relevant Health Authorities within the required timeframe.

Any substantial amendments to the protocol must be submitted in writing to the Investigator's Ethics Committee and the Health Authorities for approval before the changes proposed in the

amendment are implemented. Depending on the magnitude of the change, the recruitment may be temporally halted.

The sponsor does not have to notify non-substantial amendments to the Health Authorities or the Ethics Committee. However, any non-substantial amendments will be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. Documentation of any non-substantial amendments will be available on request for inspection at the trial site or the sponsor premises as appropriate.

Whenever important new information becomes available that may be relevant to the subject´s consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

12.5 Audits and inspections

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The clinical Trial Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor´s Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the trial drug, and the subject's original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent quality assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

12.6 Insurance

The sponsor contracts an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable Spanish legislation.

[redacted]

12.7 Publications

The sponsor commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their study site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal.

The sponsor and Investigator(s) will agree with all aspects related to any proposed publications with regards to the following: 1) any proposed publications will be drafted in agreement with international recommendations, such as those from the International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement (2010), to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis of the overall results of the trial.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

The principal investigator will maintain a record of all center staff involved in the clinical trial (doctors, nurses and other staff involved) ensuring that they receive appropriate training to perform the study, and that any new information of relevance to the study will be transmitted to them.

Researchers will be instructed about the procedures of the trial in the investigator meeting and/or initiation visits made by monitors at each participating center prior to the study start.

13.2 Monitoring of the study

Spanish Lung Cancer Group is the company responsible for monitoring the study (see appendix 5). The clinical monitors have the obligation to follow the trial closely so that all aspects of the trial are carefully monitored for compliance with applicable government regulations and with ICH E6 (R1) guidelines.

The clinical monitors will visit the study sites and Investigators at intervals as defined in the monitoring plan, in addition to maintaining necessary contact through telephone, e-mail, and letter. The clinical monitors will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the study site Investigators and staff.

13.2.1 Source data

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include enrolment log, investigational product accountability log, laboratory notes, memoranda, material dispensing records, subject files, etc. The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified.

Each Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. All supportive documentation submitted with the eCRF, such as laboratory data should be clearly identified with the study, visit and subject number. Any personal information (e.g., subject name, initials) should be removed or rendered illegible to preserve individual confidentiality.

13.2.2 Study documentation

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 25 years after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor. All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and / or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

13.3 Study timetable and end of study

End of study is defined as Last Subject Last Visit.

- Recruitment period will be 12 months

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14. DATA MANAGEMENT

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO and follow the data entry guidelines. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs and to sign the case report forms.

The data will be entered into a validated database. The CRO will be responsible for data review and processing, in accordance with the CRO's data management procedures.

The principal CRO functions in data management are CRF tracking and query generation, tracking and resolution as well as to perform Eligibility, Treatment, AE, Response checks and inform Medical Reviewers if any doubt regarding eligibility comes up.

Data Manager (DM) will check the database twice a week or when necessary, depending on the recruitment of the Study.

Queries issued by the DM will show up in the eCRF.

DM will send an e-mail to the investigators according the quantity of queries to be solved requesting their resolution as soon as possible. If there would be a lot of queries at the same center, DM will send an e-mail/reminder once a week.

DM have to access to the eCRF in regular intervals to check if any queries have been solved. The participant centers have to access to the eCRF to check if any queries have been issued in their patients.

The data review will be done from the first patient included until the last follow of the last patient reported in the eCRF.

The data cleaning consists of the exhaustive review of data from the baseline to the end of the follow up of the patient, performing queries when necessary.

DM reviewers will follow the most current version of the Fundación GECP's Data Management SOP.

The field which have to be reviewed by DM will be detailed in the eCRF Data Management Manual.

Database lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed.

Copies of the eCRFs will be provided to the Investigators at the completion of the trial.

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and allmedical information for the subject, and should be as complete as possible.

14.1 Study governance and oversight

The safety of all AstraZeneca products is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. LIST OF REFERENCES

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Appendix 1

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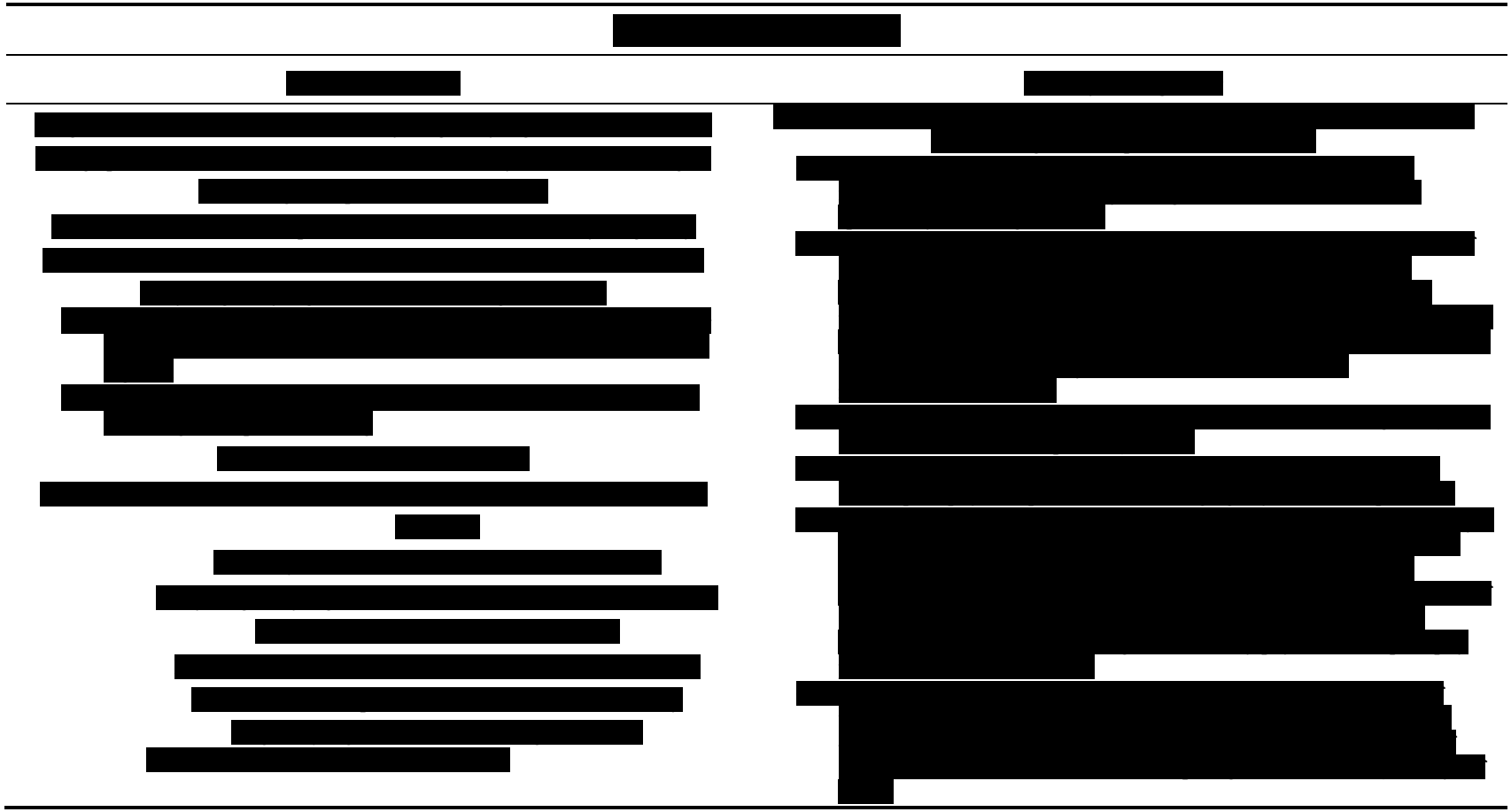

Appendix 1

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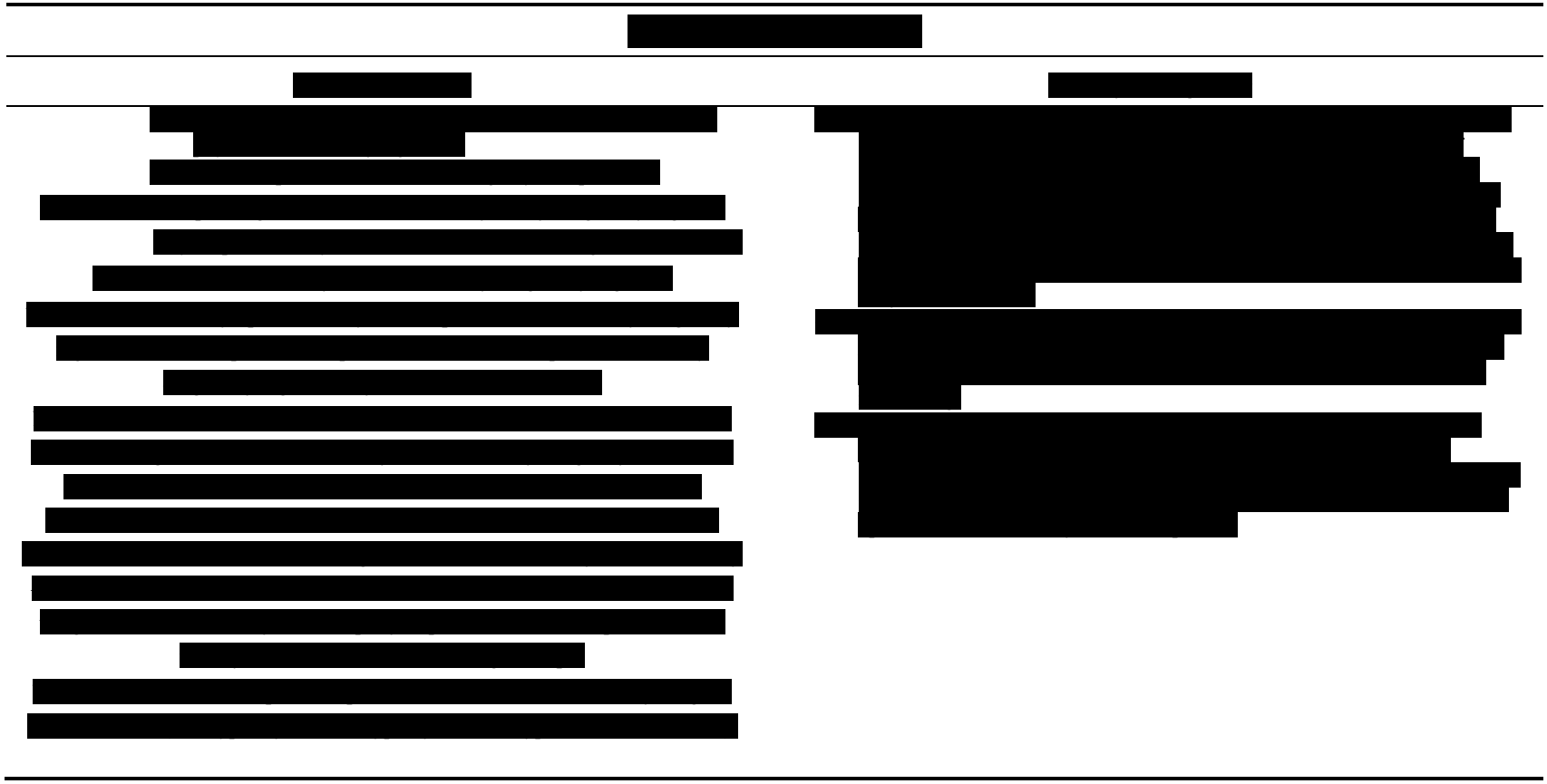

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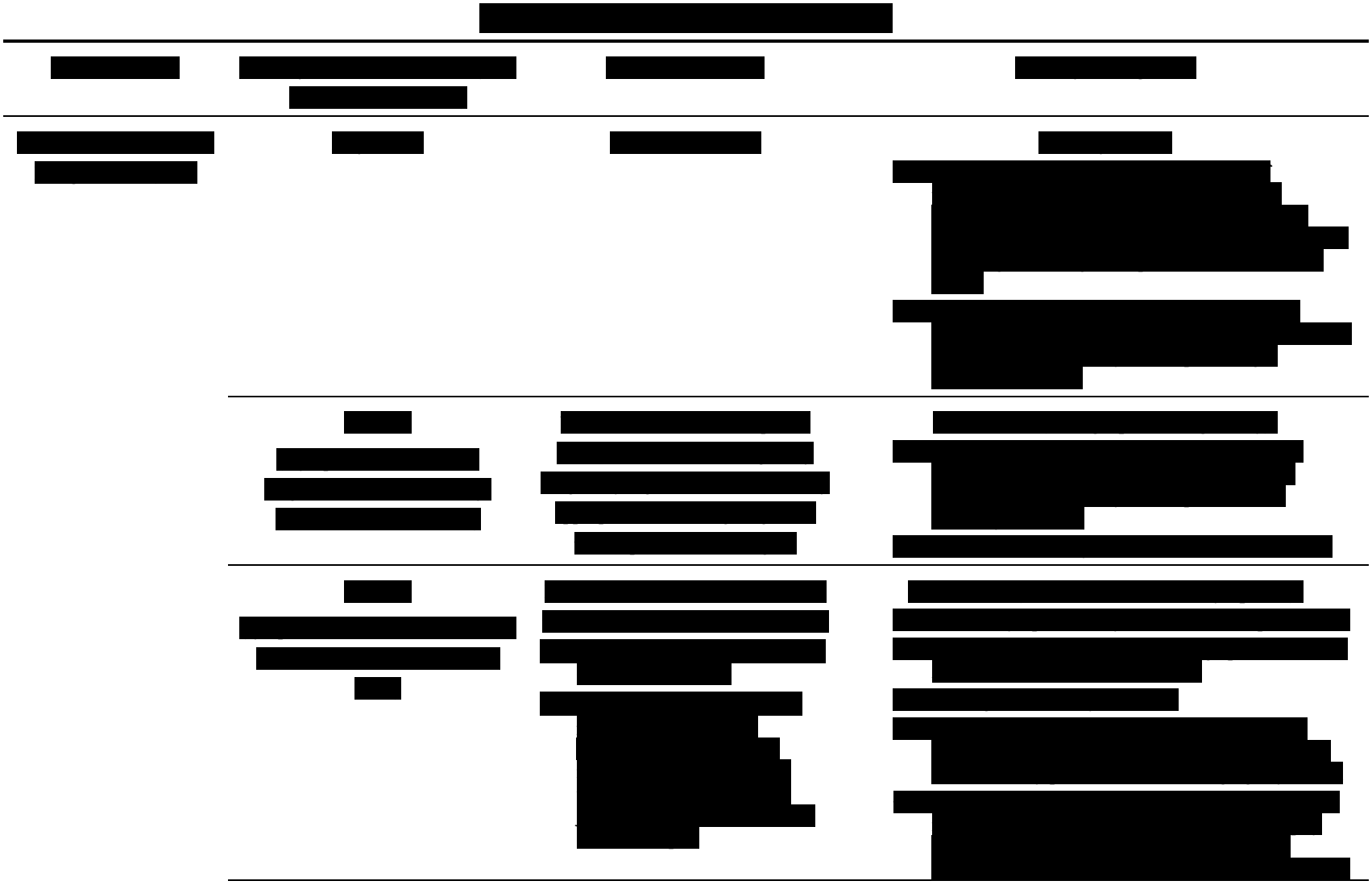

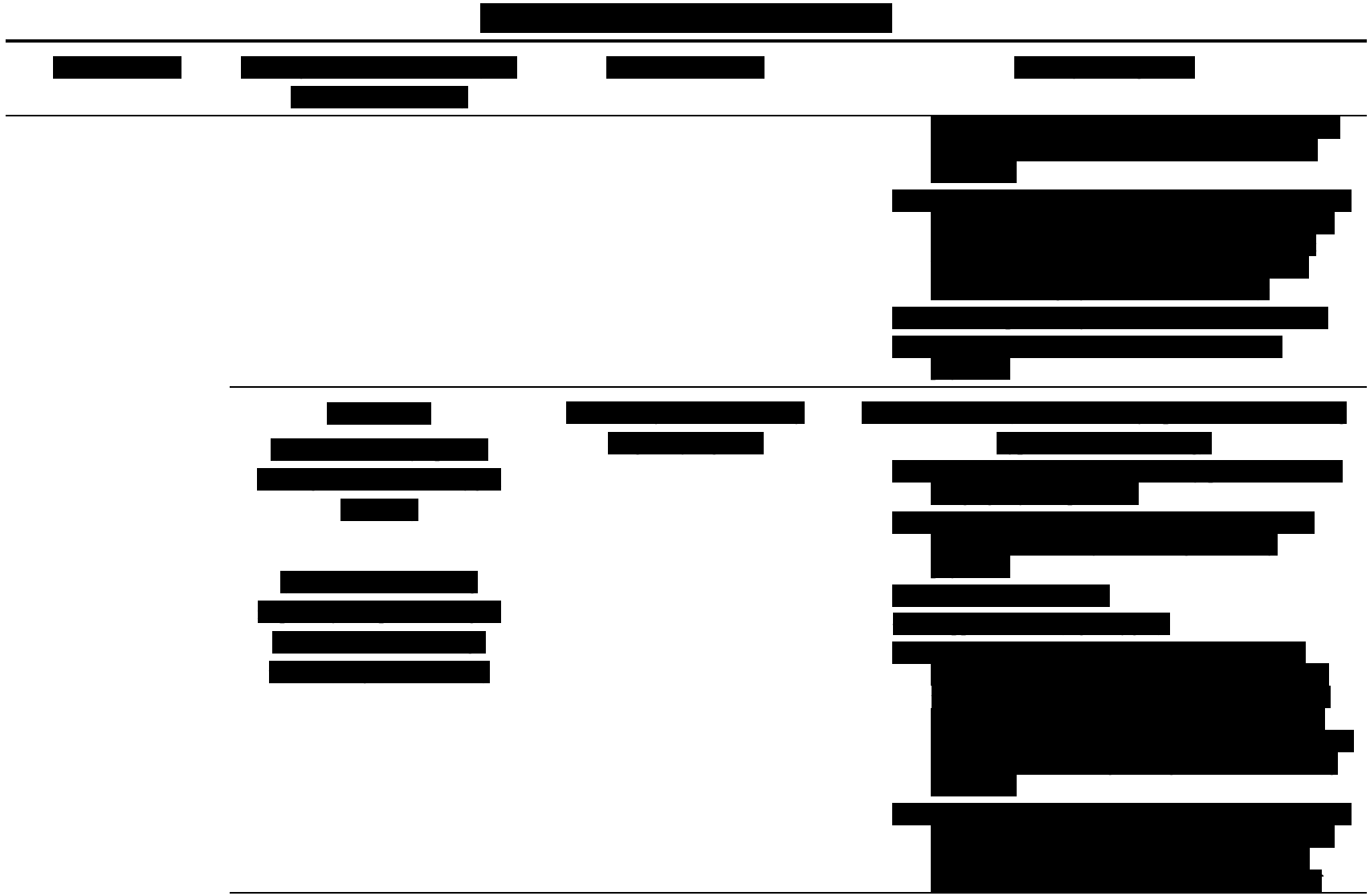

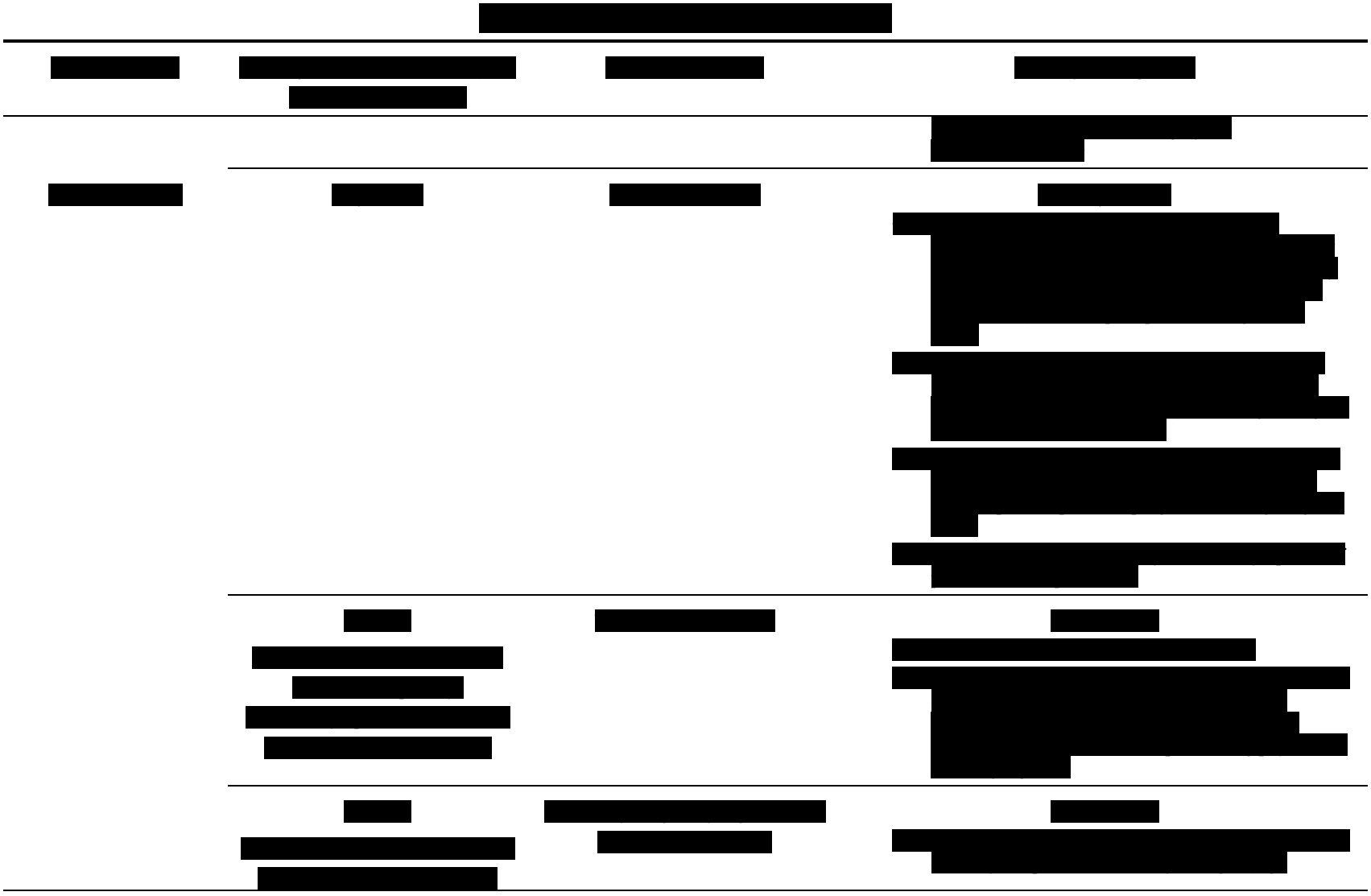

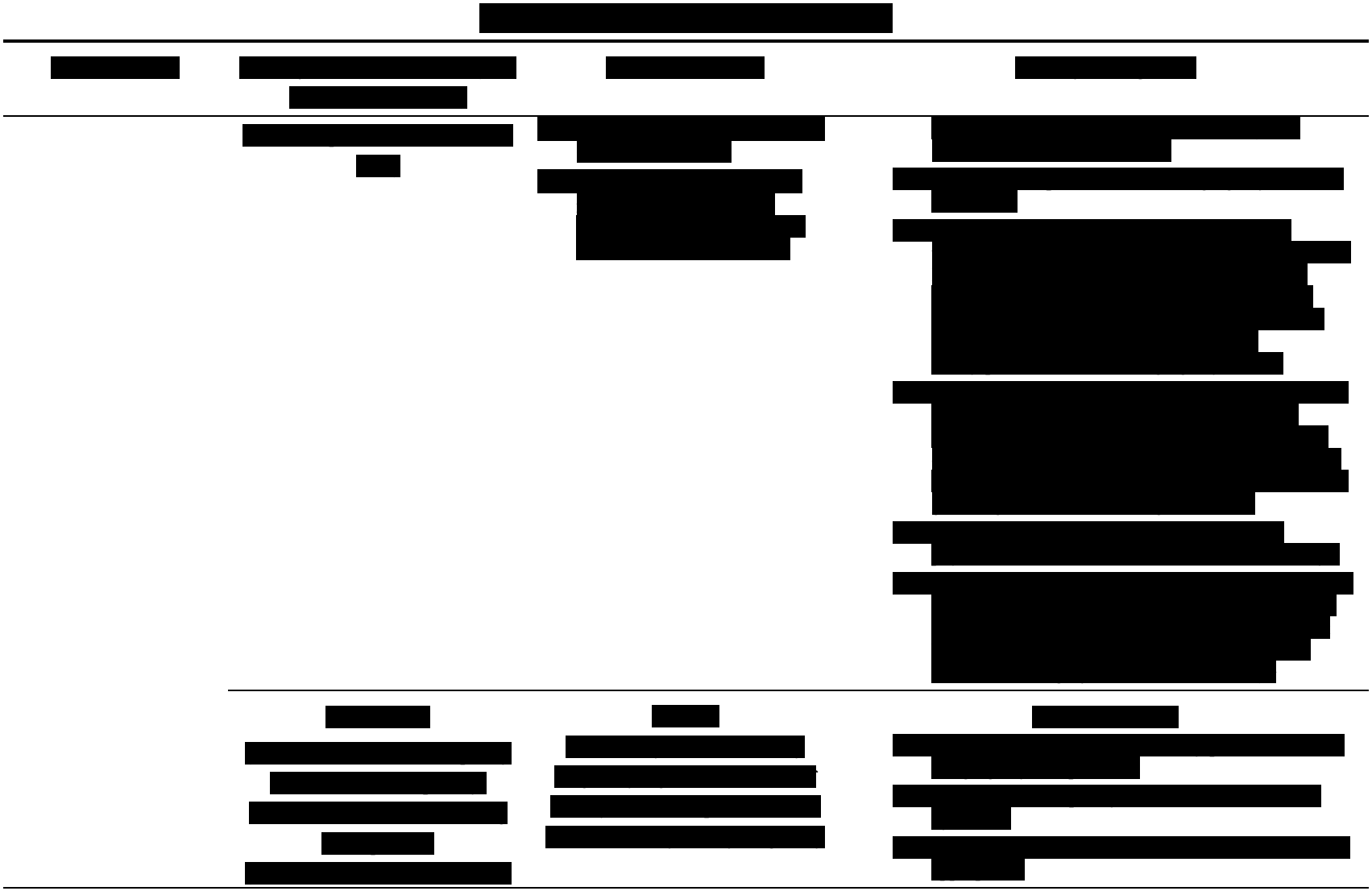

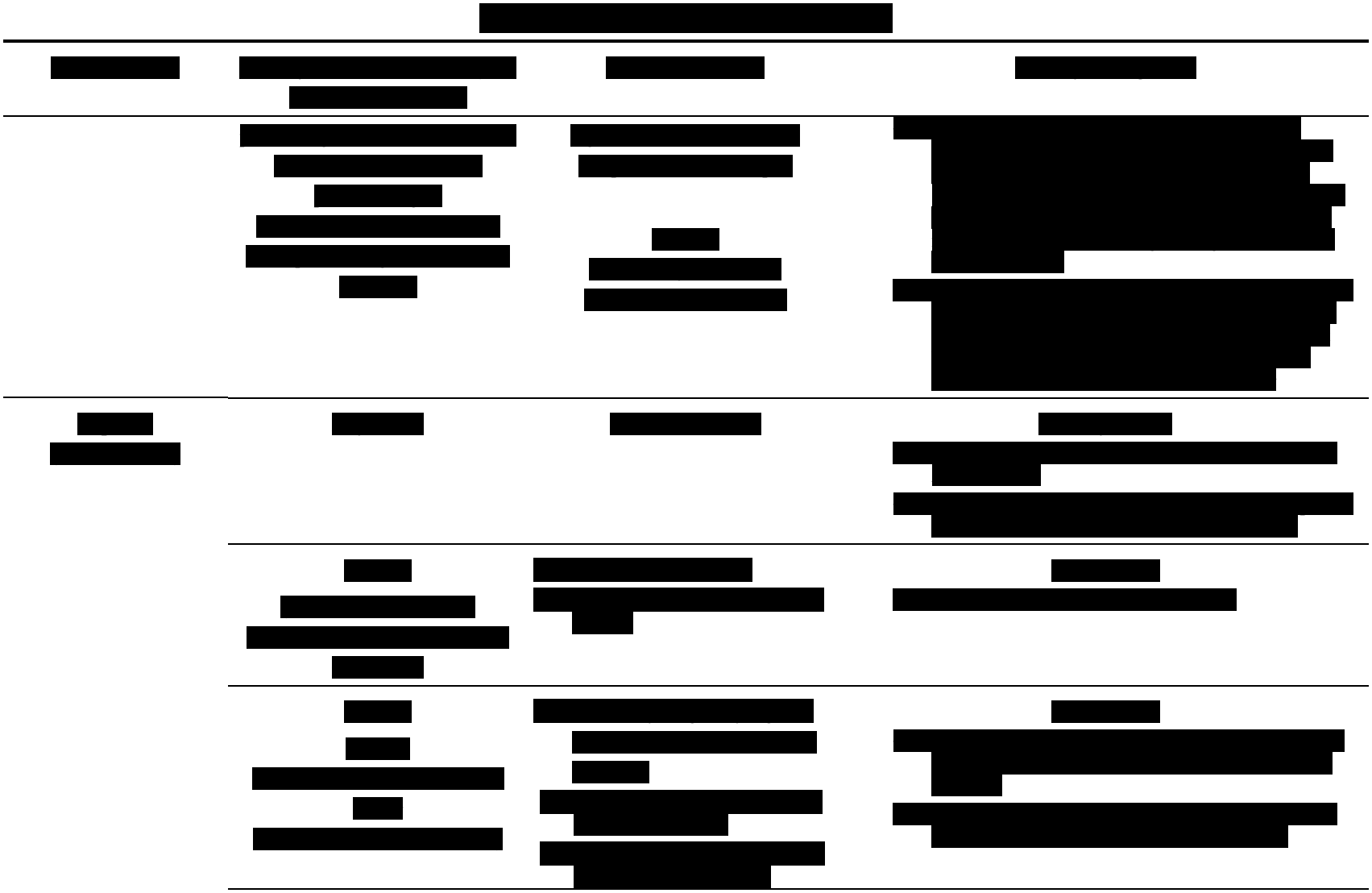

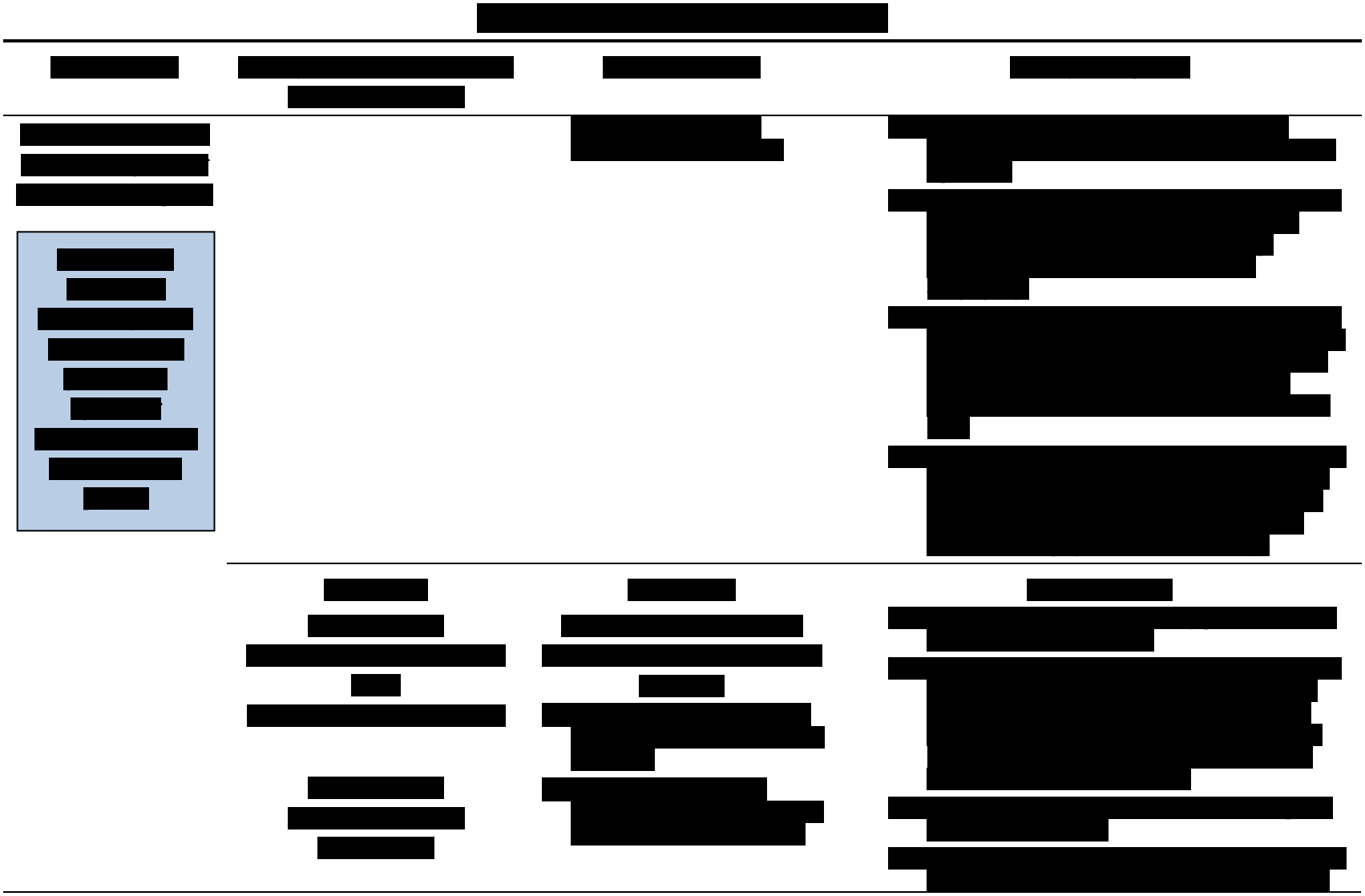

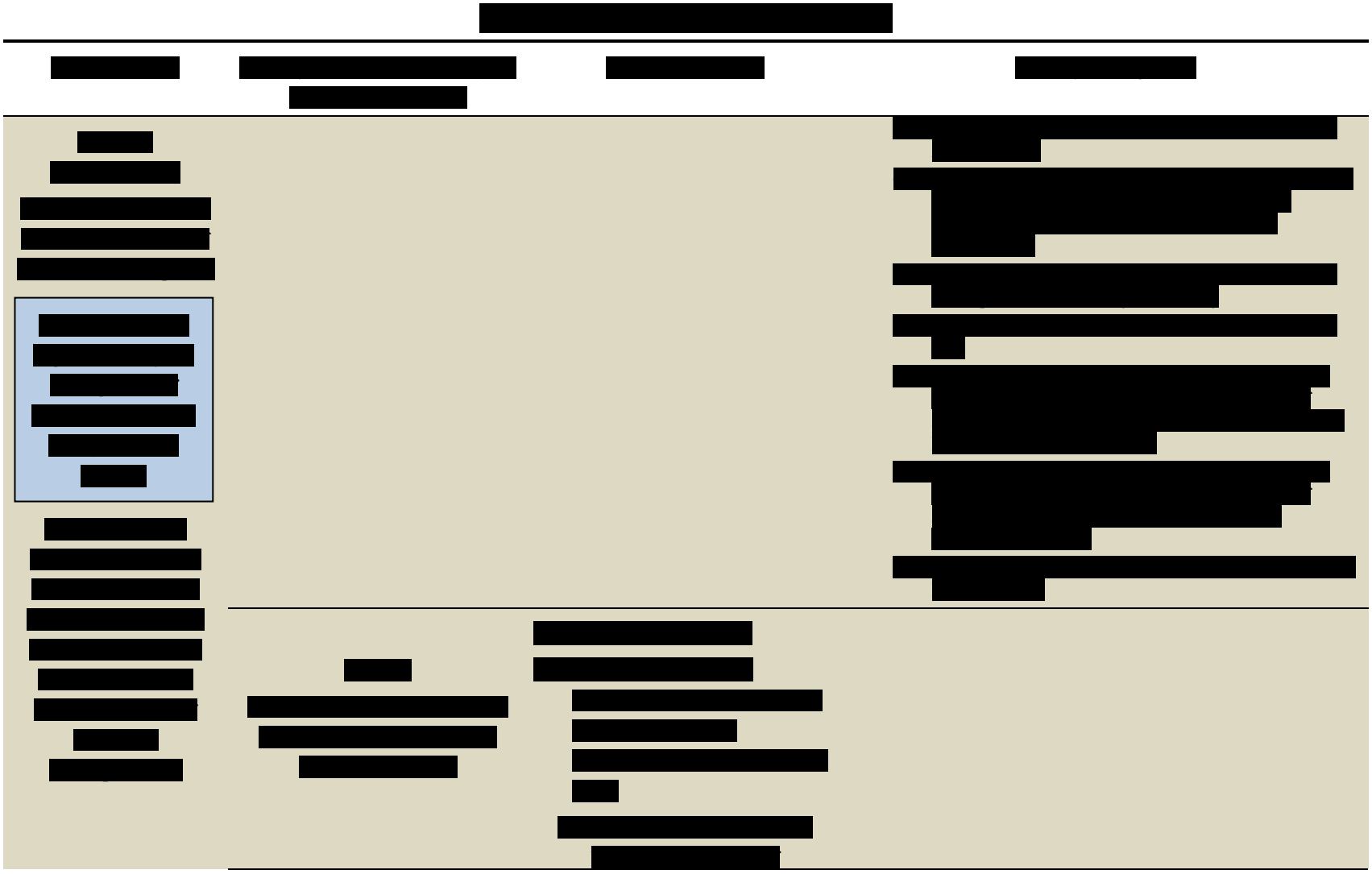

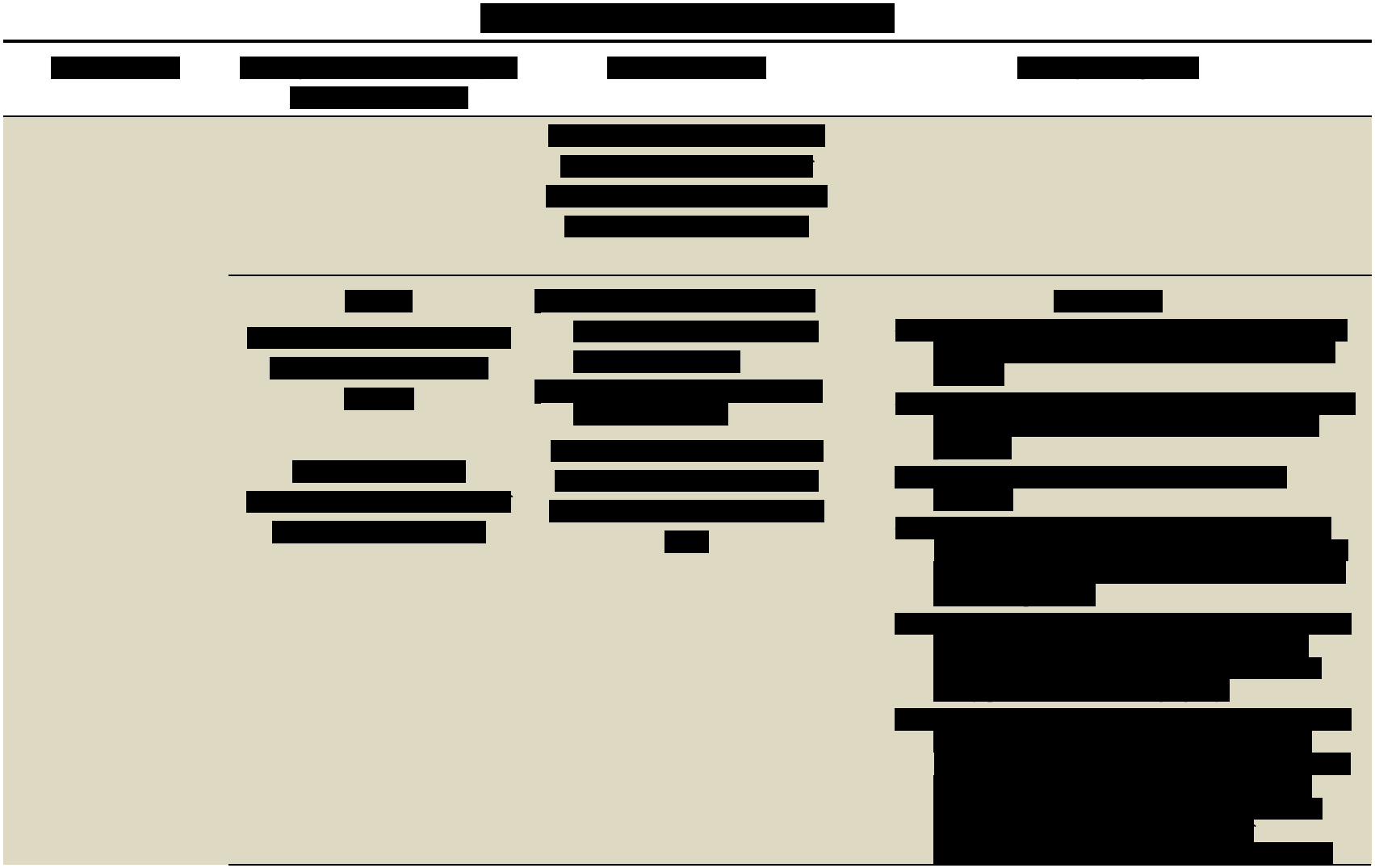

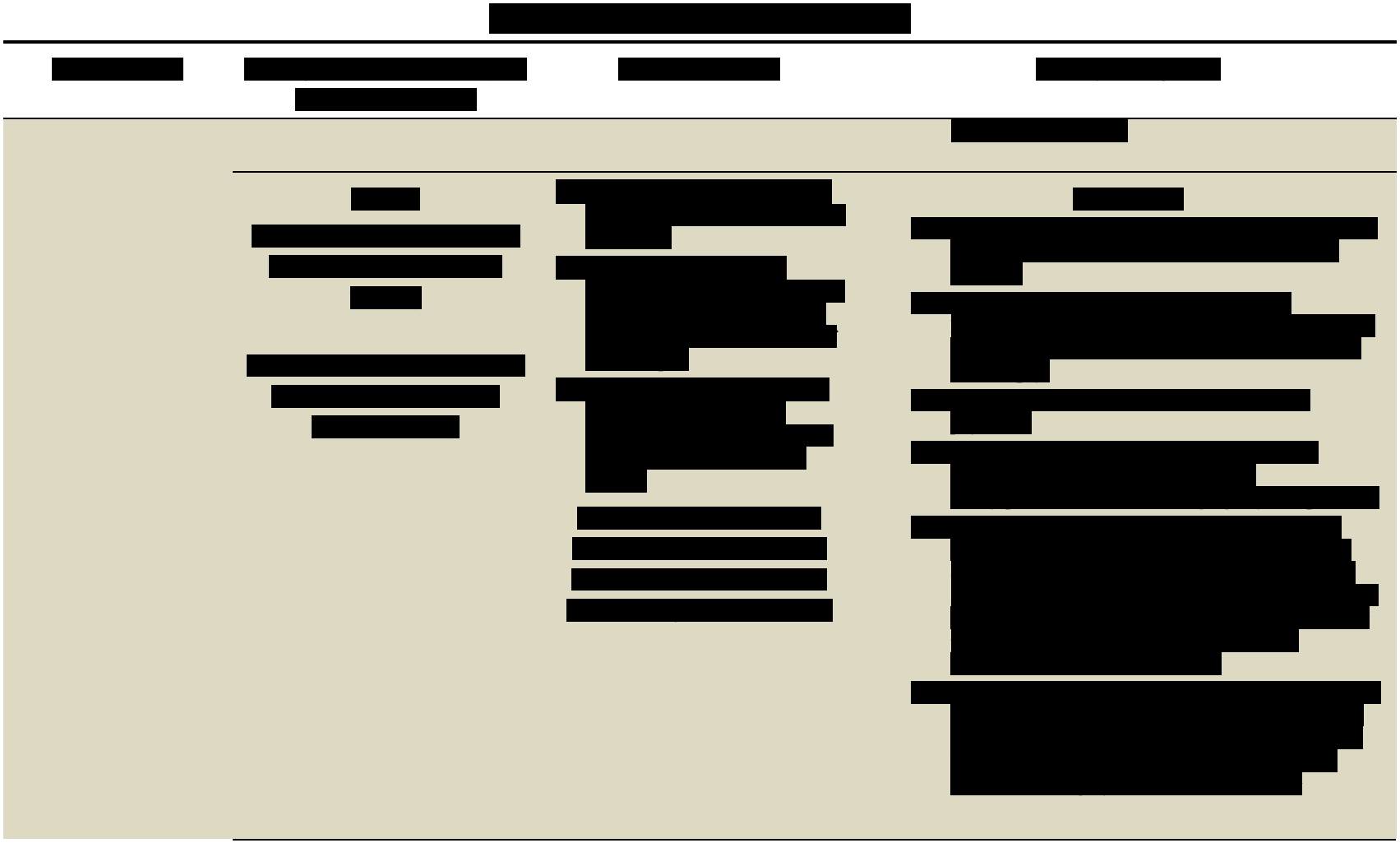

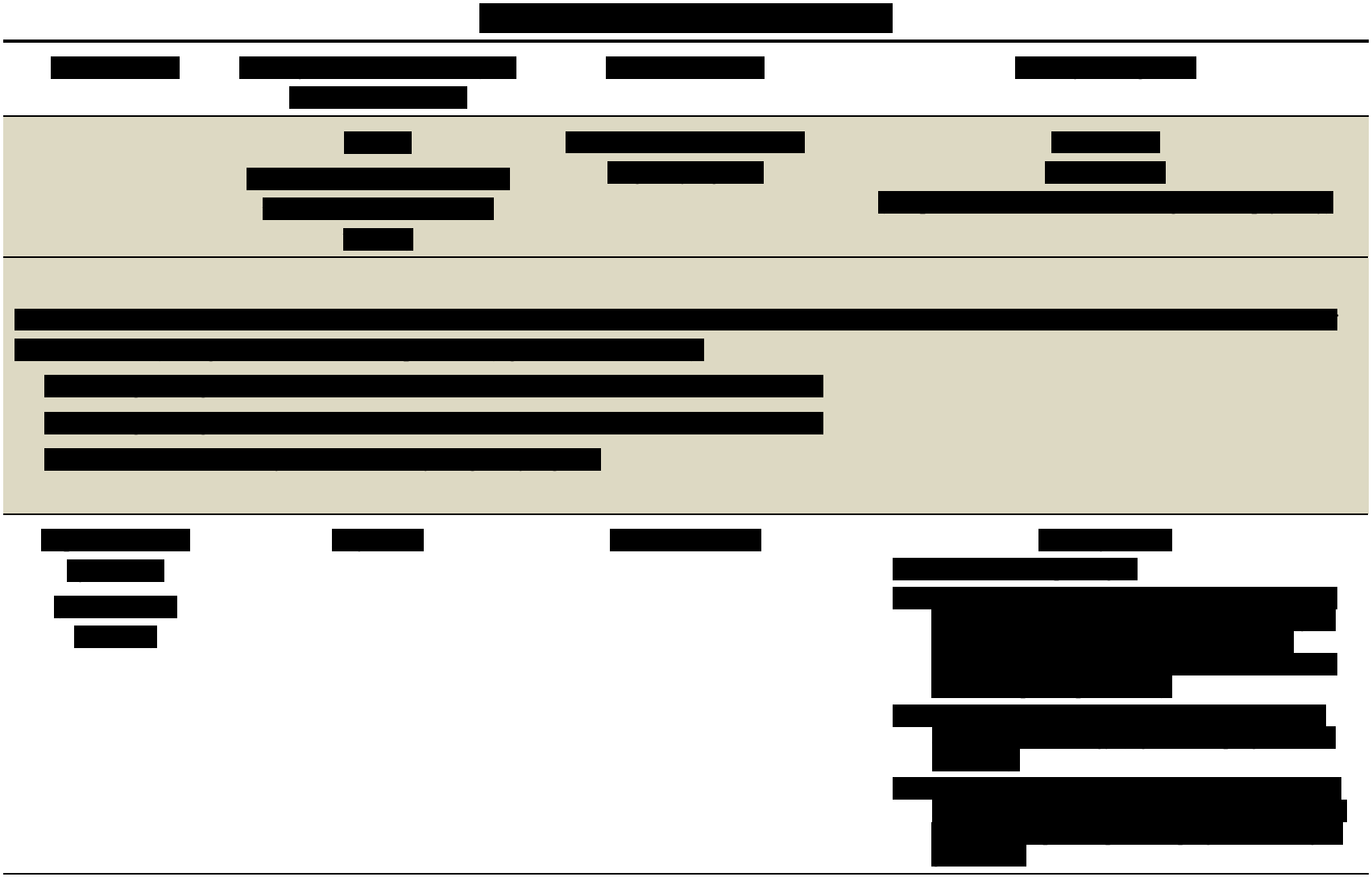

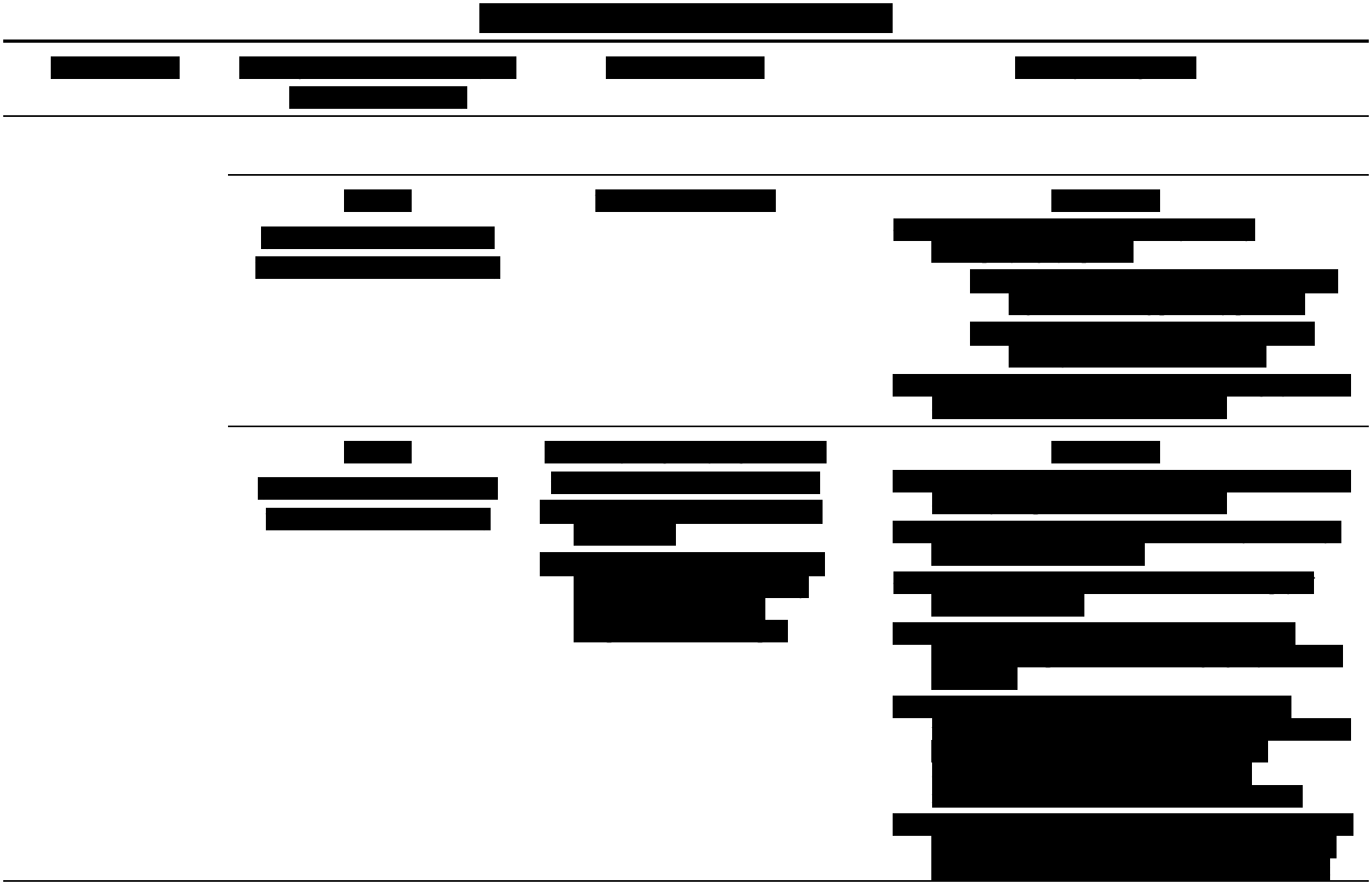

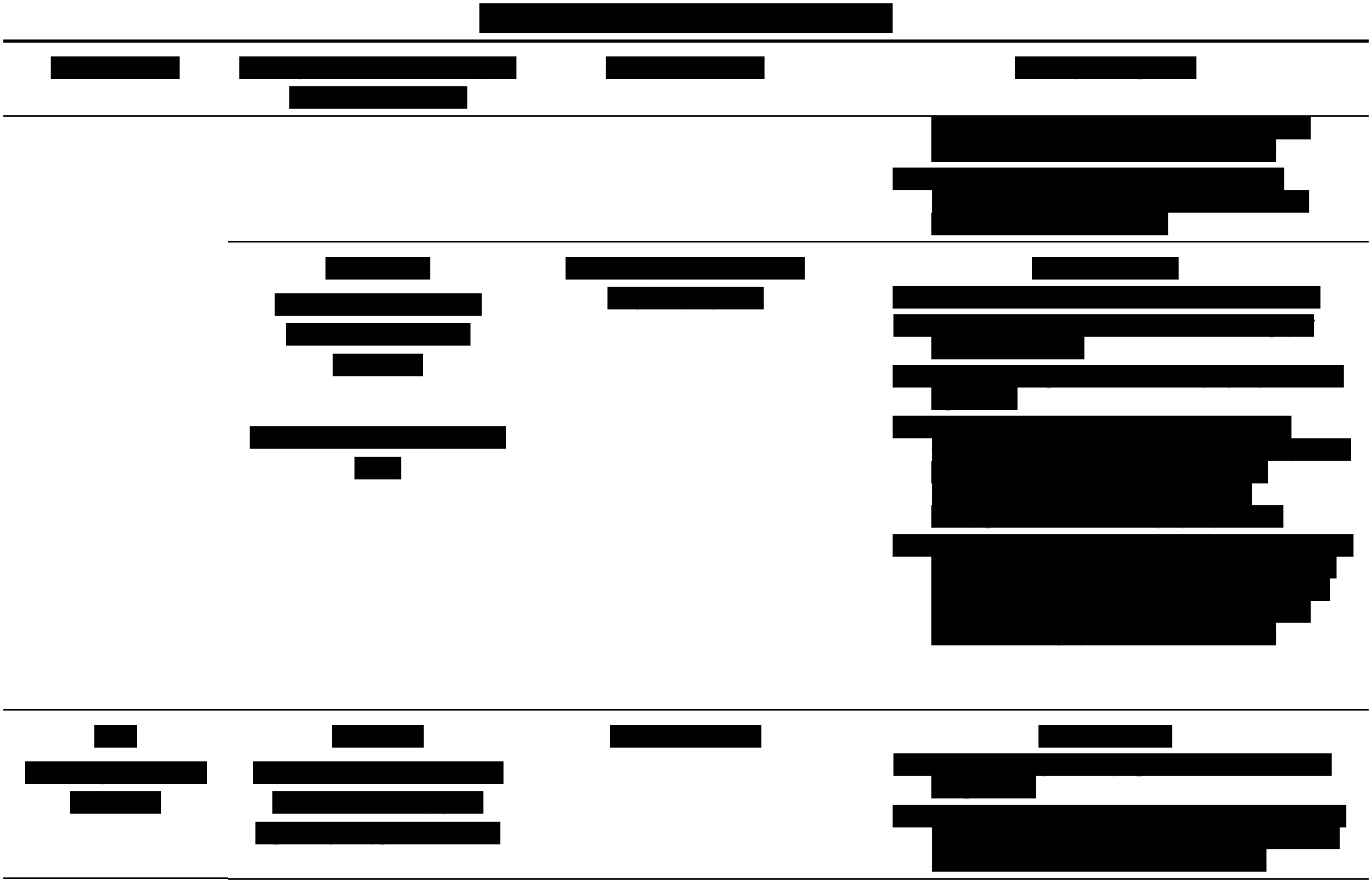

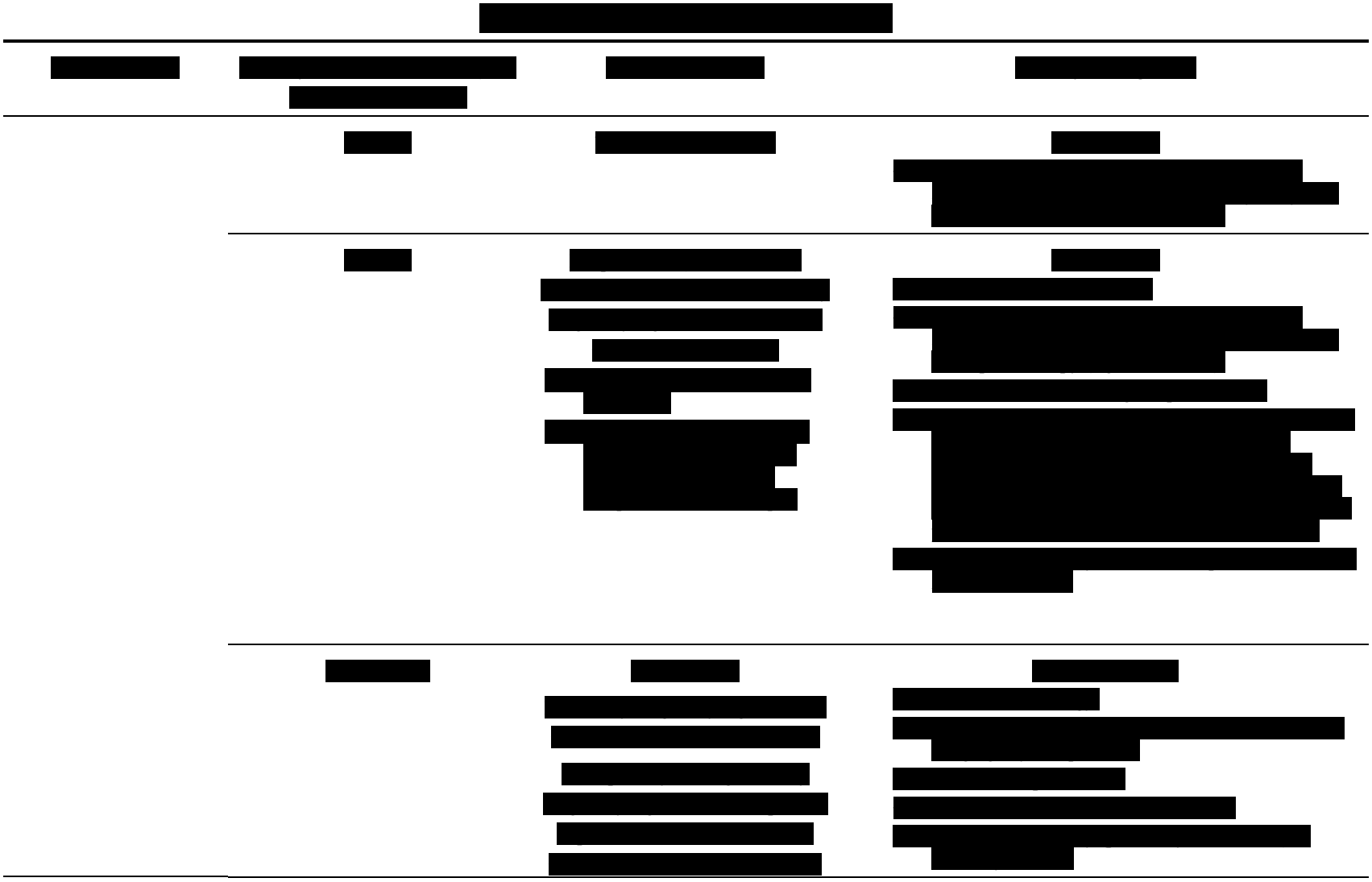

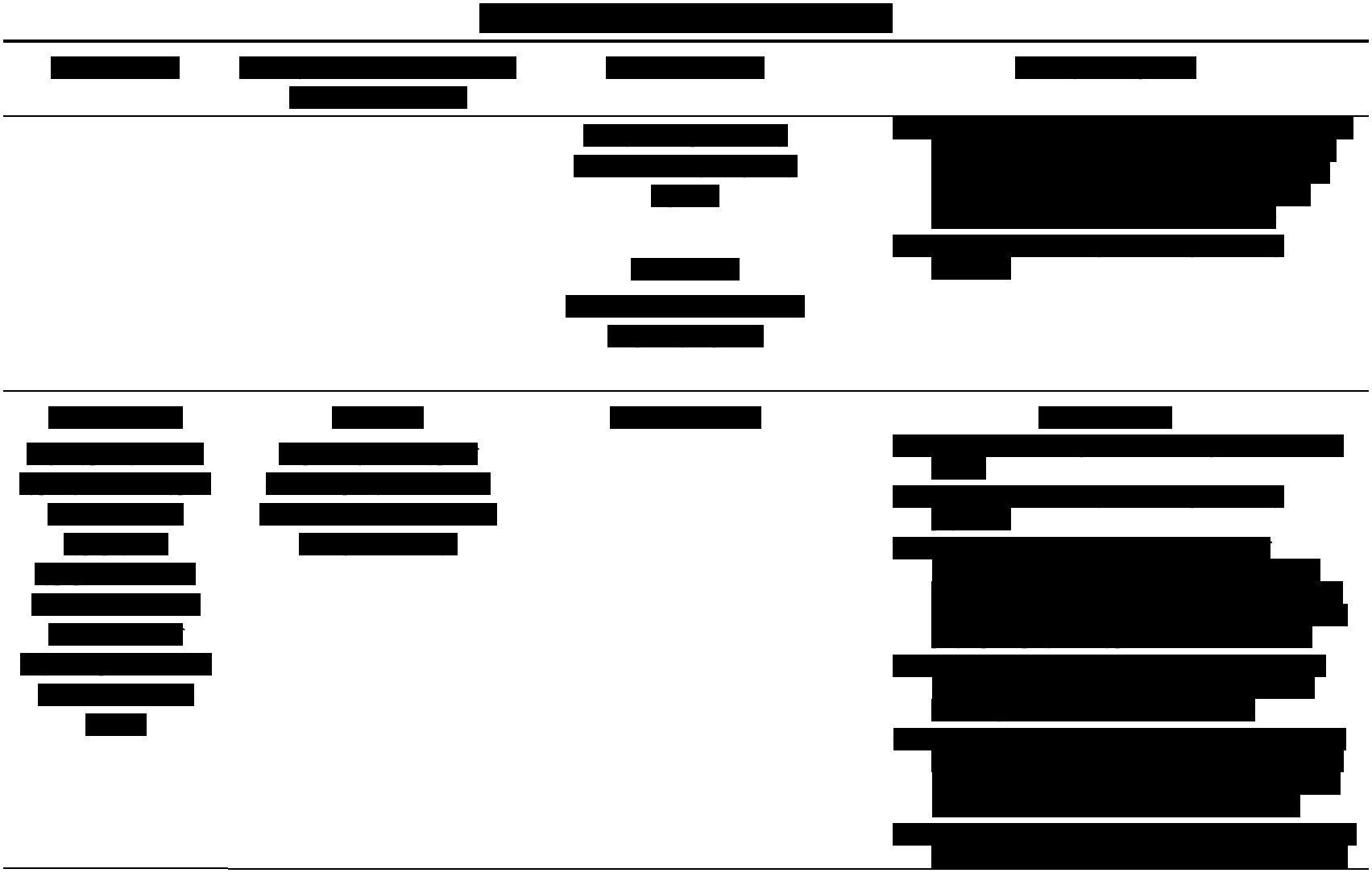

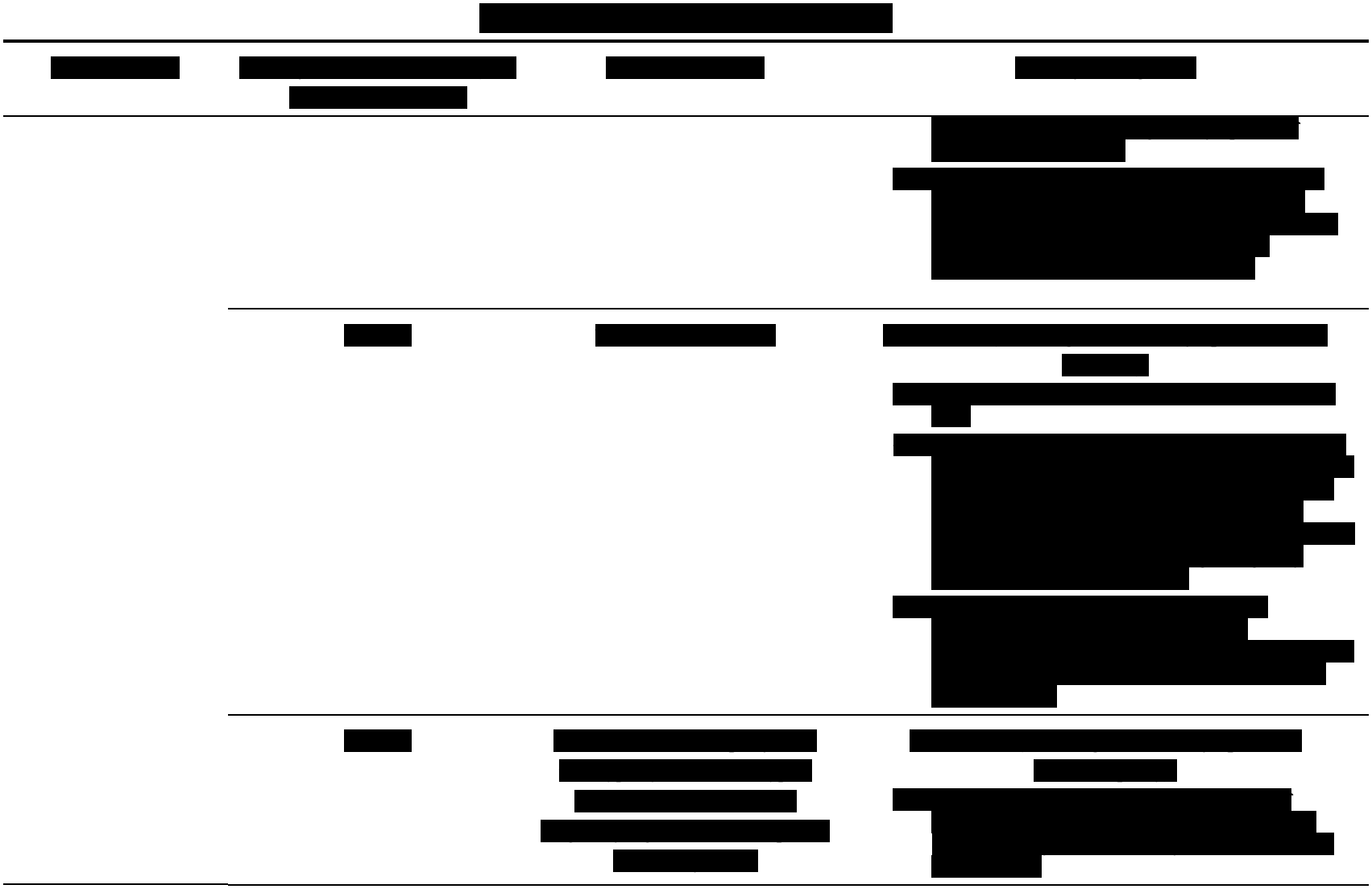

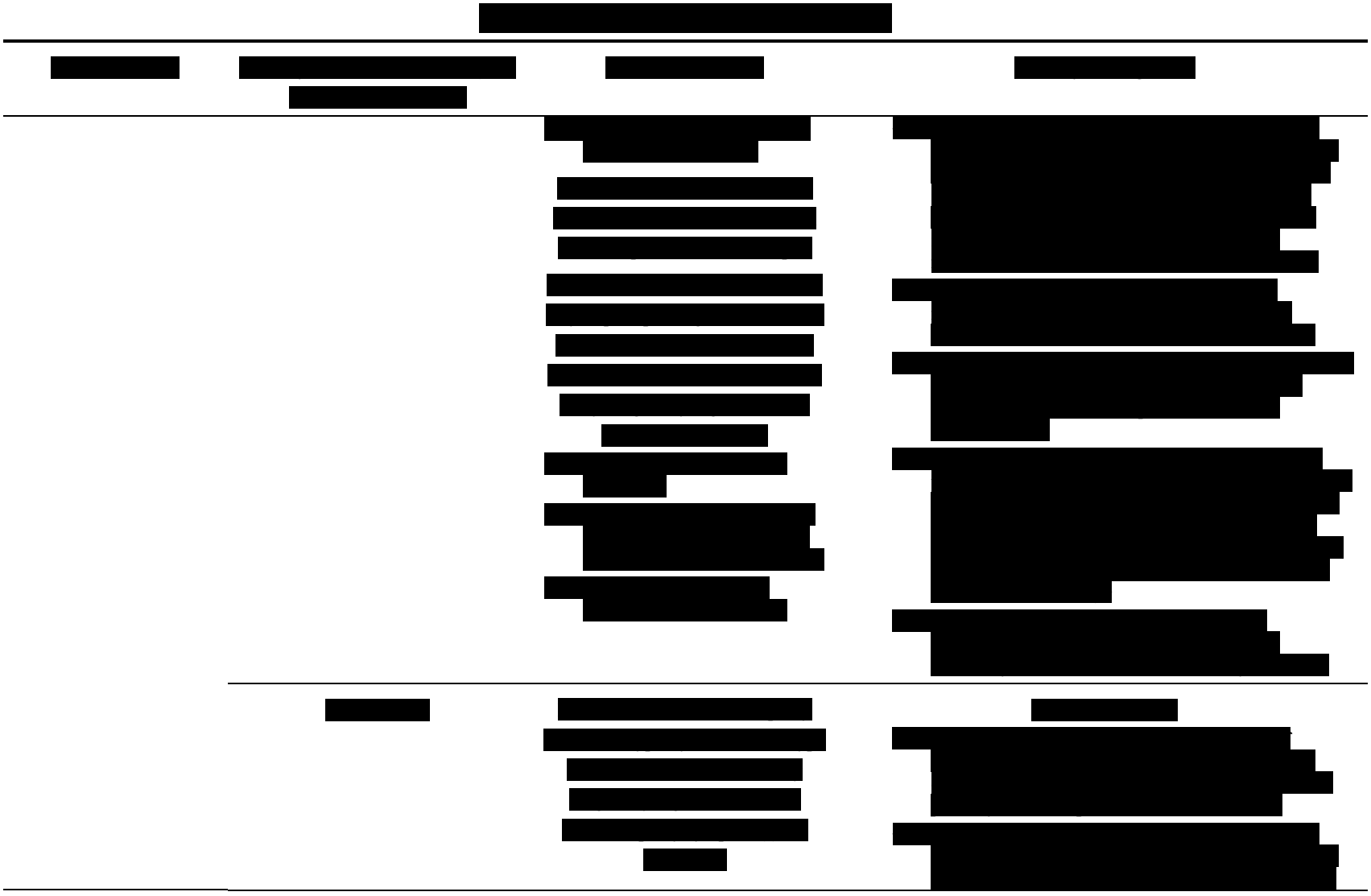

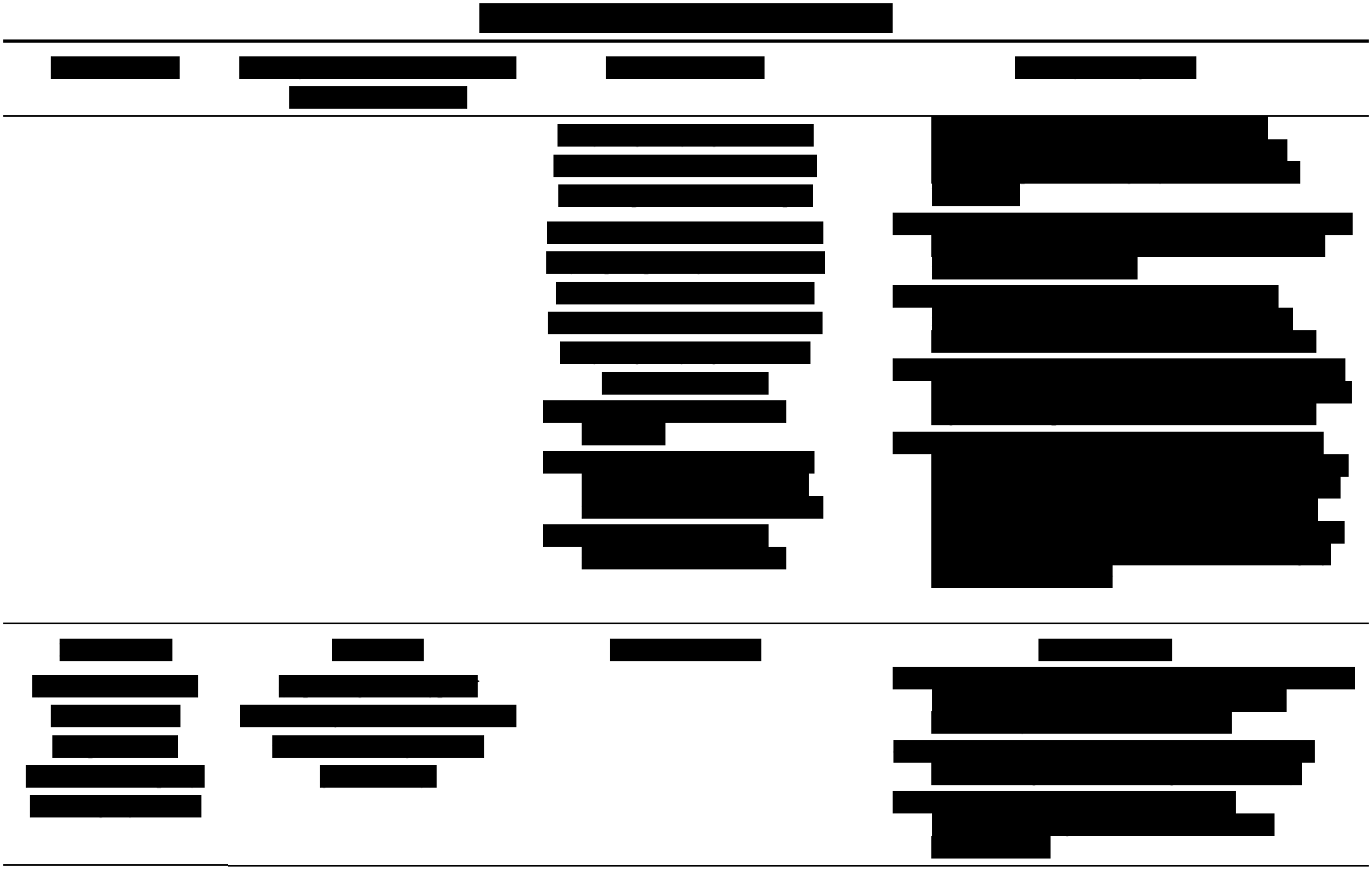

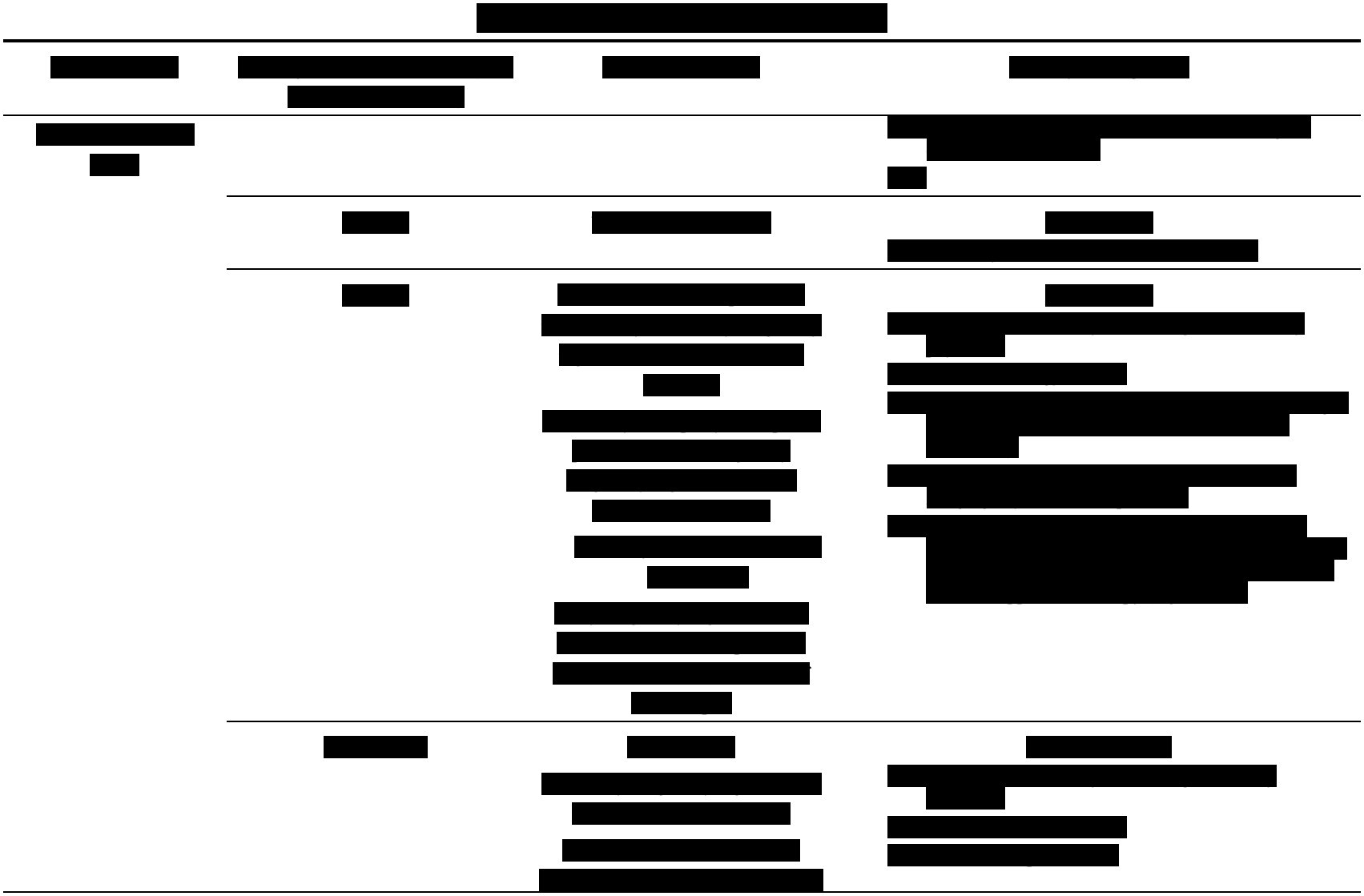

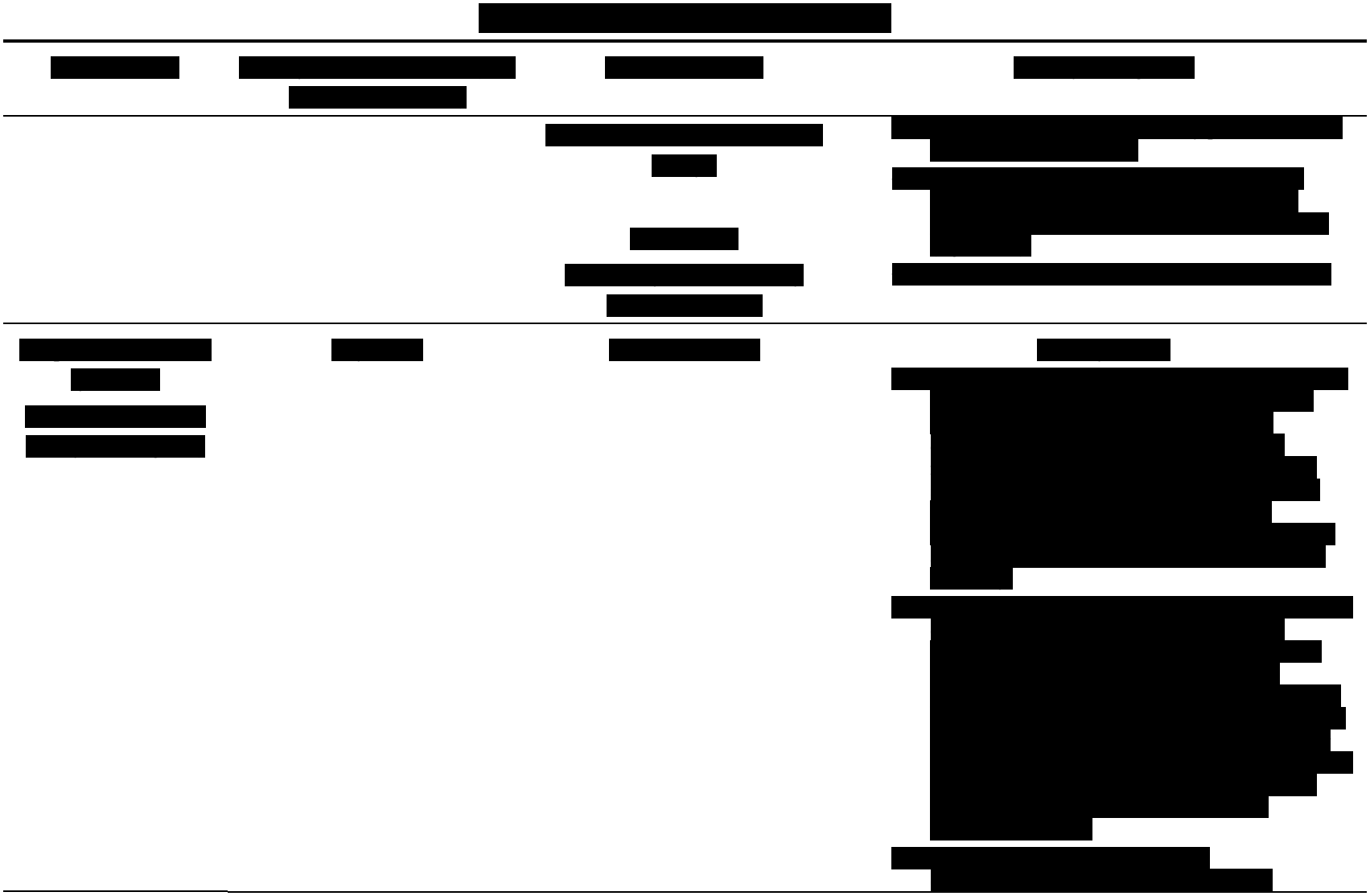

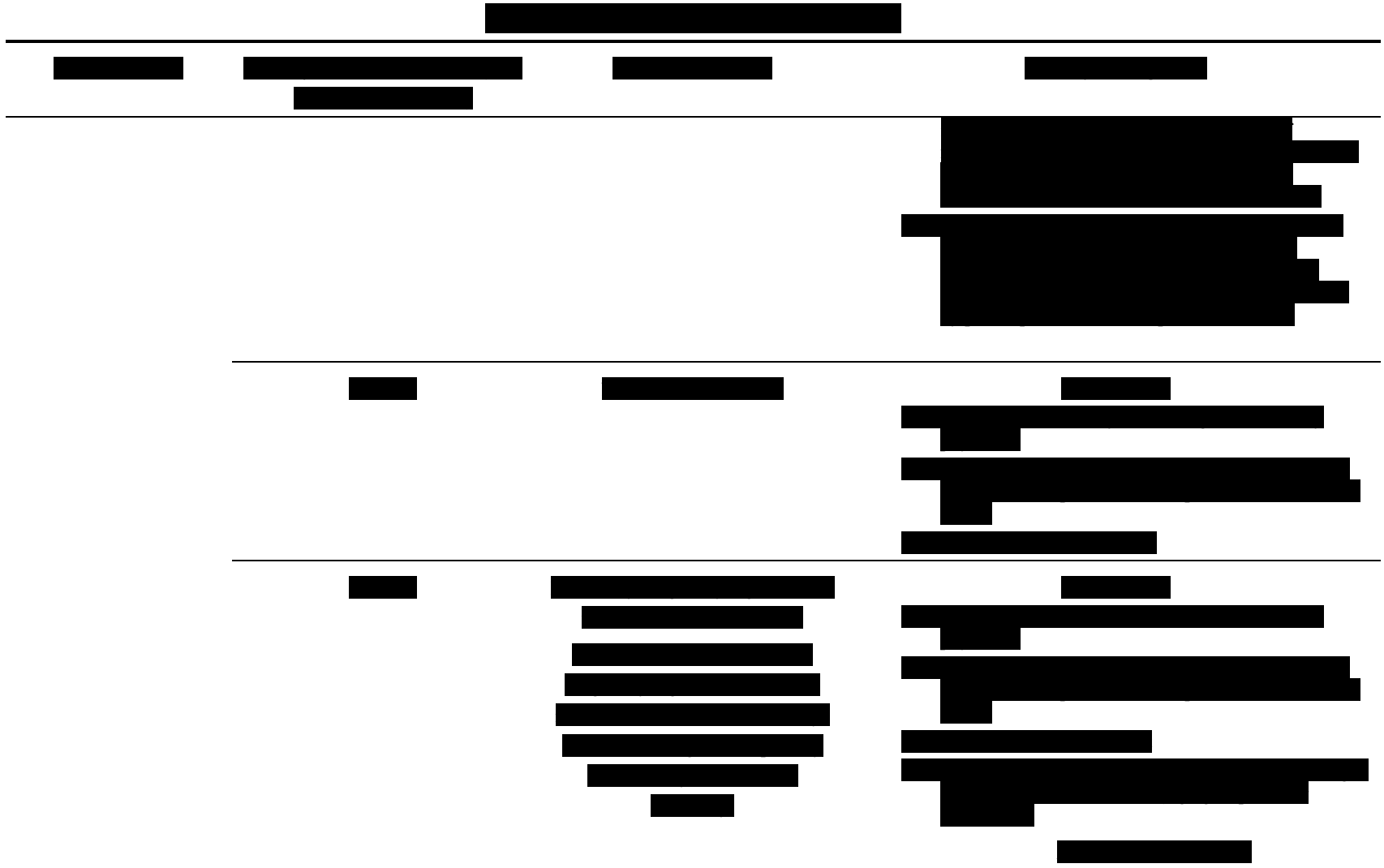

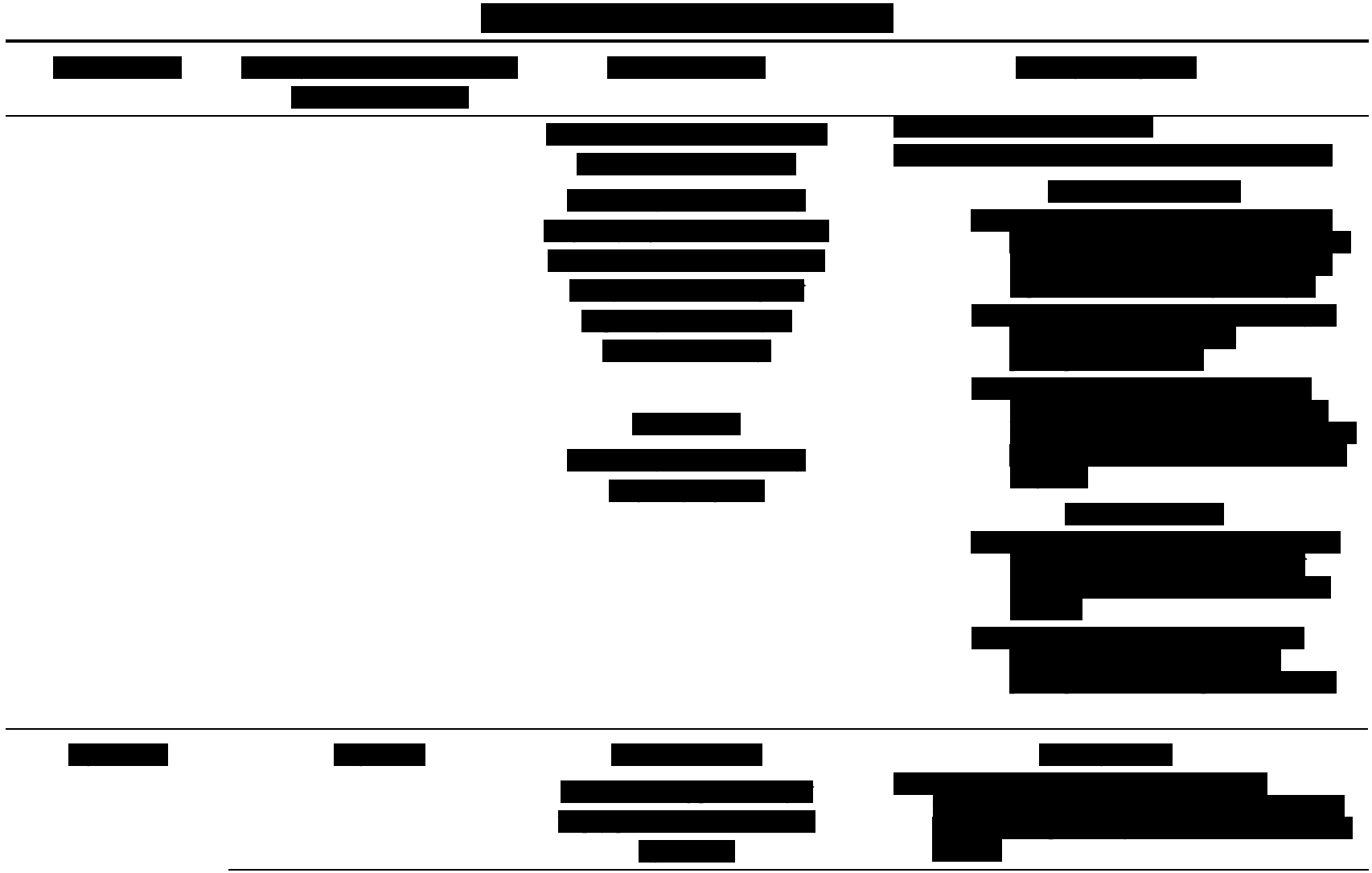

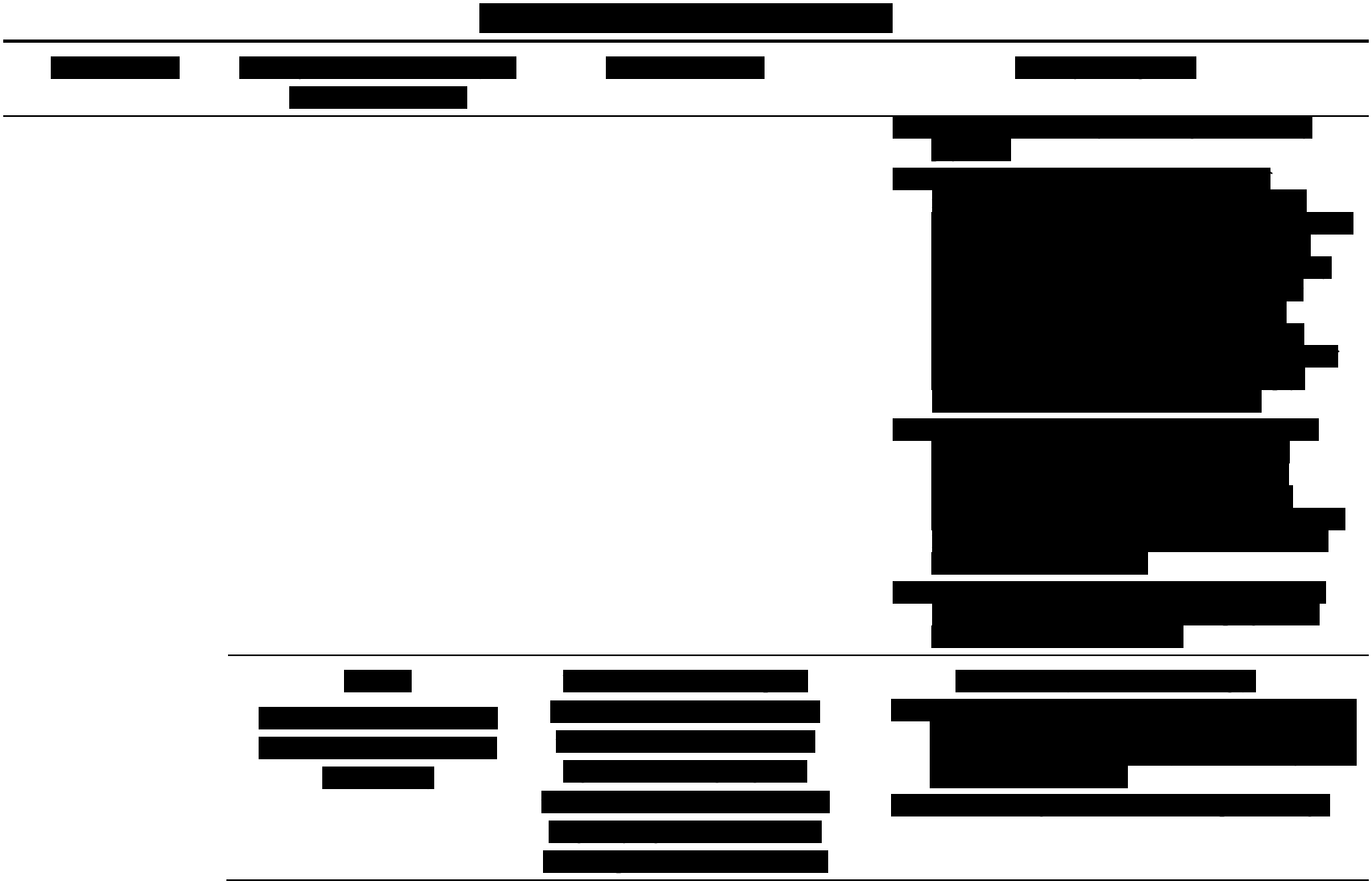

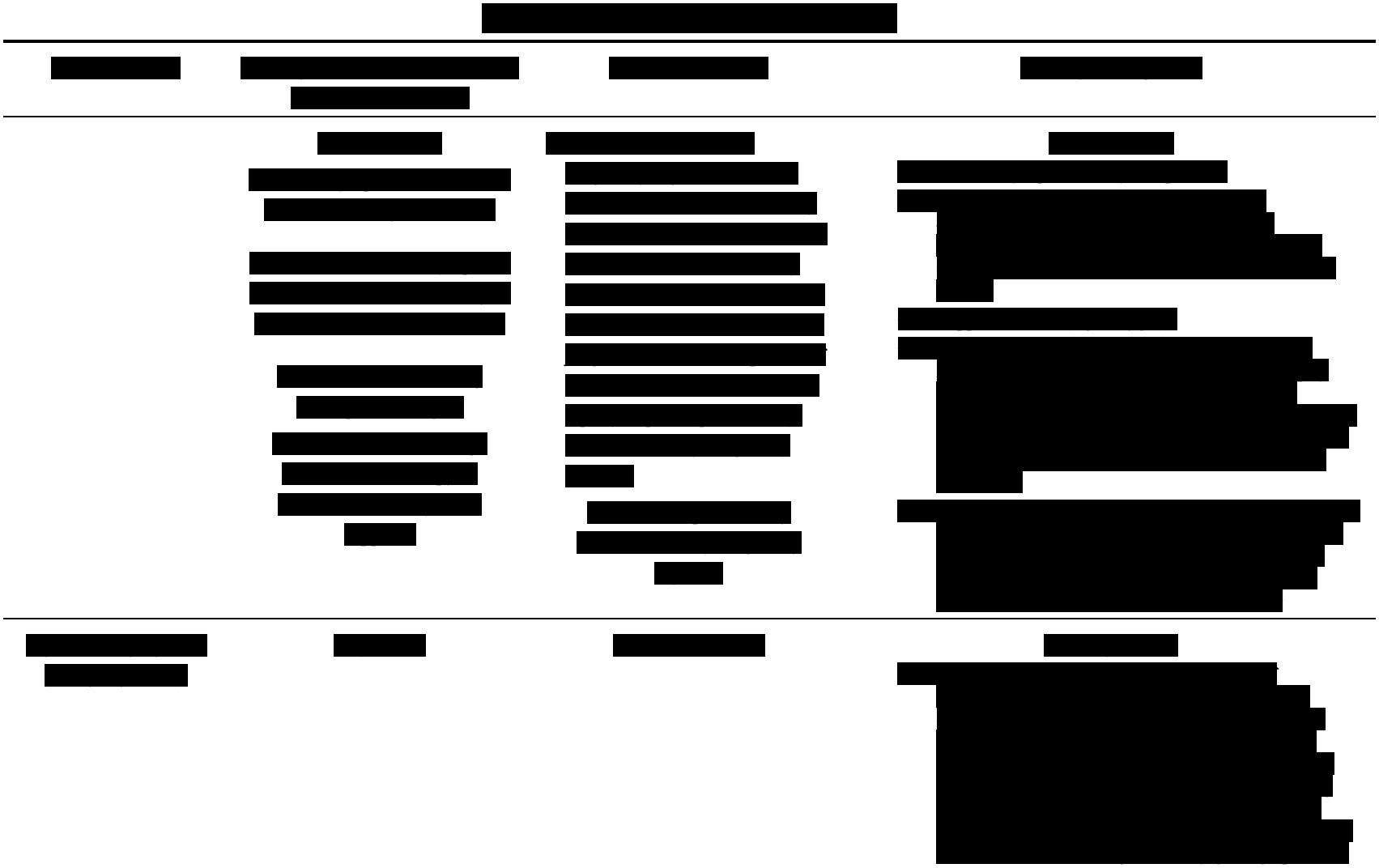

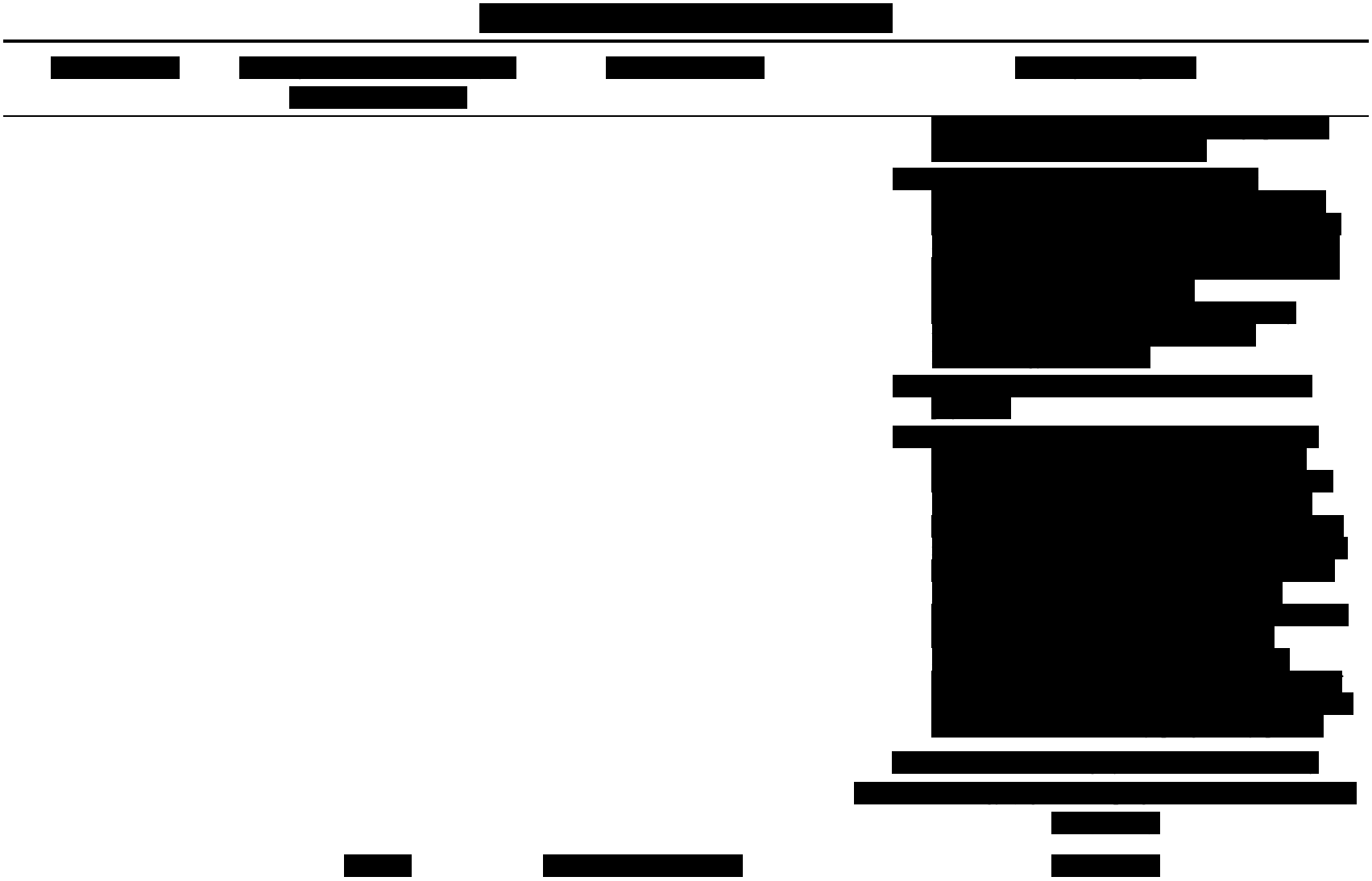

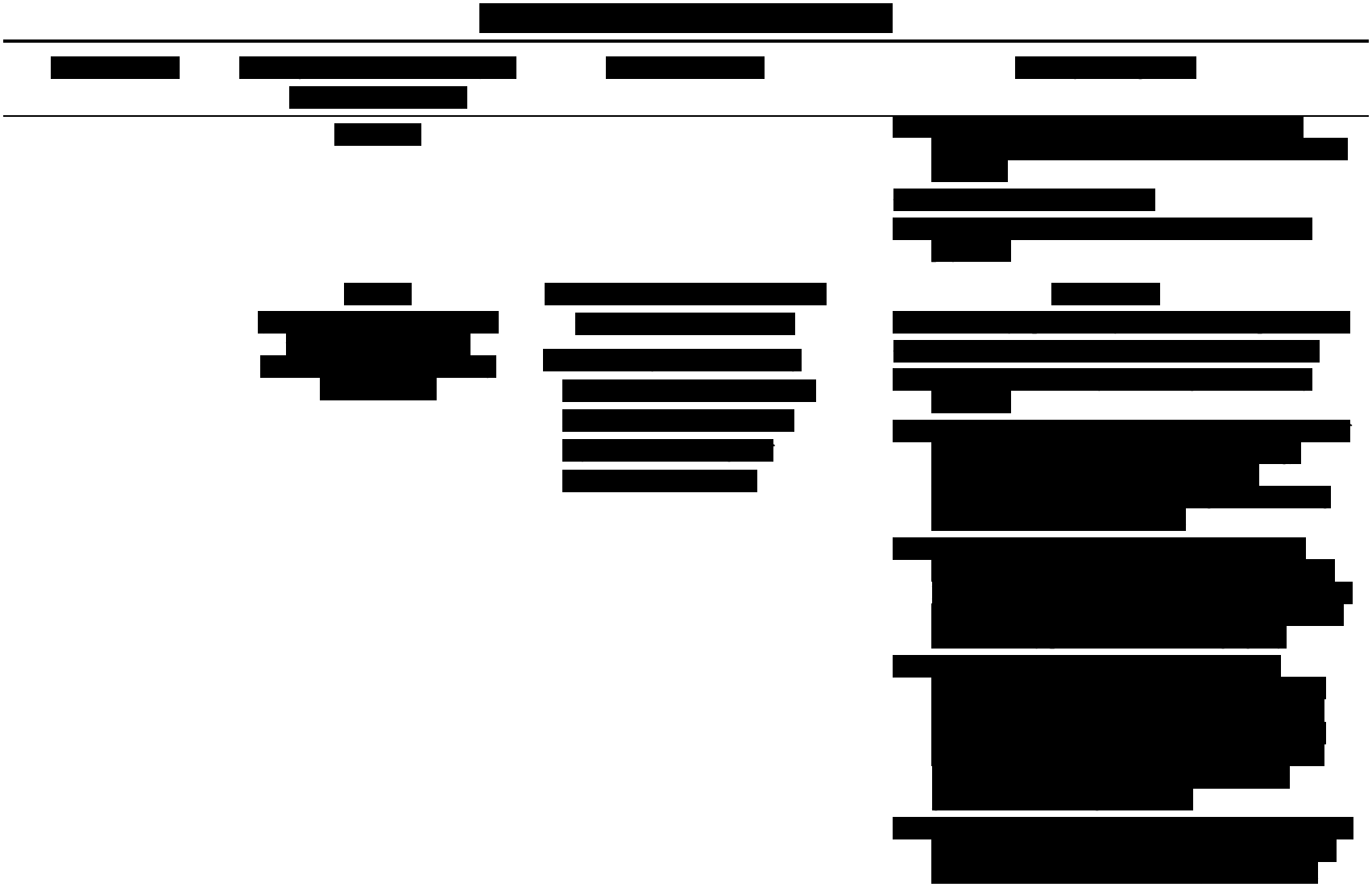

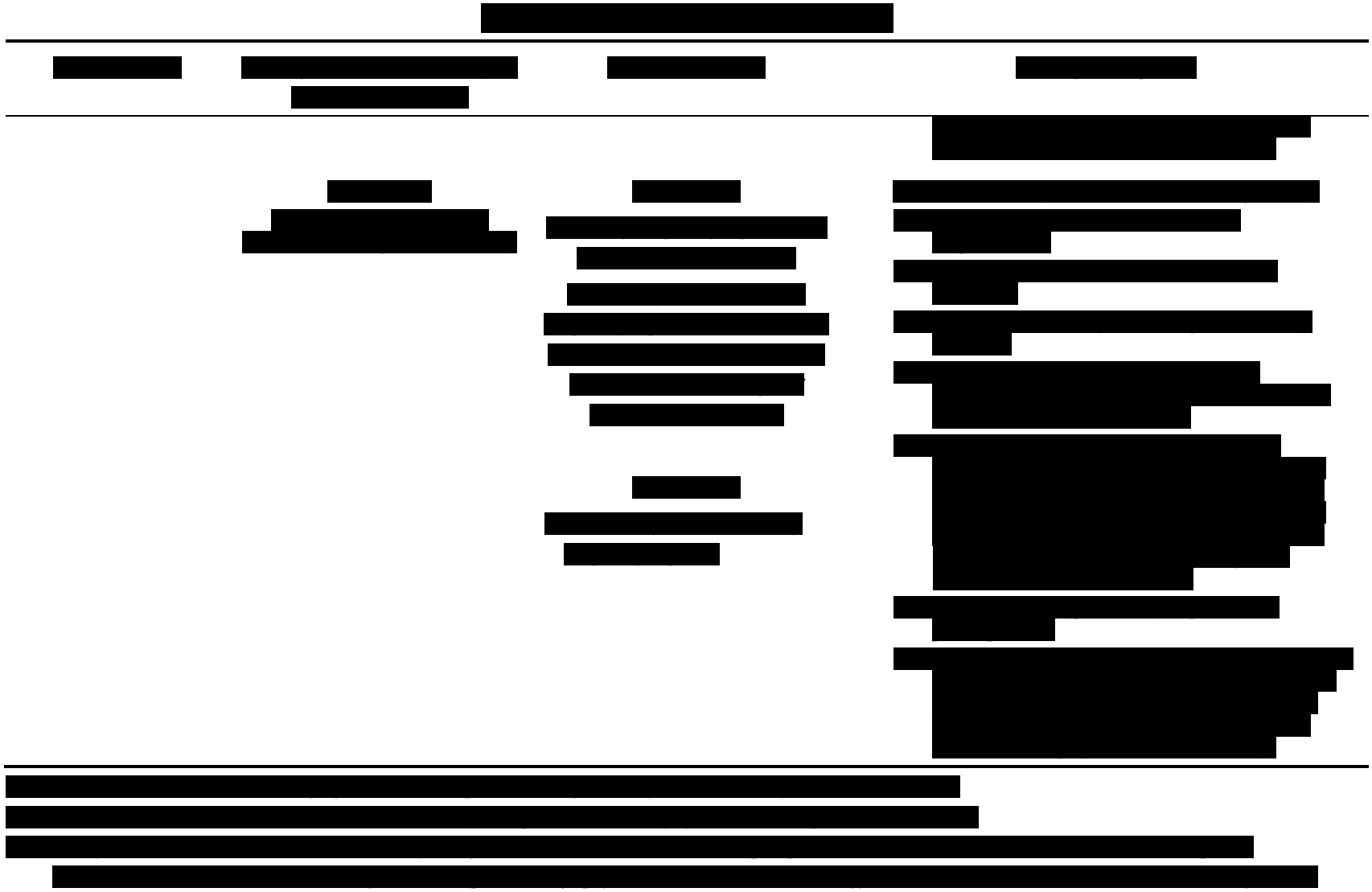

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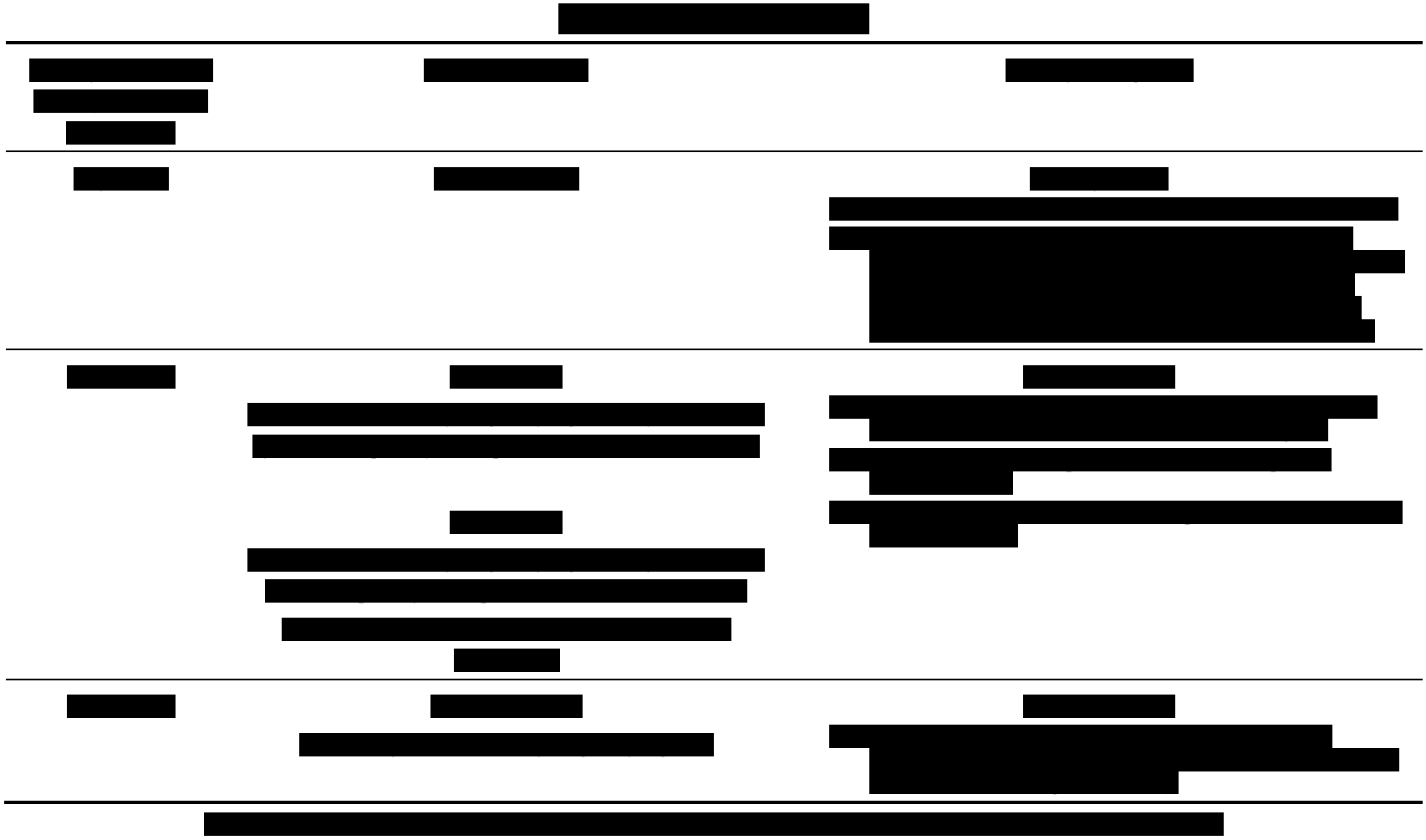

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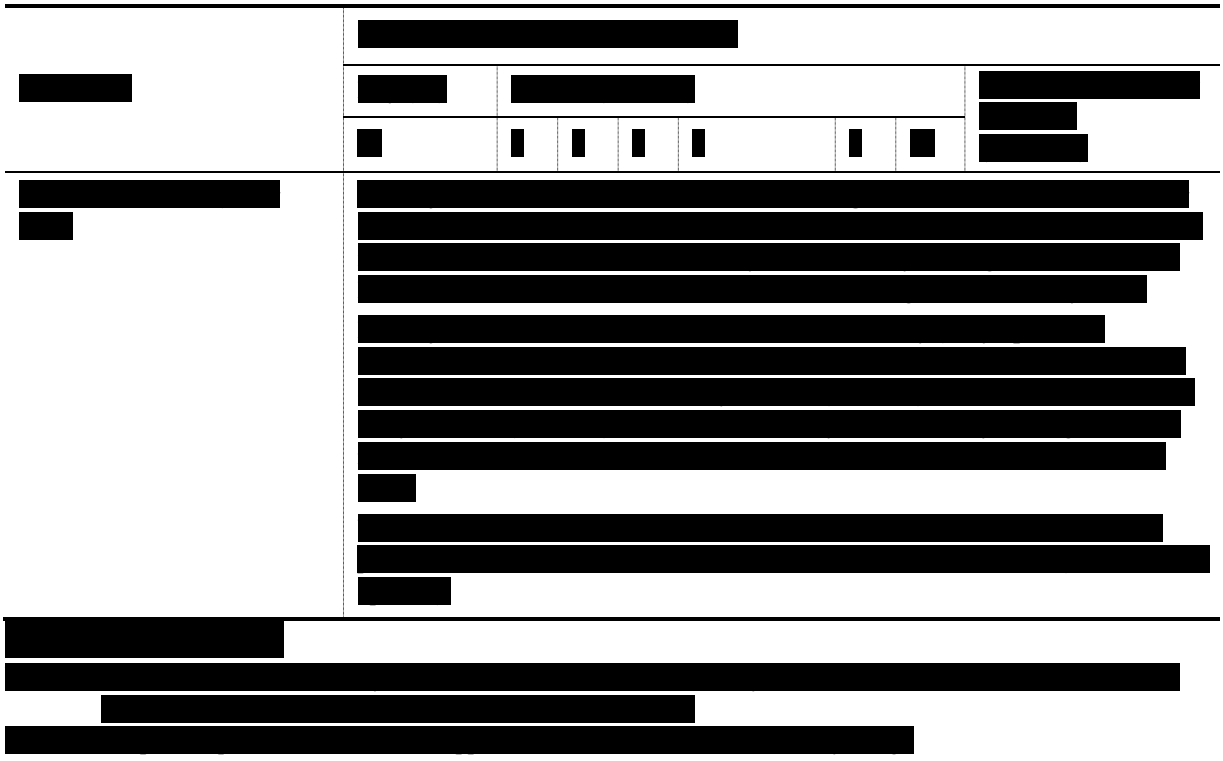

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Appendix 5: Contact Details

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