Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-cardiology (OSICAT)

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Statistical Analysis Plan

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Optimization of the Ambulatory Monitoring for Patients With Heart Failure by Tele-Cardiology

Optimisation de la Surveillance ambulatoire des Insuffisants CArdiaques par Télécardiologie

OSICAT

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By signing this form in one original copy, the methodologists/statisticians members of the study Scientific Committee confirm that they approve the contents of this Statistical Analysis Plan:

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Statistical Analysis Plan Final Version # 1.0 dated 21 March 2019

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	Angiotensin-Converting Enzyme
AE	Adverse Event
AIC	Akaike's Information Criterion
ALSI	Air Liquide *Santé* International
ARB	Angiotensin Receptor Blocker
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BNP	B-type Natriuretic Peptide
CHF	Chronic Heart Failure
CI	Confidence Interval
CIC	Clinical Investigation Centre
COPD	Chronic Obstructive Pulmonary Disease
CRO	Contract Research Organisation
CST	Clinical Study Technician
DBP	Diastolic Blood Pressure
DL	Days Lost
DRM	Data Review Meeting
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GFR	Glomerular Filtration Rate
HLGT	High-Level Group Term
ITT	Intention To Treat
LVAD	Left Ventricular Assistance Device
LVEF	Left Ventricular Ejection Fraction
MCS	Mental Component Summary
MedDRA	MEDical Dictionary for Regulatory Activities
MH	Mental Health
NT-pro-BNP	N-Terminal-pro-B-type Natriuretic Peptide
NYHA	New-York Heart Association
PCS	Physical Component Summary
[redacted]	[redacted]
PT	Preferred Term
Q1	25th percentile
Q3	75th percentile
REML	Restricted Maximum Likelihood
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SOC	System Organ Class
WHO	World Health Organisation

This Statistical Analysis Plan (SAP) describes the statistical methods to be used for the reporting and analyses of clinical data collected under OSICAT protocol.
The SAP is based on the relevant sections of the protocol *(Revised Version 14.0 dated 27th July 2018 revised on 6th September 2018 (Amendment # 14))* and the corresponding electronic Case Report Form *(eCRF version 2.0 dated 26th April 2017)*. The SAP contains a more technical and detailed elaboration of the principal features of the statistical analyses described in the study protocol.

1. SUMMARY OF THE STUDY PROTOCOL

1.A STUDY OBJECTIVES

PRIMARY OBJECTIVE

Assess the impact of a Tele-cardiology program on morbidity-mortality in heart failure patients *versus* standard monitoring.

SECONDARY OBJECTIVES

1) Assess the effect of management by Tele-cardiology *versus* standard management on hospitalisations and deaths of cardiovascular origin.

2) Compare the kinetics of evolution in quality of life between D0 and M18 in the 2 groups.

3) Assess the differential cost-effectiveness and cost-utility ratios of both patient management strategies.

4) Assess societal acceptability of management by Tele-cardiology among healthcare professionals and patients.

5) Collect data concerning the hospitalisations and deaths during the extension period of monitoring of the Tele-cardiology program among the patients who wish to participate in the latter.

1.B STUDY DESIGN

The OSICAT study consists of a comparative, randomised, 18-month period followed by a non-comparative extension period for patients from the first period willing to participate in the latter.

The study design is:

- comparative study *(management by Tele-cardiology versus standard care)*
- 2 parallel groups
- randomised ratio *(2:2)*
- open-label
- in Chronic Heart Failure (CHF) patients
- multicentric
- national *(in France)*.

It was scheduled to recruit a total of 990 patients over a 3.5-year period in 46 planned participating centres.

This study comprises an Inclusion Visit with the investigating cardiologist followed by 4 telephone contacts by Clinical Study Technicians (CST) at Clinical Investigation Centre (CIC) Toulouse.

1.C STUDY INTERVENTIONS

Patients were randomised in one the 2 following study groups:

- Standard care: standard follow-up, including patient's home return with monitoring during consultations with their general practitioners or referring cardiologists,
- Tele-cardiology: personalised telephone support and supervision of patient's daily signs and symptoms at their home via tele-monitoring.

1.D DETERMINATION OF SAMPLE SIZE

The study sample size detailed below was initially fixed at 870 patients in total. This sample size was increased to **990 patients** in protocol amendment # 7 dated 7th January 2016 as recommended by the study Scientific Committee to counterbalance the estimated 10% loss of patients in the Tele-cardiology group before its effective set-up with no modification of the first assumptions made to estimate the study sample size.

It was hypothesised that the intervention would reduce the number of re-hospitalisations and deaths *(composite primary criterion)* in the Tele-cardiology group *versus* the standard care control group. A bilateral hypothesis test was chosen. Calculations were performed based on a type I error alpha risk of 0.05 and a power of 90%.

The following hypotheses were used as a basis for the study sample size estimation:

- The first hypothesis is based on a frequency of the composite primary criterion without intervention of 42% and a reduction in the relative risk of 46% *(according to Cochrane meta-analysis (Inglis, 2010))*, the number of patients required per study group is 118, *i.e.*, a total of 236 patients.
- If a lower hypothesis for the frequency of the composite primary criterion is formulated, *i.e.*, 32% and the reduction in the relative risk of occurrence of the composite criterion is estimated at 30% *(according to the data observed in Germany, with the same device, but for cohort management, in an open manner without randomisation)*, the number of patients required per study group is around 446, *i.e.*, a total of 890 patients.
- The data of the French and European registers are in favour of a frequency of occurrence of the composite primary criterion of 35%. If the reduction in the relative risk is 30%, the number of patients required per study group is 393, *i.e.*, a total of 786 patients to which 10% of loss to follow-up is added, *i.e.*, a scheduled overall cohort of 864 patients rounded up to a total of 870 patients. Finally, this hypothesis was compared with the most recent bibliographical data in the area *(Teerlink, 2013 and Takeda, 2012)*. These figures are similar to those obtained above, which comforts the hypothesis of a total of 870 patients.

2. EVALUATION CRITERIA

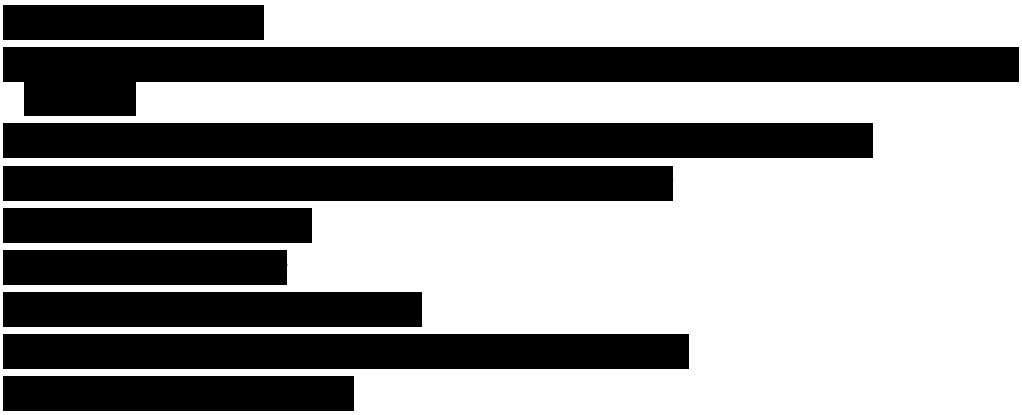
2.A DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics recorded by the study investigators in the eCRF for each participating patient at Inclusion Visit include:

- Demographic data: gender and date of birth *(month/year only will be part of the study database locked and age will be calculated as detailed in section 5.C.1)*
- Study disease characteristics: NYHA classification, cardiopathy and heart failure description
- Last available echocardiography results: Left Ventricular Ejection Fraction (LVEF) and end-diastolic diameter with their date
- Last available measurement of cardiac markers: B-type Natriuretic Peptide (BNP) or N-terminal-pro-BNP (NT-pro-BNP)
- Cardiovascular risk factors: smoking, family history, dyslipidemia, arterial hypertension and diabetes
- Medical and surgical history and concomitant diseases:
  - Associated diseases: chronic renal disease, Chronic Obstructive Pulmonary Disease (COPD) and coronary heart disease
  - Medical and surgical history and other concomitant diseases
- Concomitant treatments:
  - Pre-specified Chronic Heart Failure (CHF) treatments including: Angiotensin-Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARBs), beta-blockers, loop diuretics, digoxin, aldosterone antagonists and ivabradine
  - Other concomitant treatments reported at Inclusion Visit
- Last available serum chemistry evaluation: potassium, plasma urea, creatinine and creatinine clearance with their date
- Vital signs at Inclusion Visit:
  - Weight, height and Body Mass Index (BMI)
  - Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and pulse rate measured in both supine and standing positions
- Other baseline characteristics: previous participation to an educational therapeutic program and date.

During the month following the Inclusion Visit, after the patient's home return, the first telephone contact *(Visit 1)* was to be performed by Clinical Study Technicians (CST) at Clinical Investigation Centre (CIC) Toulouse to collect:

- Socioeconomic status at baseline:



- SF-36 self-questionnaire phone answers.

2.B EFFICACY CRITERIA

2.B.1 *Primary Criterion*

The primary efficacy criterion is a composite morbidity-mortality criterion combining the number of unplanned hospitalisations for any cause and death from any cause during the 18-month comparative study follow-up period.

2.B.2 *Secondary Criteria*

Secondary efficacy criteria related to the 18-month comparative study follow-up period include:

- Death from any cause
- Number of unplanned hospitalisations for any cause
- Composite criterion combining the number of unplanned hospitalisations for cardiovascular cause and death from cardiovascular cause
- Number of unplanned hospitalisations for cardiovascular cause
- Death from cardiovascular cause
- Number of unplanned hospitalisations for heart failure
- Cumulative number of days in hospital for any unplanned cause
- Cumulative number of days in hospital for any unplanned cardiovascular cause
- Cumulative number of days in hospital for any unplanned heart failure cause
- Days lost due to unplanned cardiovascular hospitalisations or to all-cause death
- SF-36 questionnaire scores including 8 general dimensions and 2 composite scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS).

Secondary efficacy criteria related to the non-comparative study extension period include:

- Annualised number of unplanned hospitalisations for any cause during the extension period
- Death from any cause during the extension period
- Annualised number of unplanned hospitalisations for cardiovascular cause during the extension period
- Death from cardiovascular cause during the extension period.

2.C SAFETY CRITERIA

Not Applicable as study investigators only perform the Inclusion Visit

2.D OTHER CRITERIA

[redacted]

The medico-economic evaluation in terms of cost-effectiveness and cost-utility will be covered by a separate document, as well as the societal assessments of the study intervention among healthcare professionals and patients separately.

3. STATISTICAL METHODS

3.A DATA COLLECTION

Data collected by phone *(during the 18-month comparative study follow-up period, apart from Visit 1 detailed in section 2.A)*
During the 3 telephone contacts planned to be performed by Clinical Study Technicians (CST) at CIC Toulouse at Visit 2 *(Month 6 (± 15 days))*, Visit 3 *(Month 12 (± 15 days))* and Visit 4 *(Month 18 (± 15 days) or at the time of study end in case of premature withdrawal)*, the following information is collected in the eCRF:

- SF-36 self-questionnaire *(collected at baseline (see section 2.A), as well as at Month 12 and Month 18)*

[redacted]

Hospitalisations and deaths

All hospitalisations occurring between patient's inclusion and individual study end are looked for by CST in the study centres investigator's source documents or in their computerised system. All corresponding hospitalisations reports are to be retrieved in a pseudonymised manner.

[redacted]

For each hospitalisation with an available source hospitalisation report, the following information are entered by investigators in the eCRF:

- Dates of hospital admission and discharge and hospitalisation location
- Initial reason for hospital admission
- Primary diagnosis of hospitalisation
- Secondary diagnosis or associated diagnoses during hospitalisation
- Planned hospitalisation: Yes/No/Unknown
- Hospitalisation from cardiovascular origin: Yes/No/Unknown.

Additionally, whenever relevant, death information letters are retrieved and information about death are entered in the eCRF.

Study e-Health platform data
Patients in the Tele-cardiology group should have received at their home a communicating electronic weighing scale and a box for answering the questionnaire assessing the progressiveness of their symptoms. Each patient was asked to weight him/herself and then to answer to 8 simple questions by Yes/No every day.

These self-monitoring parameters were remotely transmitted via standard telephone lines to the secure server. These data were analysed automatically by an expert system that generated pre-specified alerts. The patient was contacted by a call centre nurse to check the relevance of the automatic alert and he/she was advised to contact his/her general practitioner or referring cardiologist if the alert was confirmed. A follow-up phone call was then organised a few days later.

3.B GENERAL CONSIDERATIONS

At the end of the study, after the database lock, the statistical analysis will be performed [redacted]

Thorough description of all parameters reported will be presented separately by study group, using the observed case approach. Summary tabulated results will be provided by study group and assessment time, if relevant or they will be replaced by the corresponding individual data listings if too few patients are concerned.

Tabulations of quantitative parameters will include the following summary statistics: Number of Patients / Mean / Standard Deviation (SD) / Minimum / Median / Q1 / Q3 and Maximum. The results will be presented with a number of decimals appropriate to the parameter studied: if for a given parameter, the raw value has been collected with n decimal places, the mean, median and standard deviation will be rounded to n+1 decimal places, while the minimum and maximum values, as well as Q1 and Q3 will be tabulated as reported with n decimal places.

Tabulations of frequencies for categorical data will include all possible categories and they will display the number of observations in a category, as well as the percentage (%) relative to the respective study group. Percentages will be rounded to 1 decimal place. The category 'Missing' will be displayed only if there are actually missing values. Percentages will be calculated on the total of non-missing recorded categories.

Dictionaries:

- Medical and Surgical History, Concomitant Diseases and Reasons for Hospitalisation will be coded using the MedDRA dictionary version 19.0.
- Concomitant Treatments will be coded using the WHO Drug dictionary version March 2016.

3.C DEFINITION OF AN "HOSPITALISATION" EVENT

An "hospitalisation" event is defined by the period between the day a patient is admitted in hospital until either *i)* home return, or *ii)* planned admission in nursing facility following hospitalisation or *iii)* death at hospital. Recorded "home hospitalisations" are considered as hospital stays up to their end date.

Consecutive hospital stays in several wards/ hospitals *(i.e., without home return or a time interval of 0 or 1 day between 1 hospital discharge and the next hospital admission)* are considered as the same "hospitalisation" event.

Hospitalisations without date change between hospital admission and hospital discharge *(i.e., hospitalisations of less than 24 hours, with start date equal to end date)* are not accounted as "hospitalisation" events except for cardiac transplants.

In case of **cardiac transplant**, patients were to be withdrawn from the study and the corresponding hospitalisation was to be recorded by convention in the eCRF with hospitalisation end date equal to cardiac transplant date. This hospitalisation will be counted in the efficacy analysis according to the assessment made by the Clinical Events Adjudication Committee.

In case of death occurring during patient's hospitalisation, the following convention will be used:

- If death occurs **1 day or more** after hospital admission, 2 events *(corresponding to both hospitalisation + death)* will be counted in the composite morbidity-mortality criterion in the efficacy analysis.
- If death occurs **the same day** as hospital admission, 1 event *(corresponding to death)* will be counted in the composite morbidity-mortality criterion in the efficacy analysis.

Investigators report all hospitalisations occurring during the patient's study period in the eCRF. Investigators also assess for each hospitalisation if the hospitalisation is planned or not and if the hospitalisation is of cardiovascular origin or not. For all deaths recorded, investigators also assess if the death is of cardiovascular origin or not.

A Clinical Events Adjudication Committee has been established to review in an independent blind manner all hospitalisations reported by investigators for each randomised patient during their 18-month comparative study follow-up period, as well as all deaths outside hospital. Each member of the Clinical Events Adjudication Committee has independently evaluated the hospitalisation reports and the death certificates and they have provided a written adjudication form signed by the Clinical Events Committee chairperson for each of them. Whatever the investigators' recordings in the eCRF, the conclusions of the members of the Clinical Events Adjudication Committee on the planned or not status of each hospitalisation recorded and on the definition of the secondary efficacy criteria *(hospitalisations and deaths from cardiovascular cause, as well as hospitalisations for worsening of heart failure)* will override the investigators recordings and they will be used for the primary analysis of the primary efficacy criterion *(see section 5.E.1)* and for the main analyses of the secondary efficacy criteria *(see section 5.E.5)*.

For consecutive hospital stays in several wards/ hospitals *(i.e., without home return or a time interval of 0 or 1 day between 1 hospital discharge and the next hospital admission)* which are considered as the same "hospitalisation" event, the following conventions will be used:

- The hospitalisation will be considered to be **unplanned** if at least 1 hospital stay constituting the "hospitalisation" event was not planned.
- The hospitalisation will be considered to be from **cardiovascular origin** if *i)* at least 1 hospital stay constituting the "hospitalisation" event was unplanned and of cardiovascular cause or if *ii)* the whole "hospitalisation" event was planned and at least 1 hospital stay of cardiovascular cause.

[redacted]

3.D COMPARATIVE ANALYSIS PERIOD

Patient's randomisation may have been performed during a hospitalisation, before its end while patient's follow-up could only start when patient went back home. Moreover, due to the telephone contacts schedule, hospitalisations and death information may have been collected beyond the planned 18-month comparative study follow-up period.

Therefore, an effective comparative analysis period will be defined as detailed below. Only hospitalisations and deaths occurring during this analysis period will be counted in the efficacy analyses of the 18-month comparative study follow-up period.

Start of analysis period (T0)

When patient's randomisation was performed **during a hospitalisation**, a record of dummy hospitalisation is entered in the eCRF with "Randomisation" as the reason for admission, informed consent signature date entered in the field "hospital admission date" and date when the patient went back home or died entered in the field "hospital discharge date". If such a record exists within the database, the start of analysis period *(referred to as T0 within the current document)* will be the date when the patient went back home *(if patient died, he/she will be excluded from the Full Analysis Set as detailed in section 5.B).*

Otherwise, for patients randomised **in ambulatory**, T0 will be the actual date of patient's randomisation.

End of analysis period (Tend)

For all patients, the theoretical end date of the 18-month comparative study follow-up period will be defined as the date of T0 + 18 months.

[redacted]

3.E EXTENSION PERIOD

Patients entering the non-comparative study extension period will be classified into one of the 2 following study groups:

- "**Standard Care / Tele-cardiology**": patients from the "standard care" group during the comparative period entering in the study extension period
- "**Tele-cardiology / Tele-cardiology**": patients from the "Tele-cardiology" group during the comparative period entering in the study extension period.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES IN THE PROTOCOL

The following changes to the study protocol *(Revised Version 14.0)* have been introduced in the current Statistical Analysis Plan:

- The primary efficacy criterion was clarified. Indeed, **unplanned** hospitalisations for any cause will be considered in addition to death from any cause.
- The definition of the Full Analysis Set (FAS) was updated from "all randomised patients" to "all patients randomised once, who left the hospital alive and were not prematurely withdrawn during the randomisation hospitalisation and who were not included in study centres where investigators withdrew their participation" as detailed in section 5.B.
- No systematic statistical test will be performed to compare study groups at baseline on any data sets analysed. Homogeneity tests will only be performed if any clinically significant imbalances between study groups appear to be of major importance for the interpretation of the primary efficacy criterion results and need to be cautiously examined in order to determine whether the randomisation has failed or not.

- Cumulative number of days in hospital will be normalised on an annual basis to take into account the effective individual follow-up duration.
- Analyses of days lost due to unplanned cardiovascular hospitalisations or to all-cause death have been added as detailed in section 5.E.5.

5. STATISTICAL AND ANALYTICAL PLANS

SAS® Version 9.4 will be used for all descriptive summaries and inferential analyses.

5.A DISPOSITION OF PATIENTS

The patients disposition table will summarise the following data for all patients, by study group *(and globally)*:

- The number of selected *(as defined in section 5.B)* and randomised patients
- The number of patients randomised twice
- The number of patients who left alive and of those who did not leave alive the hospital after their randomisation
- The number of patients who continued their study participation after the randomisation hospitalisation
- The number (%) of patients completing the study and of those prematurely withdrawn by reason during the 18-month comparative study follow-up period and during the non-comparative extension period separately.

[redacted]

5.B DATA SETS ANALYSED AND PROTOCOL DEVIATIONS

All Selected Patients

All selected patients are patients present in the database who signed the written informed consent.

Full Analysis Set (FAS)

The Full Analysis Set (FAS) will be composed of all patients randomised once, who left the hospital alive and were not prematurely withdrawn during their randomisation hospitalisation and who were not included in the study centres where investigators withdrew their participation.

[redacted]

The FAS will be used for the analyses planned for the 18-month comparative study follow-up period.

[redacted]

Extension Period Set

The Extension Period Set will be composed of all patients entering the extension period.

The Extension Period Set will be used for the descriptive evaluations planned for the non-comparative study extension period.

5.C DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

No systematic statistical test will be performed to compare both study groups at baseline.

Statistical tests will only be performed if any clinically significant imbalances between study groups appear to be of major importance for the interpretation of the primary efficacy criterion results and need to be cautiously examined in order to determine whether the randomisation has failed or not.

If this descriptive analysis provides any clues on potential imbalances, further statistical investigations will be carried out using homogeneity tests and if necessary, the factor adjusting strategy will be redefined.

5.C.1 *Demographic Data*

Age will be calculated using the number of full years elapsed between the year of birth and the date of signed written informed consent and it will be presented at Inclusion Visit as an integer.

Gender and age *(in years)* will be summarised using the FAS by study group and in total.

Age will also be described as categorical data using the 3 categories: < 60 years, [60 - 80[years and ≥ 80 years, as well as the 2 categories: ≤ 70 years and > 70 years.

5.C.2 *Study Disease Characteristics*

The following disease characteristics at Inclusion Visit will be tabulated using the FAS by study group and in total:

- NYHA classification *(I/II/III/IV)*
- Cardiopathy *(Ischemic/ Non ischemic)*
- Heart failure *(Left/ Right/ Global)*
- Previous Participation to an Educational Therapeutic Program *(Yes/ No)* and time since participation *(in months).*

Moreover, the last available echocardiography results and the last available measurement of cardiac markers will be tabulated using the FAS by study group and in total, including the following parameters:

- Left Ventricular Ejection Fraction *(LVEF in % and categorical data using the 2 categories: ≤ 40% and > 40%)*
- End-diastolic diameter (mm) as both quantitative and categorical data *(using the 3 categories: < 50 mm, [50 - 60] mm and > 60 mm)*
- BNP (pg/mL) and NT-pro-BNP (pg/mL) separately as both quantitative and categorical data *(using the following categories for each cardiac marker separately: BNP value either < 150 pg/mL or ≥ 150 pg/mL, or NT-pro-BNP value < 300 pg/mL (if applicable) or in [300 - 1000[pg/mL or ≥ 1000 pg/mL).*

5.C.3 *Cardiovascular Risk Factors*

Patient risk factors include the following parameters:

- Smoking
- Family history
- Dyslipidemia

- Arterial hypertension
- Type 1 diabetes
- Type 2 diabetes.

For each risk factor separately, the number (%) of patients with that factor will be tabulated using the FAS by study group and in total.

5.C.4 *Medical and Surgical History and Concomitant Diseases*

The number (%) of patients with the following associated diseases will be tabulated using the FAS by study group and in total:

- Chronic renal disease
- COPD
- Coronary heart disease.

Moreover, the number (%) of patients with any medical and surgical history or concomitant diseases *(apart from chronic renal disease, COPD and coronary heart disease as listed in Appendix 1)* will be tabulated by MedDRA System Organ Class (SOC), High-Level Group Term (HLGT) and Preferred Term (PT) using the FAS. Summaries will be presented by study group and in total, sorted by decreasing frequency in the total group. These summaries will include the number (%) of patients with at least 1 pathology recorded by investigators in the eCRF at Inclusion Visit.

5.C.5 *Concomitant Treatments*

The number (%) of patients for whom each pre-specified CHF treatment is prescribed at Inclusion will be tabulated by study group and in total using the FAS.

Moreover, the number (%) of patients with any concomitant treatments entered by investigators in the eCRF at Inclusion Visit will be tabulated by study group *(and globally)* and by WHO-DRUG dictionary therapeutic area *(ATC1 code corresponding to ATC system main group)* and ATC system subgroup *(ATC2 code)* using the FAS.

For cardiovascular system concomitant treatments, a second table will be provided showing the number (%) of patients with at least 1 cardiovascular system concomitant treatment by ATC system subgroups *(ATC2, ATC3 and ATC4 codes)*.

5.C.6 *Clinical Laboratory Evaluation at Inclusion*

The following last available laboratory parameters will be summarised using the FAS by study group and in total:

- Serum chemistry: potassium (mmol/L), plasma urea (mmol/L), creatinine (µmol/L) and creatinine clearance (mL/min).

Moreover, the Glomerular Filtration Rate (GFR) will be estimated using Modification of Diet in Renal Disease (MDRD) formula, *i.e.*, it will be calculated *(rounded with 1 decimal)* as:

- for males: GFR *(mL/min)* = 186 x [serum creatinine *(µmol/L)*/ 88.4]$^{-1.154}$ x age$^{-0.203}$,
- for females: GFR *(mL/min)* = 186 x [serum creatinine *(µmol/L)*/ 88.4]$^{-1.154}$ x age$^{-0.203}$ x 0.742.

It will be tabulated at Inclusion as both quantitative and categorical data *(using the 3 categories: < 30.0 mL/min, [30.0 – 60.0] mL/min and > 60.0 mL/min)*.

5.C.7 *Vital Signs at Inclusion*

Vital signs measurements at Inclusion Visit include the following parameters:

- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Systolic Blood Pressure (mmHg), measured in supine and standing positions
- Diastolic Blood Pressure (mmHg), measured in supine and standing positions
- Pulse rate (beats/min), measured in supine and standing positions.

Vital signs will be summarised using the FAS by study group and in total. Calculated BMI *(rounded with 1 decimal)* will be tabulated as both quantitative data and categorical data in 5 predefined categories *(< 18.5 kg/m², [18.5 - 25.0[kg/m², [25.0 - 30.0[kg/m², [30.0 - 35.0[kg/m² and ≥ 35.0 kg/m²).*

5.C.8 *Socioeconomic Status*

The [redacted] socioeconomic study parameters will be summarised using the FAS by study group and in total:

[redacted]

5.C.9 *Other Baseline Characteristics*

The following other baseline characteristics will be summarised using the FAS by study group and in total:

- Calculated scores of each dimension of the SF-36 questionnaire, as well as PCS and MCS scores.

[redacted]

5.D MEASUREMENTS OF INTERVENTION ADHERENCE

Patient's adherence to the Tele-cardiology intervention will be assessed using data from the study e-Health platform database generated during the comparative analysis period.

[redacted]

[redacted]

Patient's adherence will be tabulated on the FAS in the subgroup of patients in the Tele-cardiology group as [redacted] quantitative [redacted] data [redacted]

[redacted]

In addition to the overall adherence previously defined, patient's adherence will also be calculated by trimester to evaluate descriptively its evolution over time during the comparative analysis period on the FAS. The 1st study trimester will cover Days [T0 - 91], the 2nd trimester Days [92 - 183], the 3rd trimester Days [184 - 274], the 4th trimester Days [275 - 365], the 5th trimester Days [366 - 457], the 6th trimester Days [458 - 549]. [redacted] It will be tabulated descriptively as quantitative values by analysis period trimester. Arithmetic means and their 95.0% Confidence Intervals (CI) will also be represented graphically *(the x-axis being the time-axis and the y-axis being the arithmetic mean-axis).*

[redacted]

5.E EFFICACY EVALUATION

Analyses of the primary criterion are detailed in sections 5.E.1 to 5.E.4 below, while analyses of the secondary criteria are described in section 5.E.5.

5.E.1 *Primary Analysis of Primary Criterion*

The primary efficacy criterion is a composite morbidity-mortality criterion combining the number of unplanned hospitalisations for any cause and death from any cause during the 18-month comparative study follow-up period.

The primary analysis will take into account the recurrent unplanned hospitalisations. For each patient, all hospitalisations will be added up. Death outside hospital will be counted as an additional event. If death occurred during a hospitalisation with an overnight stay *(i.e., with a date change between hospital admission and hospital discharge)*, 2 events will be counted as detailed in section 3.C.

The primary analysis will be based on all unplanned hospitalisations, as assessed by the Clinical Events Adjudication Committee.

On the FAS, a summary table by study group will describe:

- The number and percentage of patients with at least one unplanned hospitalisation or who died
- The number of events, described as a quantitative variable
- The number of events, described as a categorical variable with the 5 following classes: 0 event, 1 event, 2 events, 3-5 events, > 5 events
- The number of hospitalisation events lasting < 3 nights and the number of hospitalisation events lasting ≥ 3 nights, described as a quantitative variable.

The rate of events *(number of events divided by the time of exposure)* between both study groups will be compared using a Poisson regression model.

The null hypothesis tested will be:

$$H0: \lambda_1 = \lambda_2$$

Where λ_1 = rate of events in the Tele-cardiology group
λ_2 = rate of events in the standard care group.

The Poisson regression model with log link for the expected rate of events is:

$$\log \lambda = b0 + b1\ GROUP$$

$$\log\left(\frac{\#\ events}{Duration\ of\ Follow\text{-}Up}\right) = b0 + b1\ GROUP$$

$$\log\ (\#\ events) = b0 + b1\ GROUP + \log (Duration\ of\ Follow\text{-}Up)$$

Log (Duration of Follow-Up) is called an offset:

- Duration of Follow-Up corresponds to the duration of the comparative analysis period and it will be calculated as follows: (Tend Date *(or date of death if it occurs during the 18-month comparative study follow-up period)* – Date of T0) / 365.25, thus converted in years without any rounding. T0 and Tend dates are defined in section 3.D.
    - Log is the natural log.

In case of overdispersion, a binomial negative regression model will be used.
Overdispersion will be considered if the estimate of dispersion after fitting, as measured by the deviance or Pearson's chi-square, divided by the degrees of freedom, is not near 1.

5.E.2 *Supportive Analyses of Primary Criterion to Check Its Robustness*

[redacted]

5.E.3 *Secondary Exploratory Analyses of Primary Criterion*

Subgroup analyses

The primary analysis based on unplanned hospitalisations for any cause as assessed by the Clinical Events Adjudication Committee and deaths will be repeated for each of the following factors using the FAS:

[redacted]

- NYHA stage in 2 categories: either I / II or III / IV

[redacted]

[redacted]

- Depression at Inclusion defined as patients having either *i)* SF-36 Mental Health (MH) subscore < 45, or *ii)* Mental Component Summary (MCS) composite score < 35, or *iii)* combination of MH < 50 and MCS < 40), or *iv)* medical history of depression *(identified by an High-Level Term either Depressive disorders, or Mood disorders NEC, or Mood alterations with manic symptoms, or Suicidal and self-injurious behaviour)*, or *v*) concomitant antidepressant medications belonging to ATC classes N06AA, N06AB, N06AF, N06AG, N06AX or N06CA.

A summary table by study group will describe for each subgroup:

- The number and percentage of patients with at least one unplanned hospitalisation or who died
- The number of events, described as a quantitative variable
- The number of events, described as a categorical variable with the 5 following classes: 0 event, 1 event, 2 events, 3-5 events, > 5 events
- The number of hospitalisation events lasting < 3 nights and the number of hospitalisation events lasting ≥ 3 nights, described as a quantitative variable.

The primary analysis model *(binomial negative regression model)* will be repeated including the *factor* and the interaction *factor**intervention fixed effect in the model.

If the interaction term is not significant *(p>0.10),* it will be removed from the final model.

If the interaction term is significant *(p≤0.10)*, it will be kept in the final model and further analyses and/or graphs might be produced to describe the interaction if potentially relevant from a clinical point of view.

Moreover, in the subgroup of patients from the FAS who were randomised in the Tele-cardiology group, a summary table will describe by category of overall patient's adherence to the intervention [redacted], the number and percentage of patients with at least one unplanned hospitalisation as assessed by the Clinical Events Adjudication Committee or who died, as well as their number of events, described as both a quantitative variable and a categorical variable with the 5 following classes: 0 event, 1 event, 2 events, 3-5 events, > 5 events and the number of hospitalisation events lasting either < 3 nights or ≥ 3 nights, described as a quantitative variable.

Time to first unplanned hospitalisation or death

The number of days between T0 and the day of first unplanned hospital stay as assessed by the Clinical Events Adjudication Committee or death, whichever occurred first, will be calculated and summarised by study group using the FAS [redacted]. Time to first unplanned hospital stay or death will also be described, using Kaplan-Meier's estimates and it will be represented using Kaplan-Meier's curves. Time to first unplanned hospital stay or death will be compared between both study groups using the Log-rank test.
Patients who are still alive and were not hospitalised for any unplanned cause by the end of their comparative study period will be censored at their last contact date. Patients who prematurely withdrew the study will be censored at their withdrawal date.

Time to first unplanned hospitalisation or death – Cox model

An exploratory multiple-factor Cox model analysis will be performed to identify important predictors of the time to first unplanned hospital stay as assessed by the Clinical Events Adjudication Committee or death and to express the study group effect after adjustment for these factors using the FAS.

Factors that will be investigated are:

- Gender
- Age category *(≤ 70 years and > 70 years)*
- Education level in 3 categories *(i) Former primary school certificate (CEP) or no qualifications, or Junior secondary school diploma (BEPC), or certificate of professional competence (CAP), or vocational diploma (BEP) or equivalent, or A-level or professional certificate, ii) A-level + 2 years, iii) Degree level or higher))*
- Period of randomisation *(either during a hospitalisation or in ambulatory during a visit/consultation)*
- Type of study centre: University hospital, Hospital, Private clinic, Private practice or Nursing facility
- Size of study centre in 3 categories *(< 30 patients randomised, [30 – 100] patients randomised and > 100 patients randomised)*
- NYHA stage in 2 categories *(either I / II or III / IV)*
- Left Ventricular Ejection Fraction (%) in 2 categories: either ≤ 40% or > 40%
- Type of cardiopathy *(Ischemic/ Non ischemic)*
- Previous participation to an Educational Therapeutic Program *(Yes/ No)*
- Glomerular Filtration Rate *(detailed in section 5.C.6)* in 3 categories: < 30.0 mL/min, in [30.0 – 60.0] mL/min or > 60.0 mL/min
- Cardiac marker at Inclusion in 2 categories: either *i)* BNP ≥ 150 pg/mL or NT-pro-BNP ≥ 1000 pg/mL or *ii)* any other result recorded *(including missing value)*
- Pulse rate in supine position at Inclusion in 2 categories: either < 70 beats/min or ≥ 70 beats/min
- Isolated status at Inclusion defined as patient living in an isolated accommodation without local shops within 15-min walk
- Depression at Inclusion defined as patients having either *i)* SF-36 Mental Health (MH) subscore < 45, or *ii)* Mental Component Summary (MCS) composite score < 35, or *iii)* combination of MH < 50 and MCS <40, or *iv)* medical history of depression, or *v*) concomitant antidepressant medications.

[redacted]

- Hazard ratios along with their 95% confidence intervals will be presented.

[redacted]

[redacted]

[redacted]

[redacted]

5.E.5 *Analyses of Secondary Criteria*

Death from any cause

The number and percentage of patients who died from any cause *(during an hospitalisation or not)* during the 18-month comparative analysis period *(defined in section 3.D)* will be summarised by study group using the FAS. Additionally, the number of days between the start of analysis period (T0) and the date of death will be calculated and summarised by study group. Time to death will also be described, using Kaplan-Meier's estimates and it will be represented using Kaplan-Meier's curves. Time to death will be compared between both study groups using the Log-rank test. [redacted]

Patients who are still alive by the end of their comparative study period will be censored at their last contact date. Patients who prematurely withdrew the study alive will be censored at their withdrawal date.

Moreover, for this criterion, all subgroup analyses [redacted] will be performed on the FAS [redacted] in the same manner as described in section 5.E.3 for the primary criterion.

Unplanned hospitalisations for any cause

Unplanned hospitalisations for any cause as assessed by the Clinical Events Adjudication Committee during the comparative study period will be analysed using the same methodology as for the primary analysis of the primary criterion using the FAS [redacted]

[redacted]

Composite criterion of unplanned hospitalisations for cardiovascular cause and death from cardiovascular cause

As for the primary efficacy criterion, unplanned hospitalisations for cardiovascular cause and death from cardiovascular cause will be counted as assessed by the Clinical Events Adjudication Committee.

Recurrent events

For each patient, all unplanned hospitalisations for cardiovascular cause during the comparative study period will be added up. Death for cardiovascular cause outside hospital will be counted as an additional event. If death from cardiovascular cause occurred during a hospitalisation for cardiovascular cause with an overnight stay *(i.e., with a date change between hospital admission and hospital discharge)*, 2 events will be counted as detailed in section 3.C.

Analyses using the same methodology as for the primary analysis of the primary criterion will be performed using the FAS [redacted].

Time to first unplanned hospitalisation for cardiovascular cause or death from cardiovascular cause

The number of days between T0 and the day of first unplanned hospital stay for cardiovascular cause or death from cardiovascular cause as assessed by the Clinical Events Adjudication Committee, whichever occurred first, will be calculated and summarised by study group on the FAS [redacted] using Kaplan-Meier's curves and Log-rank test and the same censoring rules as for the primary criterion. [redacted]

Unplanned hospitalisations for cardiovascular cause

Unplanned hospitalisations for cardiovascular cause during the comparative study period as assessed by the Clinical Events Adjudication Committee will be analysed using the same methodology as for the primary [redacted] analyses of the primary criterion using the FAS [redacted].

[redacted]

Unplanned hospitalisations for heart failure

Unplanned hospitalisations for heart failure during the comparative study period have been assessed by the Clinical Events Adjudication Committee. They will be analysed using the same methodology as for the primary analysis of the primary criterion using the FAS [redacted]

[redacted] all subgroup analyses and exploratory multiple-factor Cox model analysis will be performed to identify important predictors of the time to first unplanned hospitalisation for heart failure in the same manner as described in section 5.E.3 for the primary criterion.

Death from cardiovascular cause

Death from cardiovascular cause during the comparative study period as assessed by the Clinical Events Adjudication Committee will be analysed using the same methodology as for the analysis of death from any cause using the FAS, apart from subgroup analyses [redacted] will not be performed on this secondary efficacy criterion.

Annualised cumulative number of days in hospital for any unplanned cause

For each patient, the number of days of all hospital stays for any unplanned cause as assessed by the Clinical Events Adjudication Committee during the comparative study period will be added to obtain the cumulative number of days in hospital up to Tend defined in section 3.D.

In order to deal with patients followed-up over different duration, their individual recorded cumulative number of days in hospital whatever their unplanned reason *(D_i expressed in days, as recorded by the Clinical Events Adjudication Committee)* will be normalised on a yearly basis, by multiplying D_i by the ratio [365 days / total number of days of the patient's comparative study period] and rounding it at the nearest integer. Thus, a patient for whom 18 hospital days have been recorded over a 6-month *(182 days)* follow-up prior to study premature withdrawal will be analysed as having experienced a yearly estimated duration of hospitalisation of [18 x (365/182)] ~ 36 days. In the same manner, a patient for whom 18 hospital days have been recorded over a 18-month *(547 days)* follow-up will be analysed as having experienced a yearly estimated duration of hospitalisation of [18 x (365/547)] ~ 12 days.

The annualised cumulative number of days in hospital for any unplanned cause will be summarised and compared between study groups using the Wilcoxon's rank sum test on the FAS.

Annualised cumulative number of days in hospital for any unplanned cardiovascular cause

For each patient, the number of days of all hospital stays for unplanned cardiovascular cause as assessed by the Clinical Events Adjudication Committee during the comparative study period will be added to obtain the cumulative number of days in hospital for any unplanned cardiovascular cause.

It will be annualised and analysed in the same manner as the cumulative number of days in hospital for any unplanned cause.

Annualised cumulative number of days in hospital for any unplanned heart failure cause

For each patient, the number of days of all hospital stays for any unplanned heart failure cause as assessed by the Clinical Events Adjudication Committee during the comparative study period will be added to obtain the cumulative number of days in hospital for any unplanned heart failure cause.

It will be annualised and analysed in the same manner as the cumulative number of days in hospital for any unplanned cause.

Days lost due to unplanned cardiovascular hospitalisations or to all-cause death

Days lost due to unplanned cardiovascular hospitalisations as assessed by the Clinical Events Adjudication Committee or due to all-cause death during the comparative study period will be calculated for each study patient as:

Days Lost (DL) = Total number of days in hospital for unplanned cardiovascular cause + number of days dead

Where:

- **Total number of days in hospital** for unplanned cardiovascular cause is the non-annualised cumulative number of days of all hospital stays for unplanned cardiovascular cause as assessed by the Clinical Events Adjudication Committee.
- **Number of days dead:** number of days between the date of death and the cut-off date of the comparative analysis period *(i.e., Tend defined in section 3.D)*.

Percentage of days lost (% DL) will also be calculated for each study patient *(rounded with 1 decimal)* as DL divided by the total number of days of potential follow-up period defined as the number of days from:

- T0 until the date of premature withdrawal if patient withdrew prematurely the study *(before the end of the comparative analysis period)* and was alive
- T0 until the date of study completion if patient completed the study as planned before the end of the comparative analysis period
- T0 until the cut-off date of the comparative analysis period *(i.e., Tend defined in section 3.D)* if patient withdrew or completed the study after the end of the comparative analysis period
- T0 until the cut-off date of the comparative analysis period *(i.e., Tend defined in section 3.D)* if patient died during the comparative analysis period.

Both DL and %DL will be summarised and compared between study groups using the Wilcoxon's rank sum test on the FAS.

SF-36 scores

SF-36 scores and subscores will be summarised by study group and visit on the FAS. [redacted]

Quantitative descriptive statistics of each of the 8 dimensions of the SF-36 questionnaire and of both composite scores *(Physical Component Summary (PCS) and Mental Component Summary (MCS))* will be tabulated separately by study group on the FAS at each planned visit, as well as [redacted] the absolute variations of each dimension and each composite score separately. Absolute variations will be calculated 'post-*Inclusion* – baseline *(self-evaluated at Visit 1)*'.

[redacted]

[redacted]

[redacted]

An analysis over time of the mean profile of each dimension and each composite score of the SF-36 questionnaire separately will be performed within a mixed model to deal with patients followed-up over different duration, using the MIXED procedure of the current version of the SAS® software and type III sums of squares. The global parametric analysis of covariance model on repeated measurements used will include the following factors:

- score assessed at Visit 1 as covariate,
- study group and visit as fixed factors,
- interaction between study group and visit and interaction between study group and score assessed at Visit 1 *(i.e., the covariate)* as fixed factors,
- patient as random factor.

[redacted]

[redacted]

Extension period evaluations

Annualised number of unplanned hospitalisations for any cause

For each patient of the Extension Period Set, as planned in the protocol, [redacted] the annualised number of unplanned hospitalisations [redacted] during the extension period [redacted] as recorded by the investigators will be summarised by study group *(see section 3.E for the definition of study groups during the extension period)* and in total.

Annualised number of hospitalisations will be obtained by multiplying the number of hospitalisations during the studied period by the ratio [365 days / total number of days of individual follow-up during the studied period] and rounded with 1 decimal.

Annualised number of unplanned hospitalisations for cardiovascular cause

Annualised number of unplanned hospitalisations for cardiovascular cause as recorded by the investigators will be calculated and described using the same methodology as for annualised number of unplanned hospitalisations for any cause during [redacted] the extension period [redacted].

Death from any cause during the extension period

The number and percentage of patients who died from any cause during the extension period will be summarised by study group and in total on the Extension Period Set. [redacted]

Death from cardiovascular cause during the extension period

Death from cardiovascular cause during the extension period as recorded by the investigators will be analysed using the same methodology as death from any cause.

5.F OTHER CRITERIA EVALUATION

5.F.1 *Extent of Exposure*

The duration of comparative study period participation *(expressed in months)* will be summarised by study group and in total [redacted] on the FAS. It will be tabulated as [redacted] quantitative [redacted] data [redacted].

It is defined as: (Date of end of the comparative study period – Date of Inclusion Visit *(Visit 0)*) / 30.4 and rounded with 1 decimal.

[redacted]

5.F.2 *Adverse Events (AEs) Reported by the Patient*

[redacted]

5.F.3 *Concomitant Treatments Reported by the Patient*

[redacted]

6. LIST OF TABLES, FIGURES AND LISTINGS

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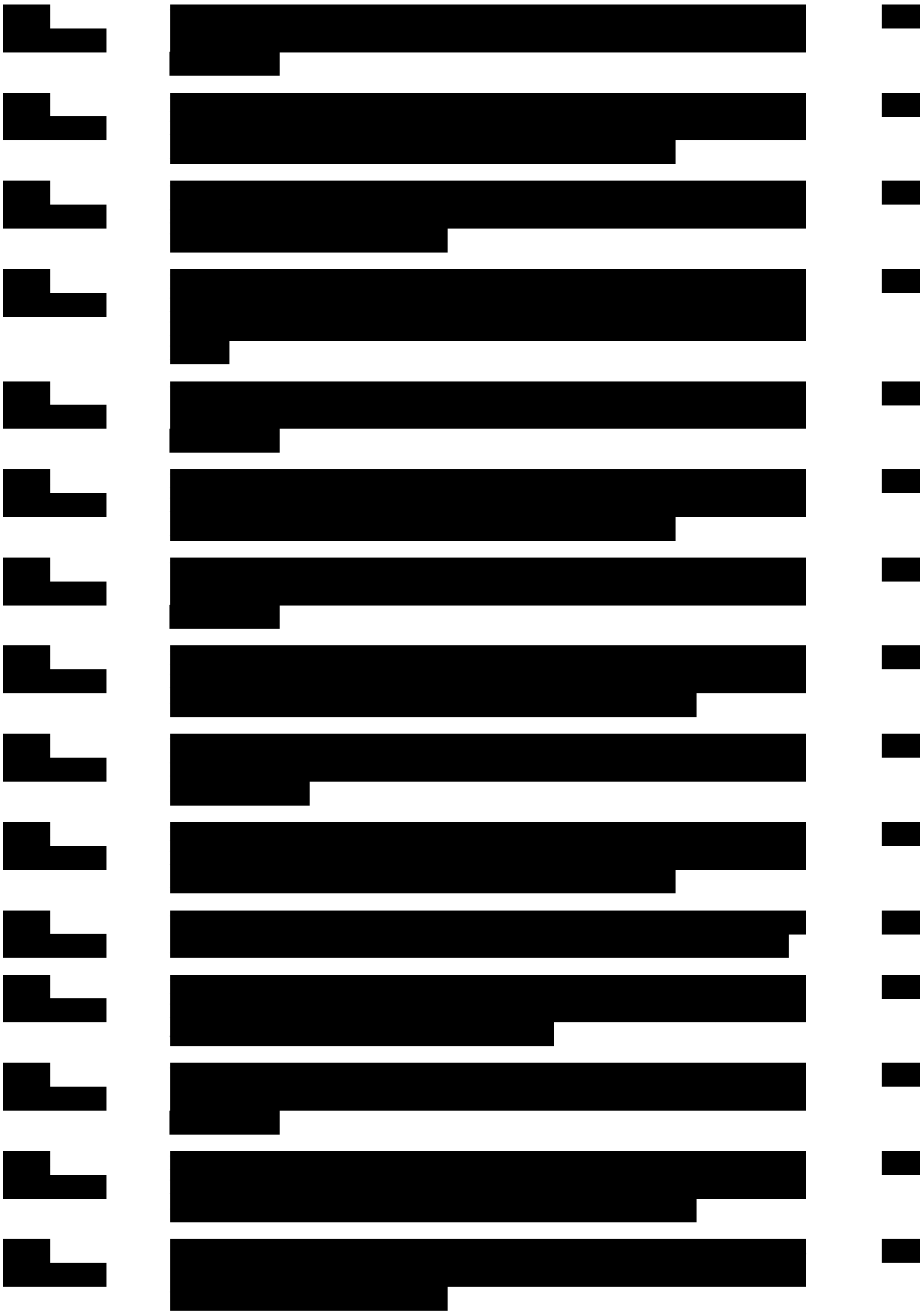

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7. SHELLS FOR TABLES, FIGURES AND LISTINGS

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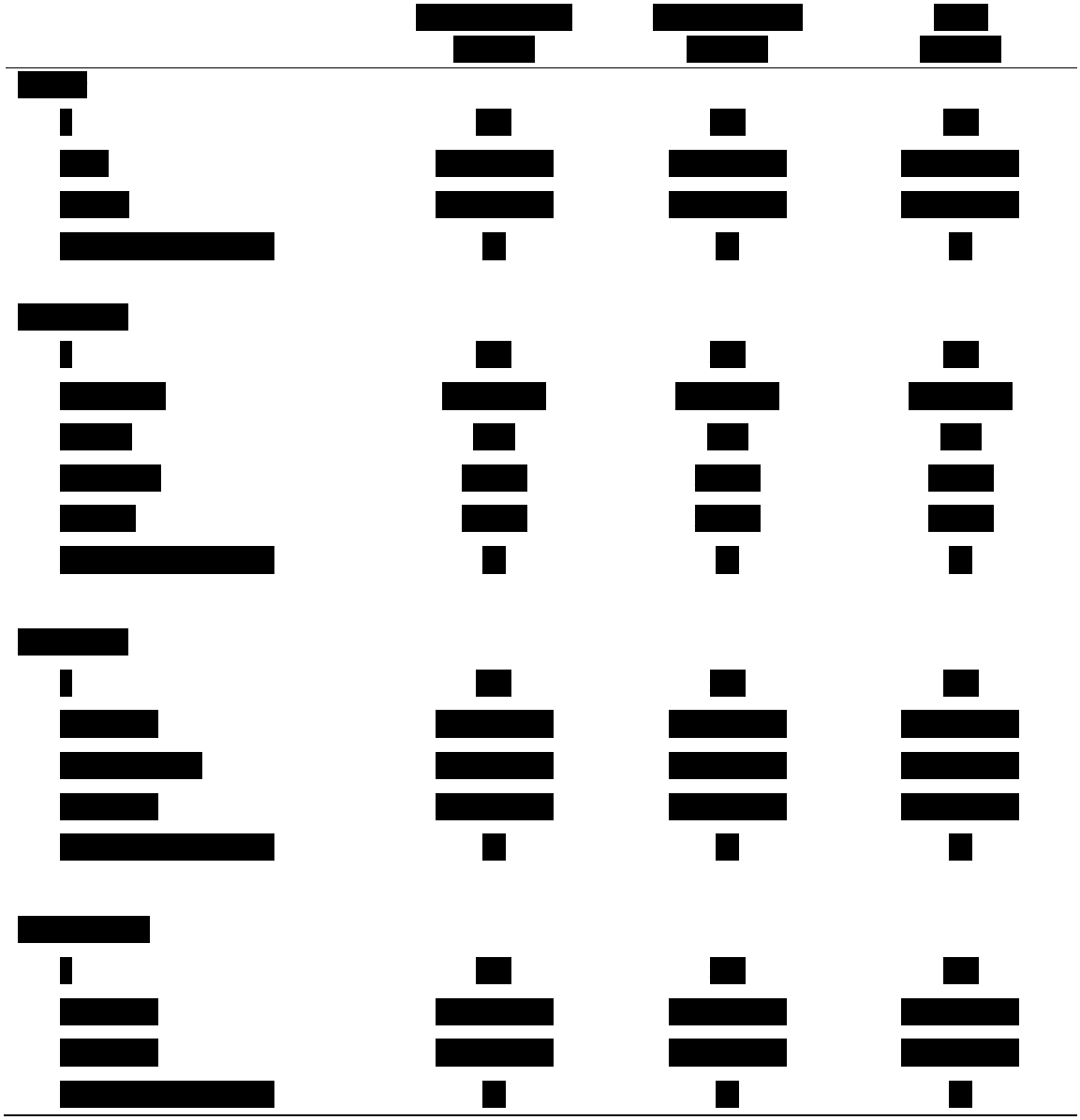

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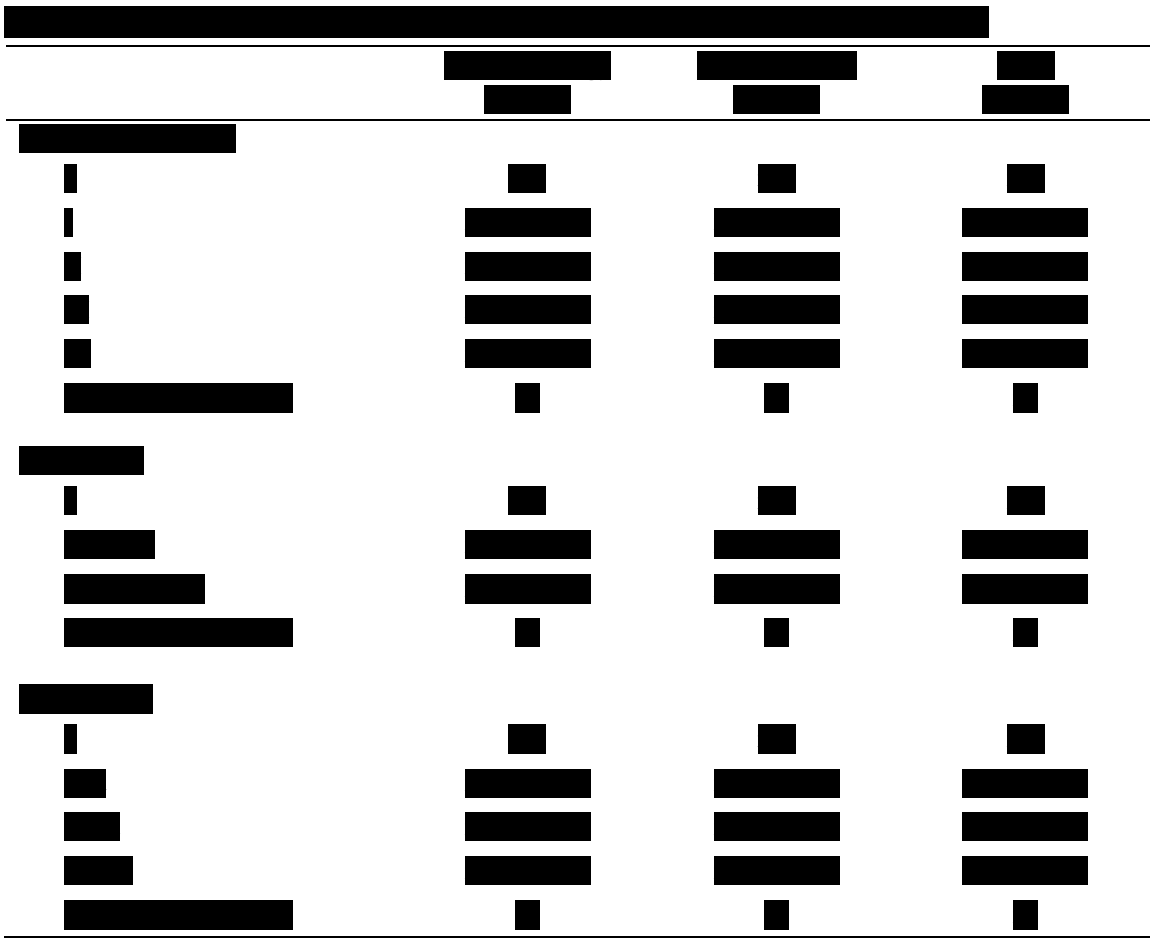

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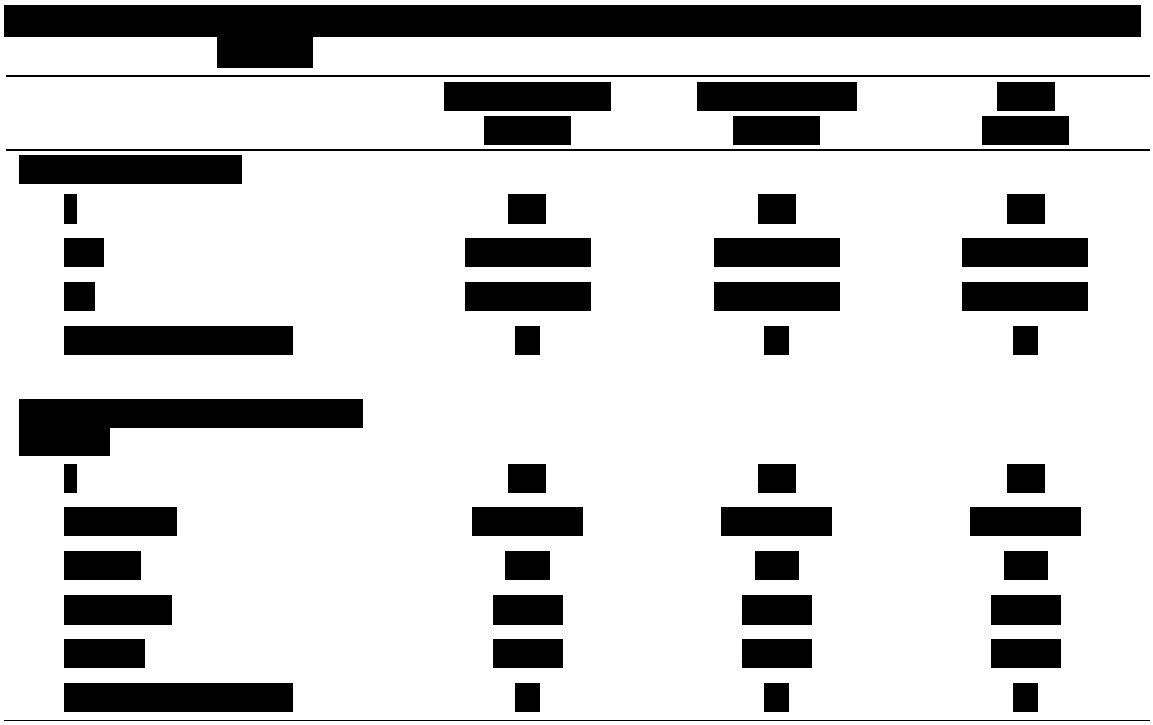

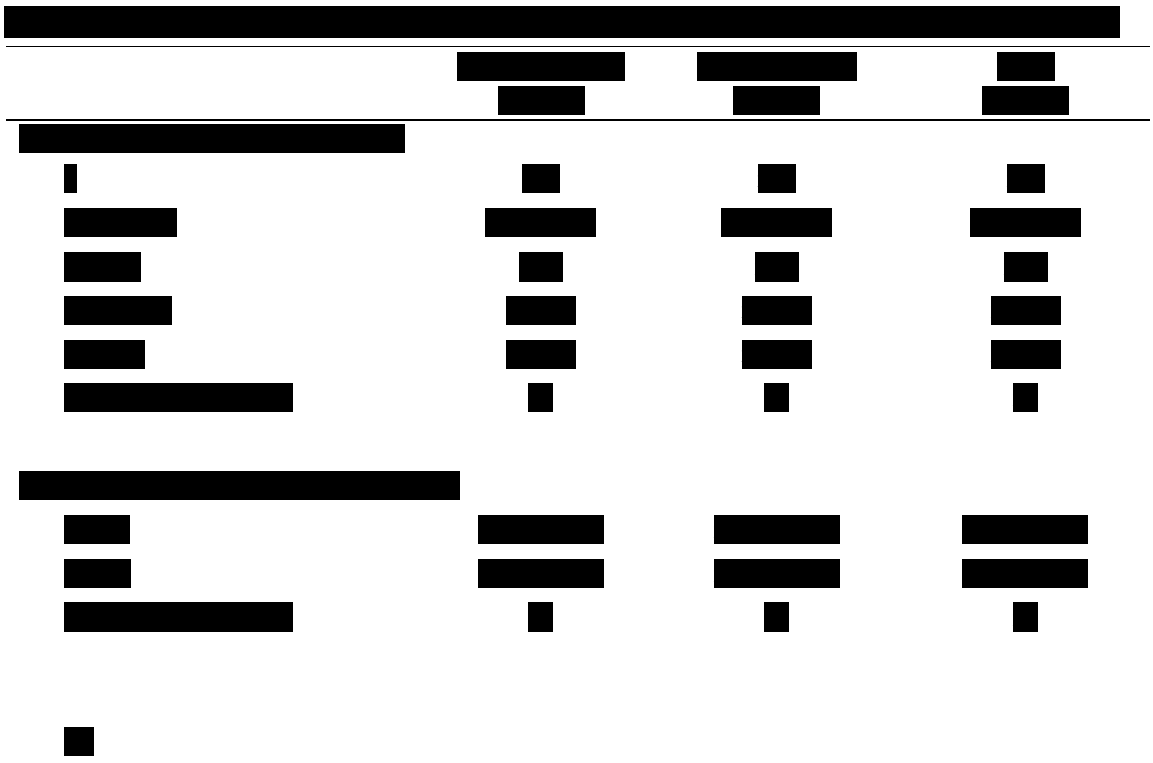

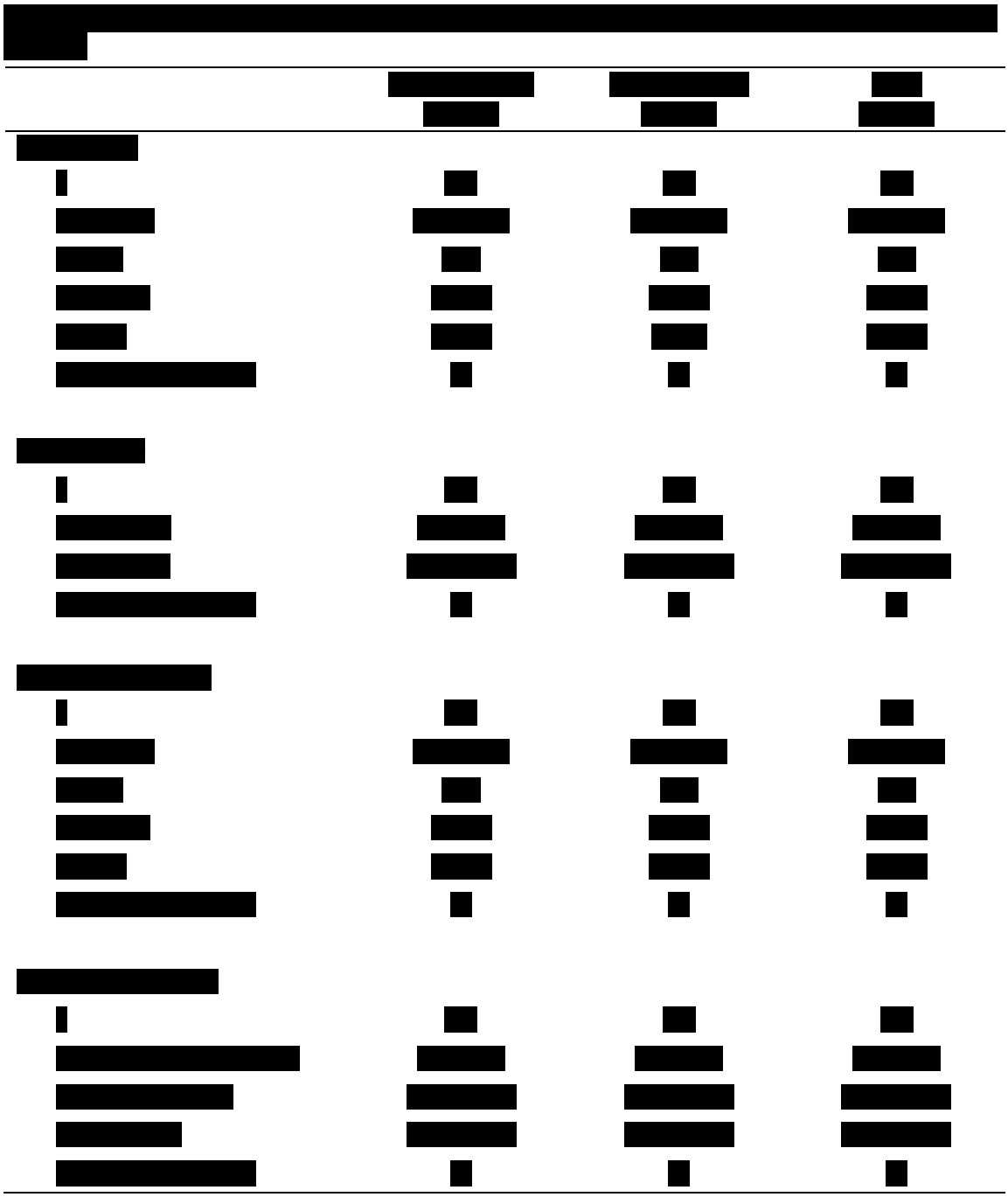

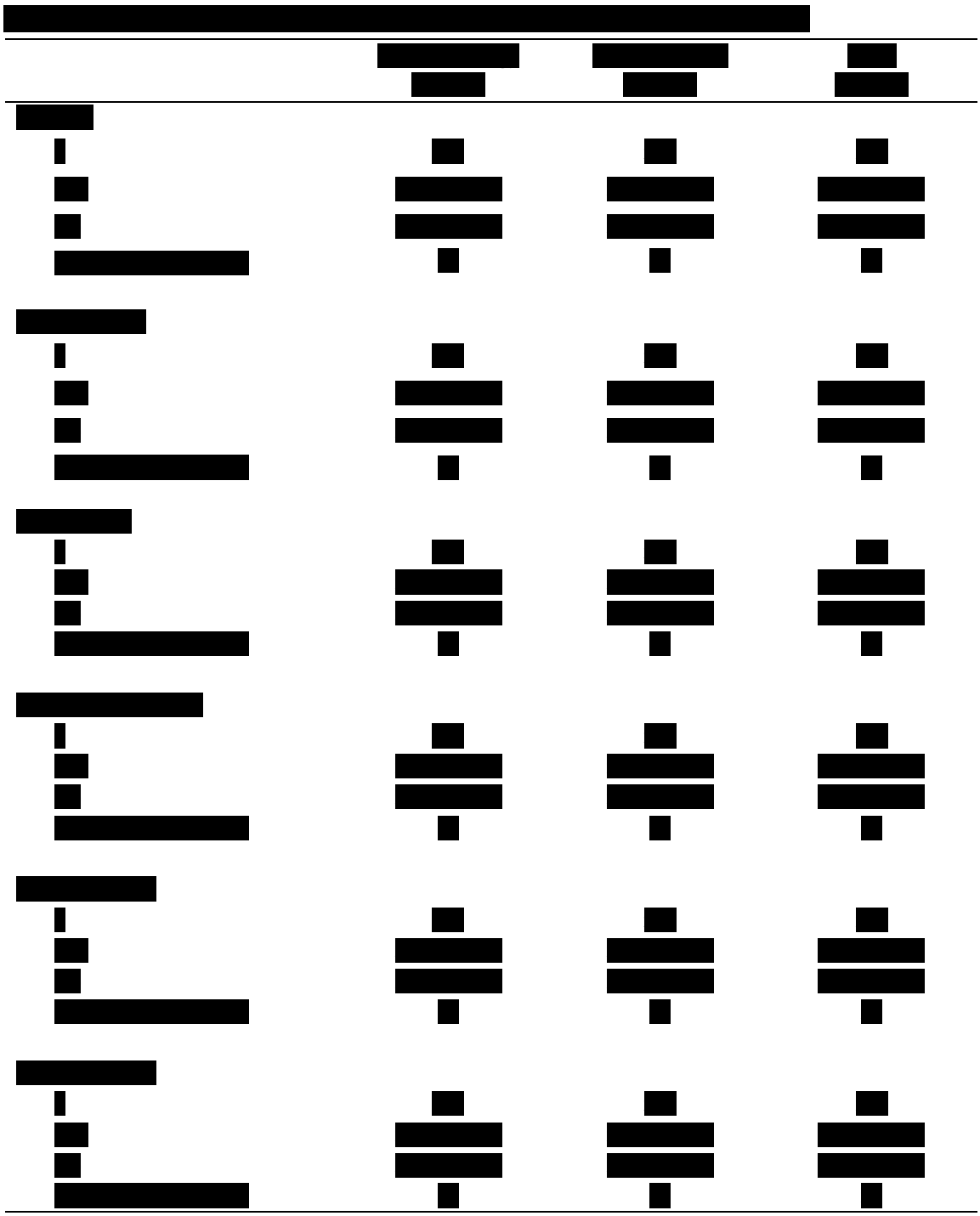

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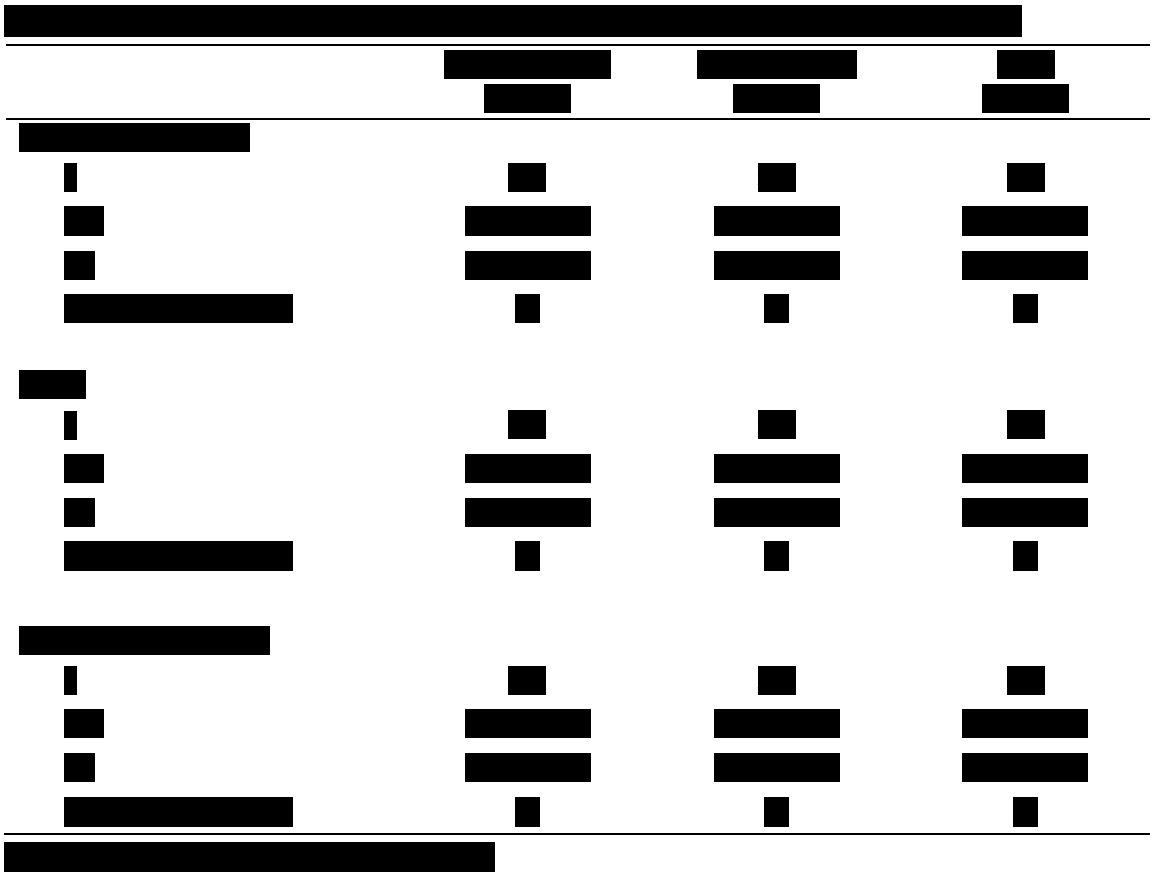

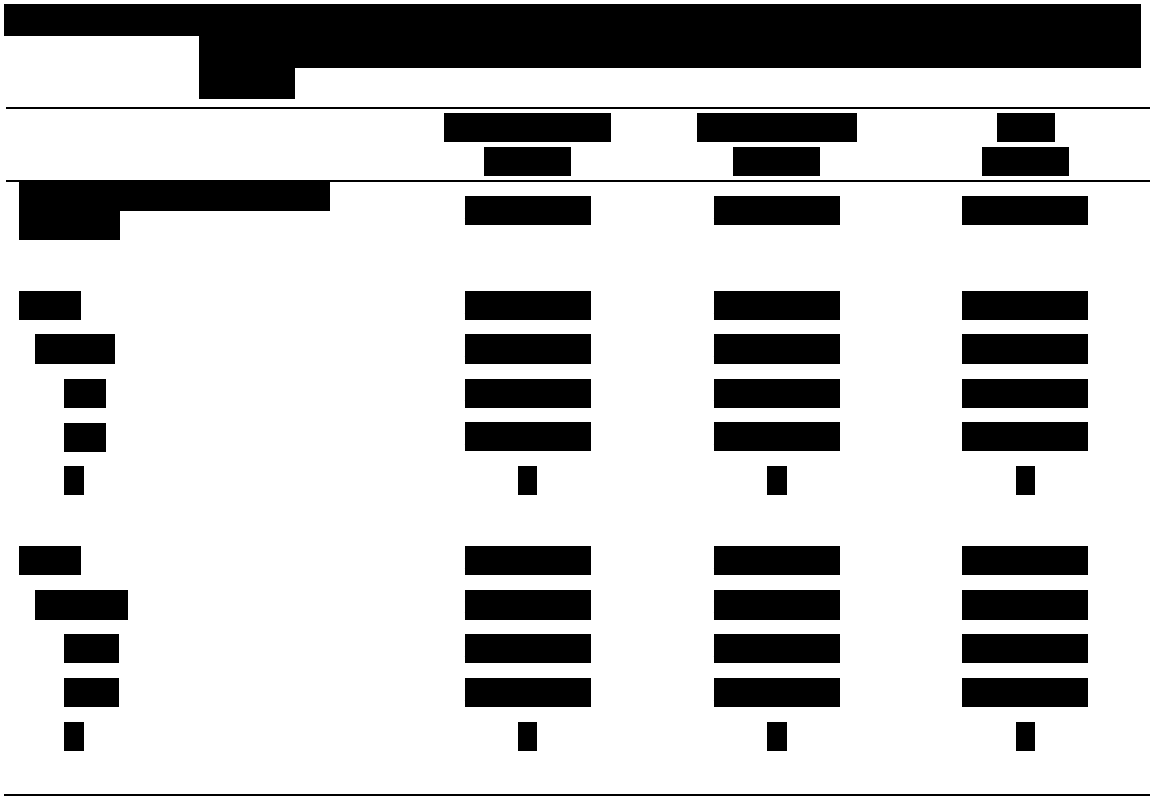

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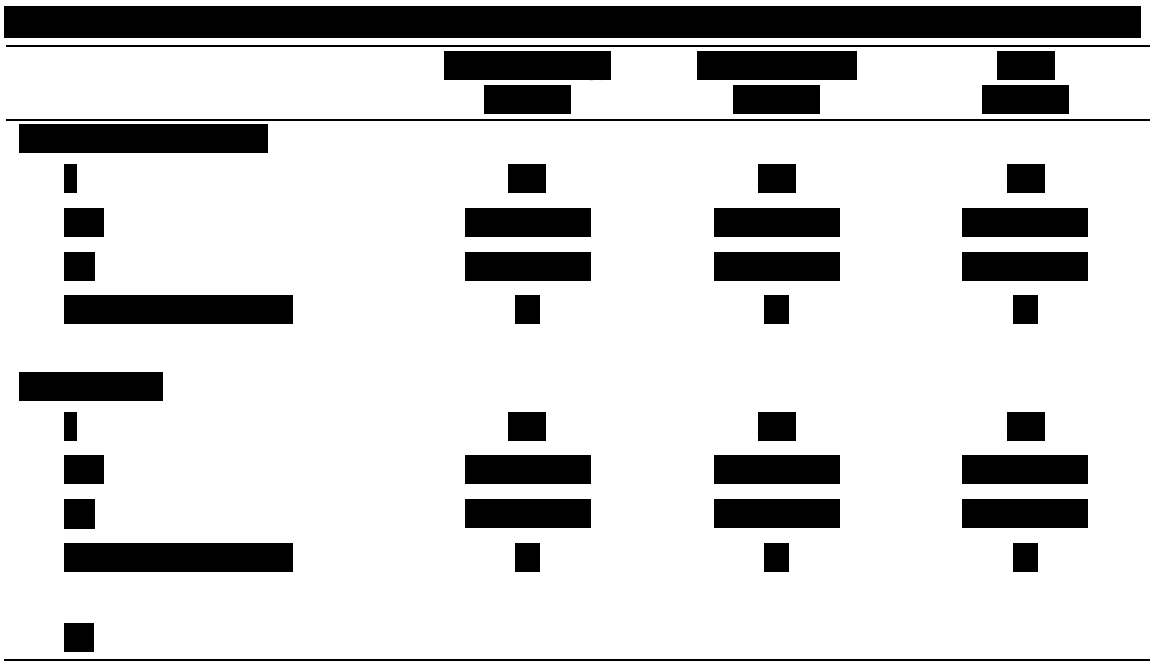

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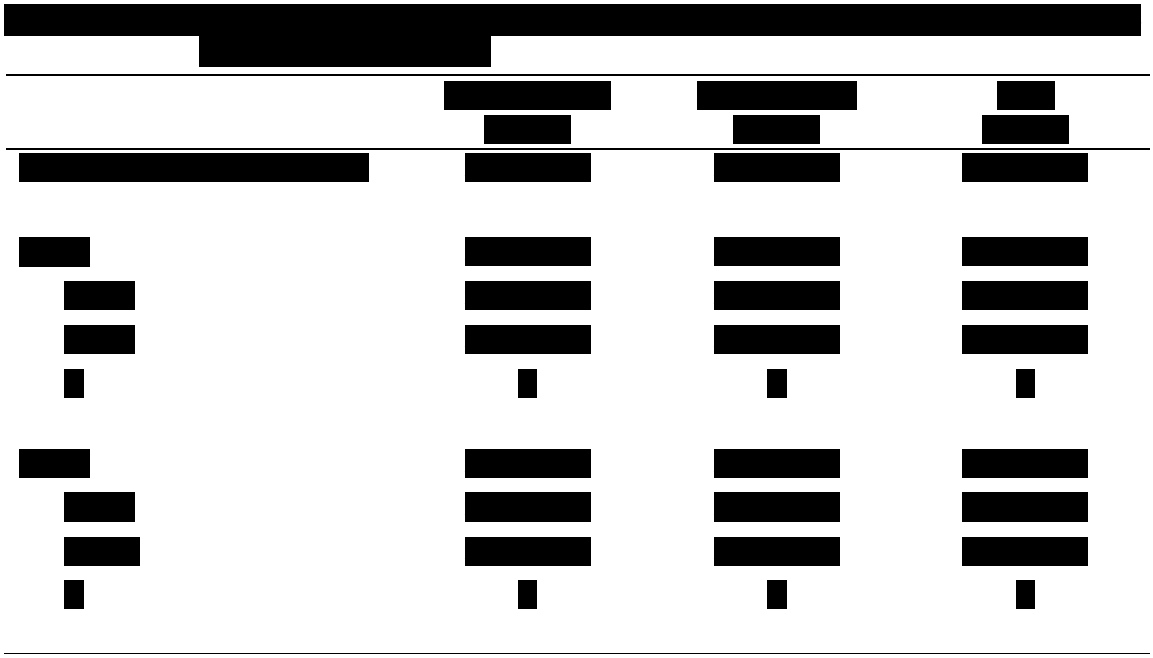

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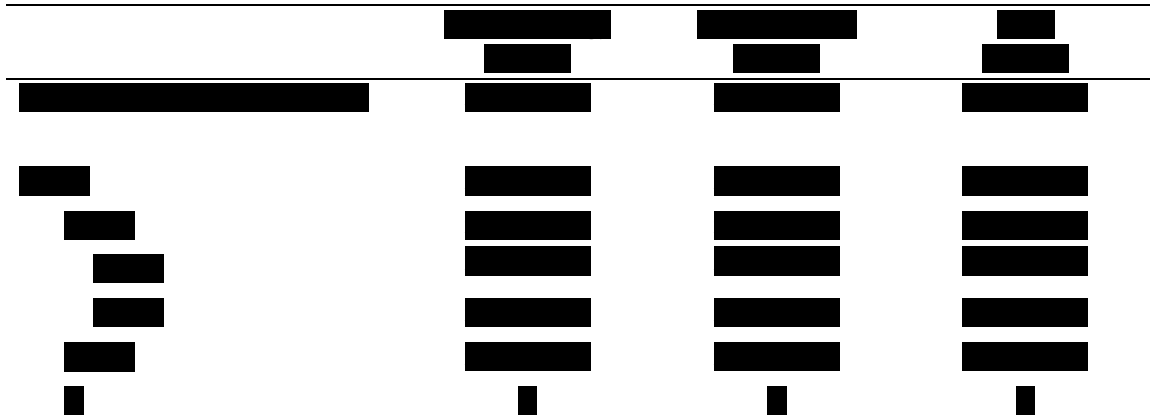

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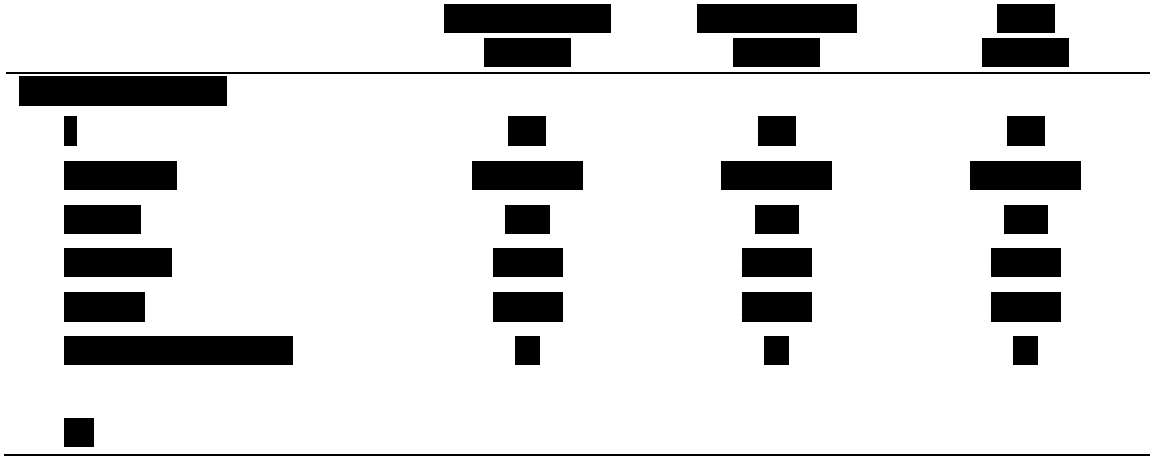

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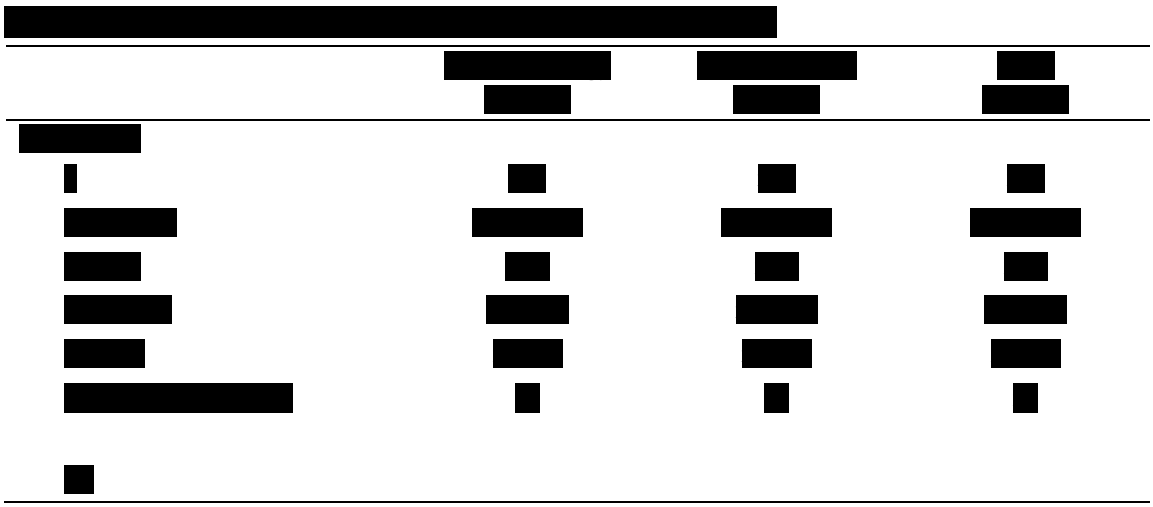

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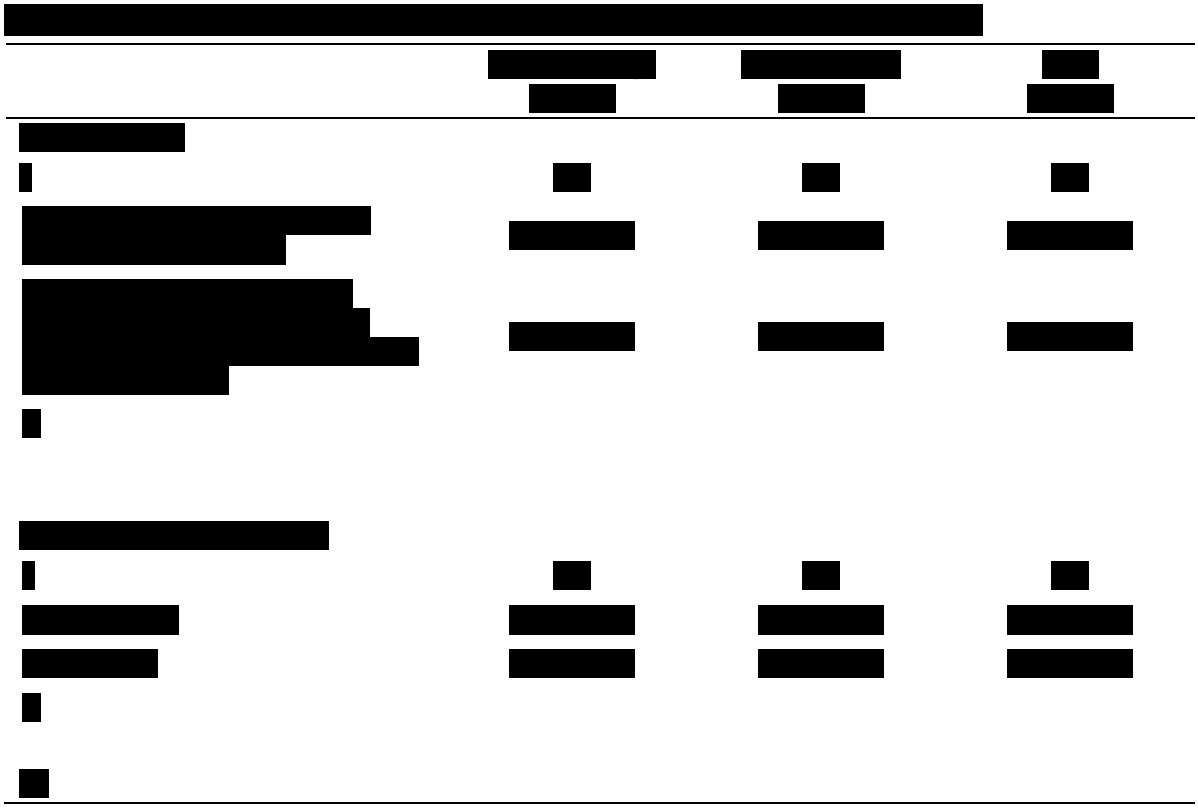

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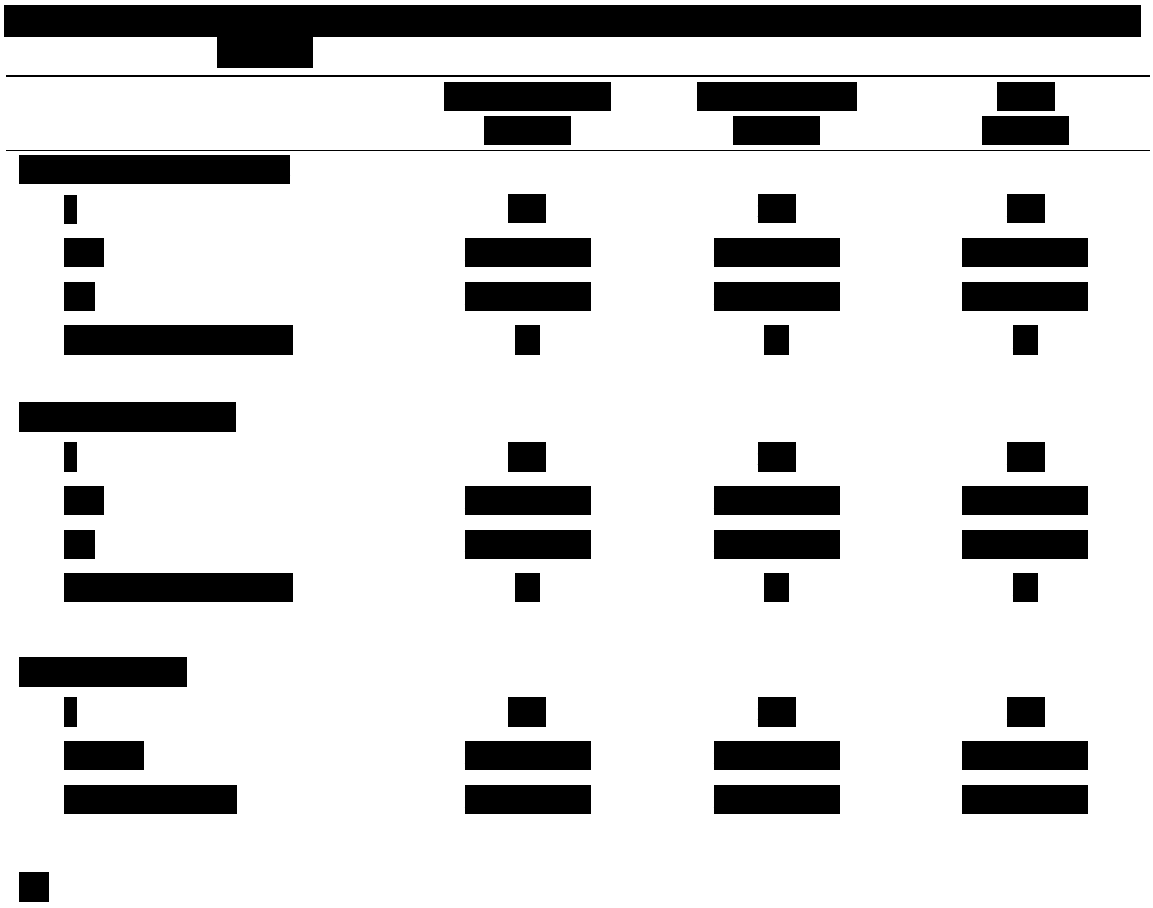

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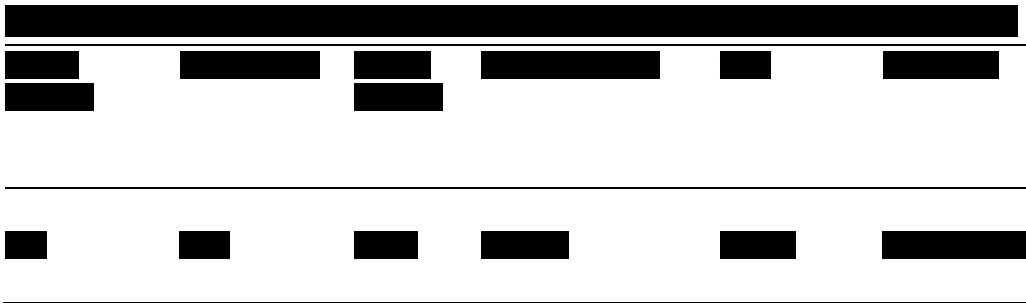

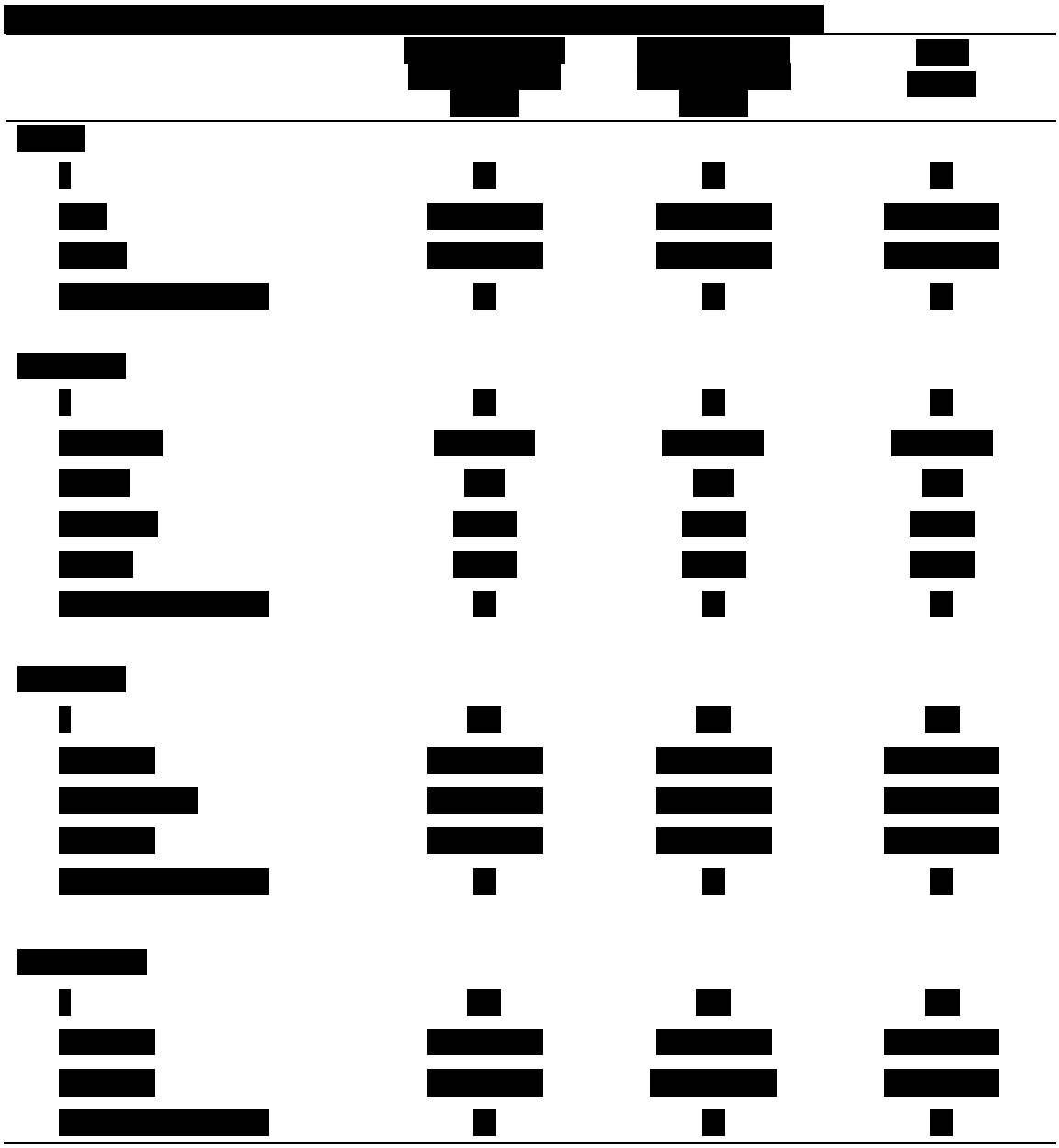

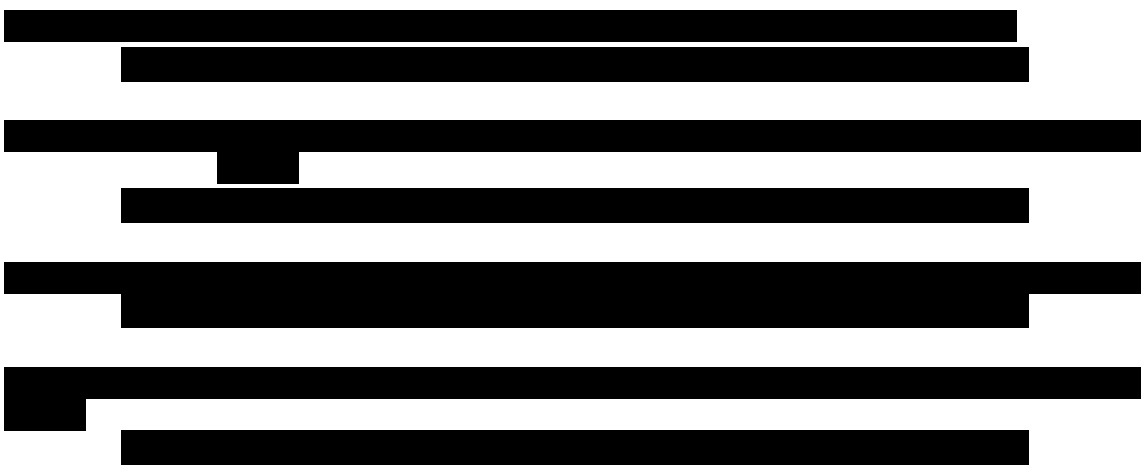

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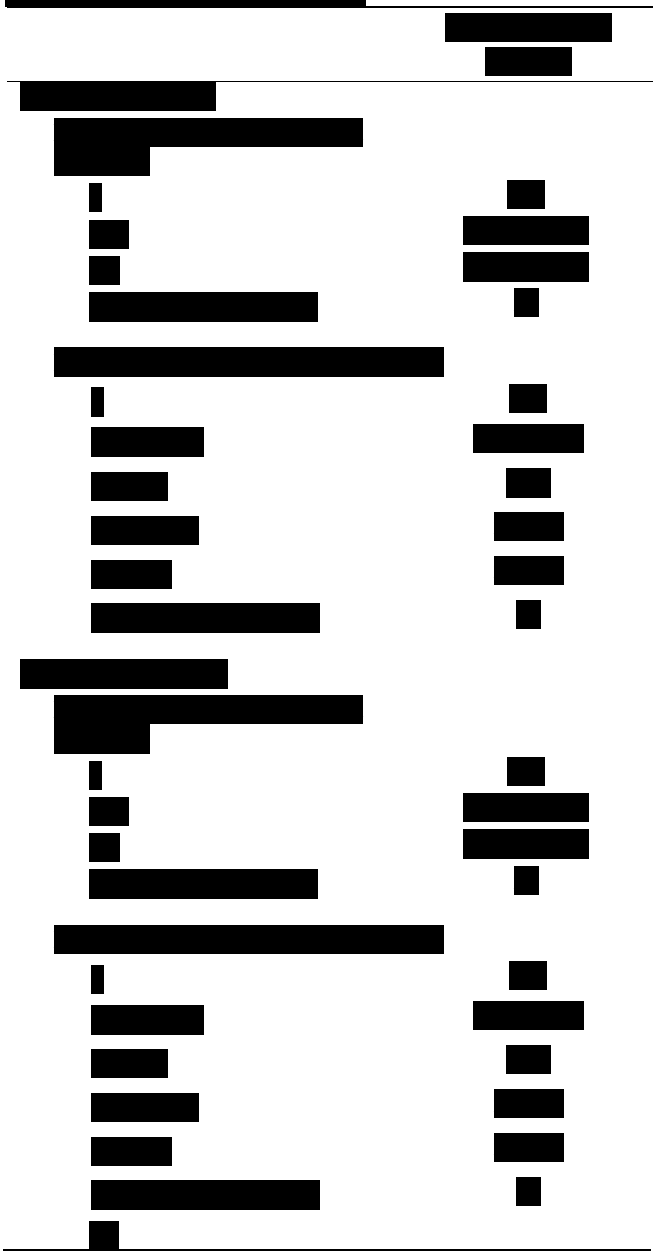

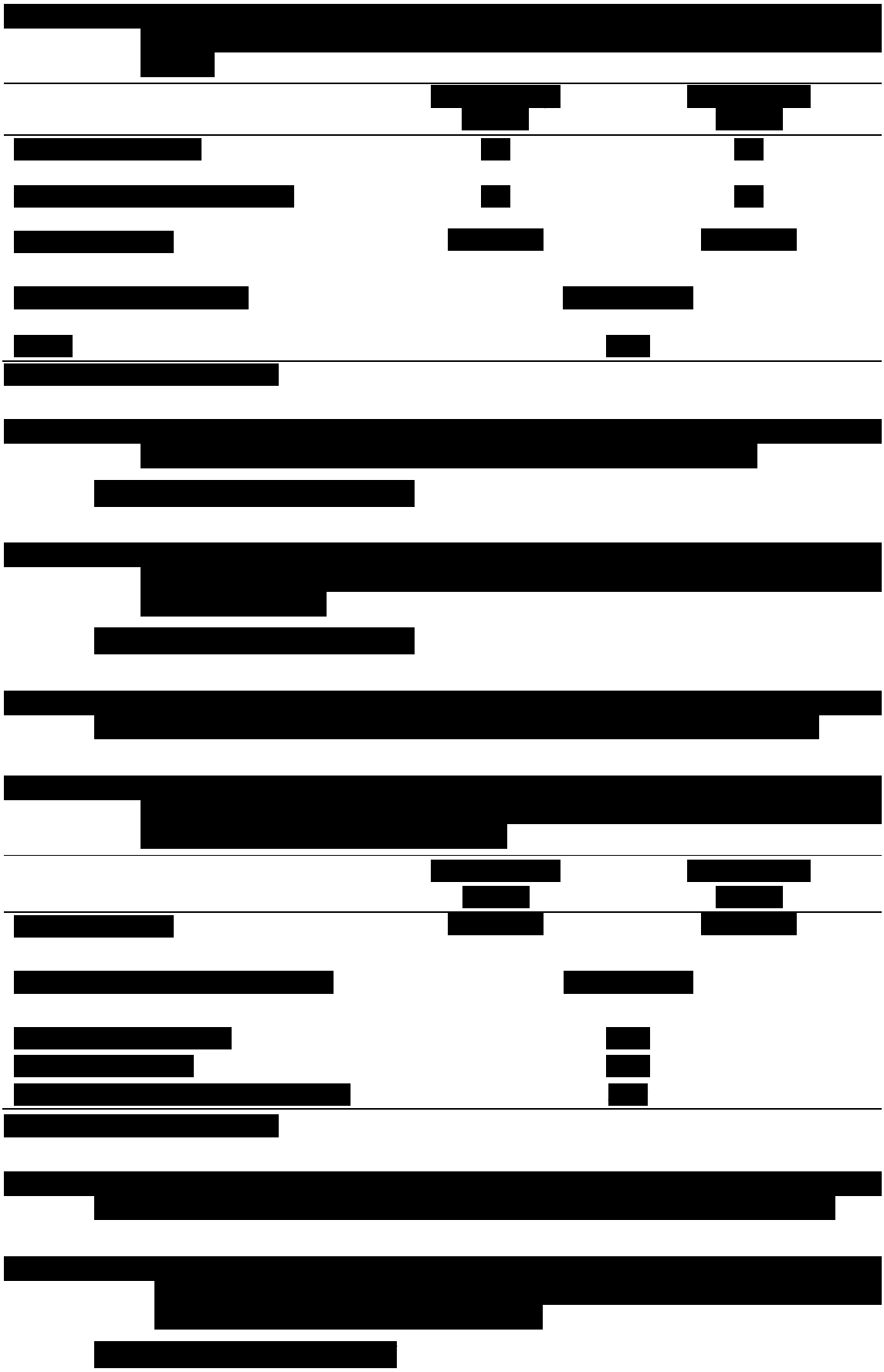

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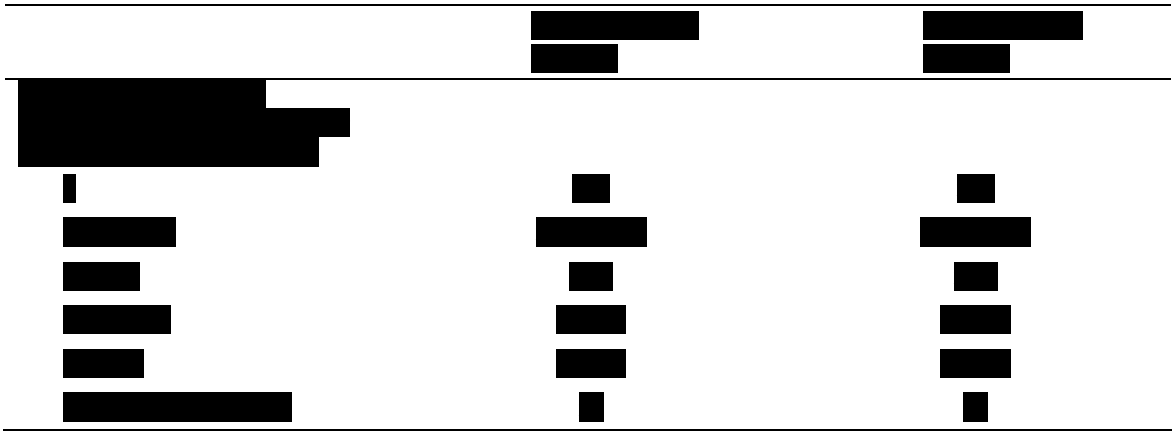

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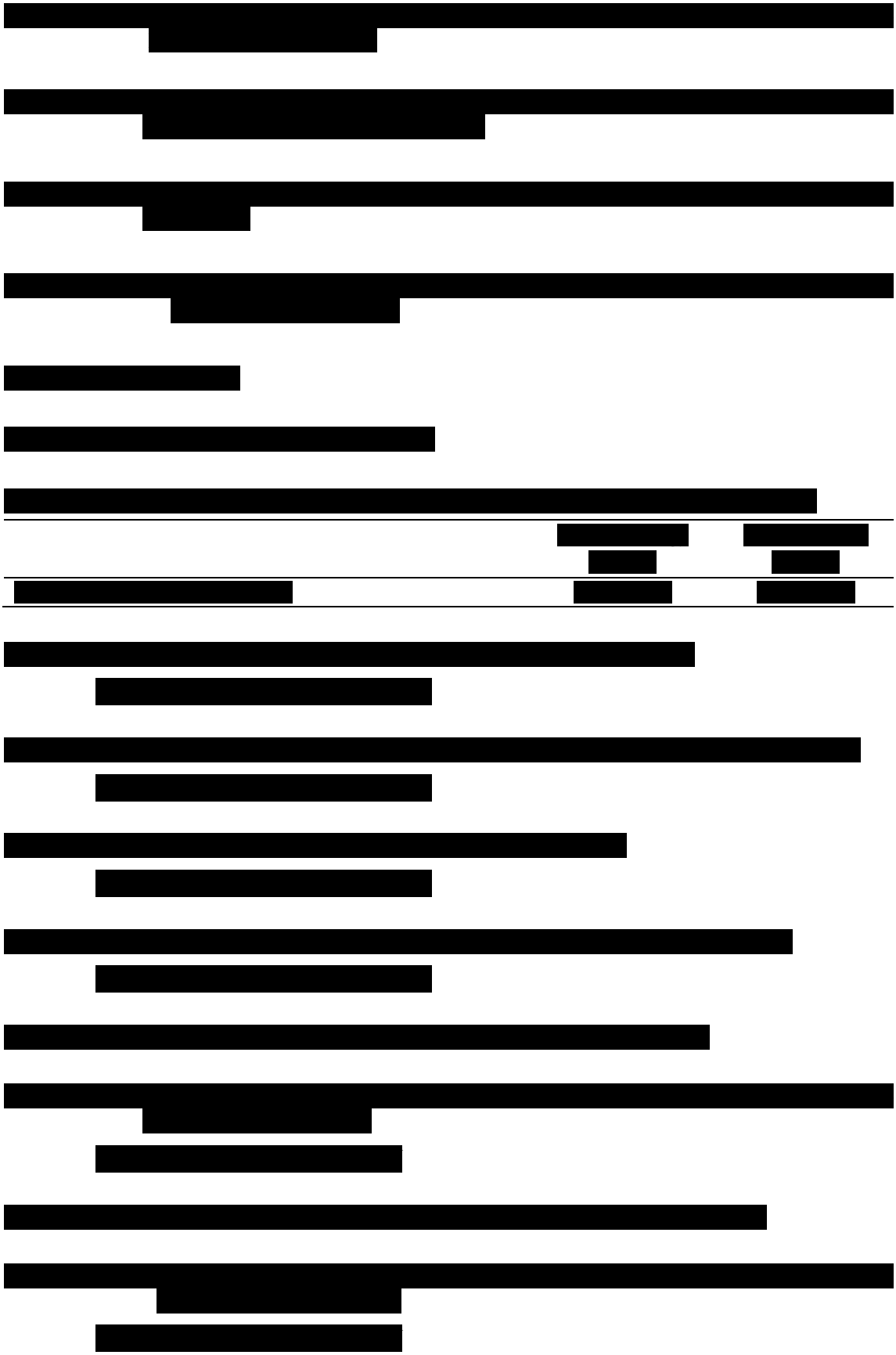

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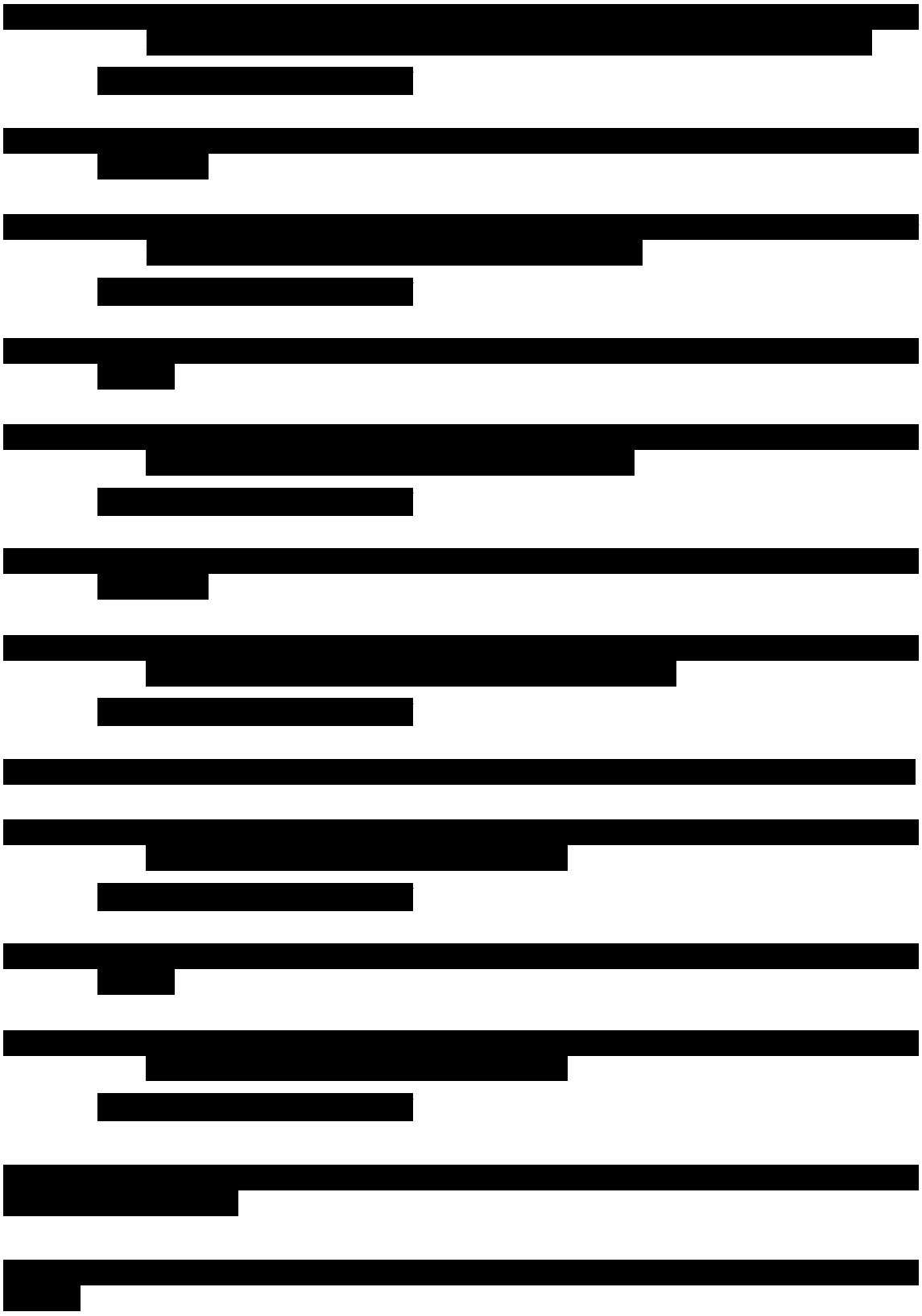

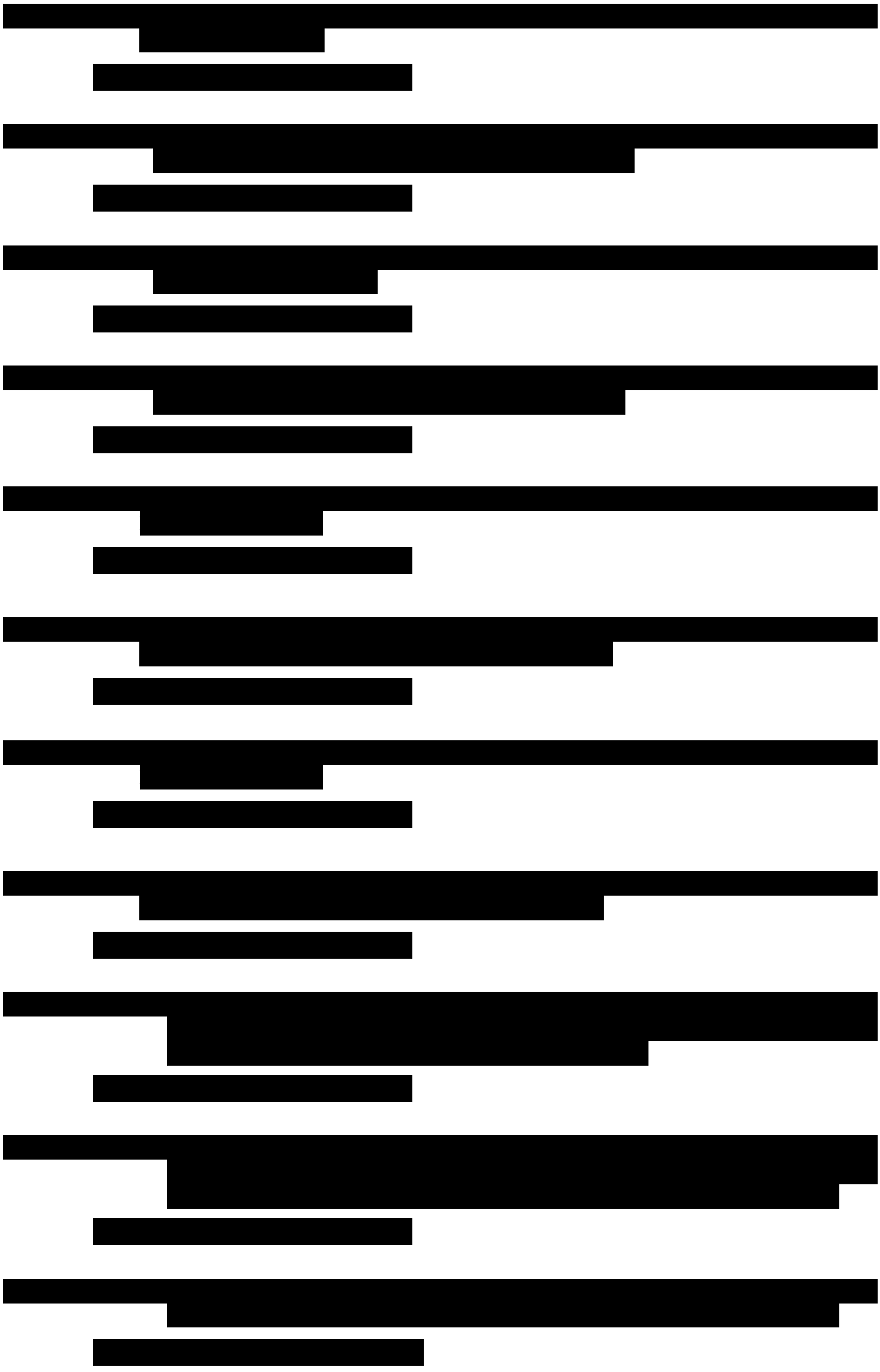

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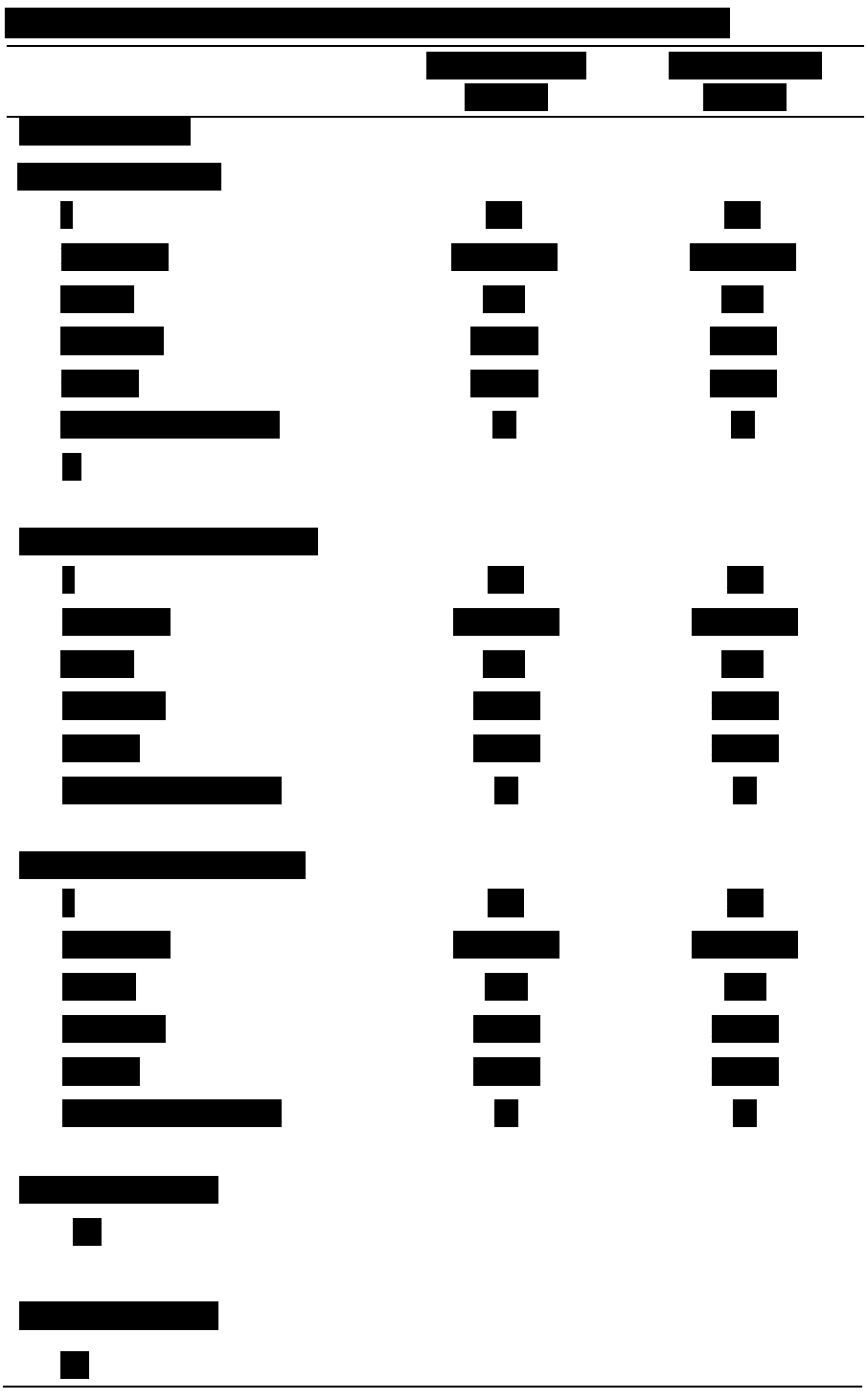

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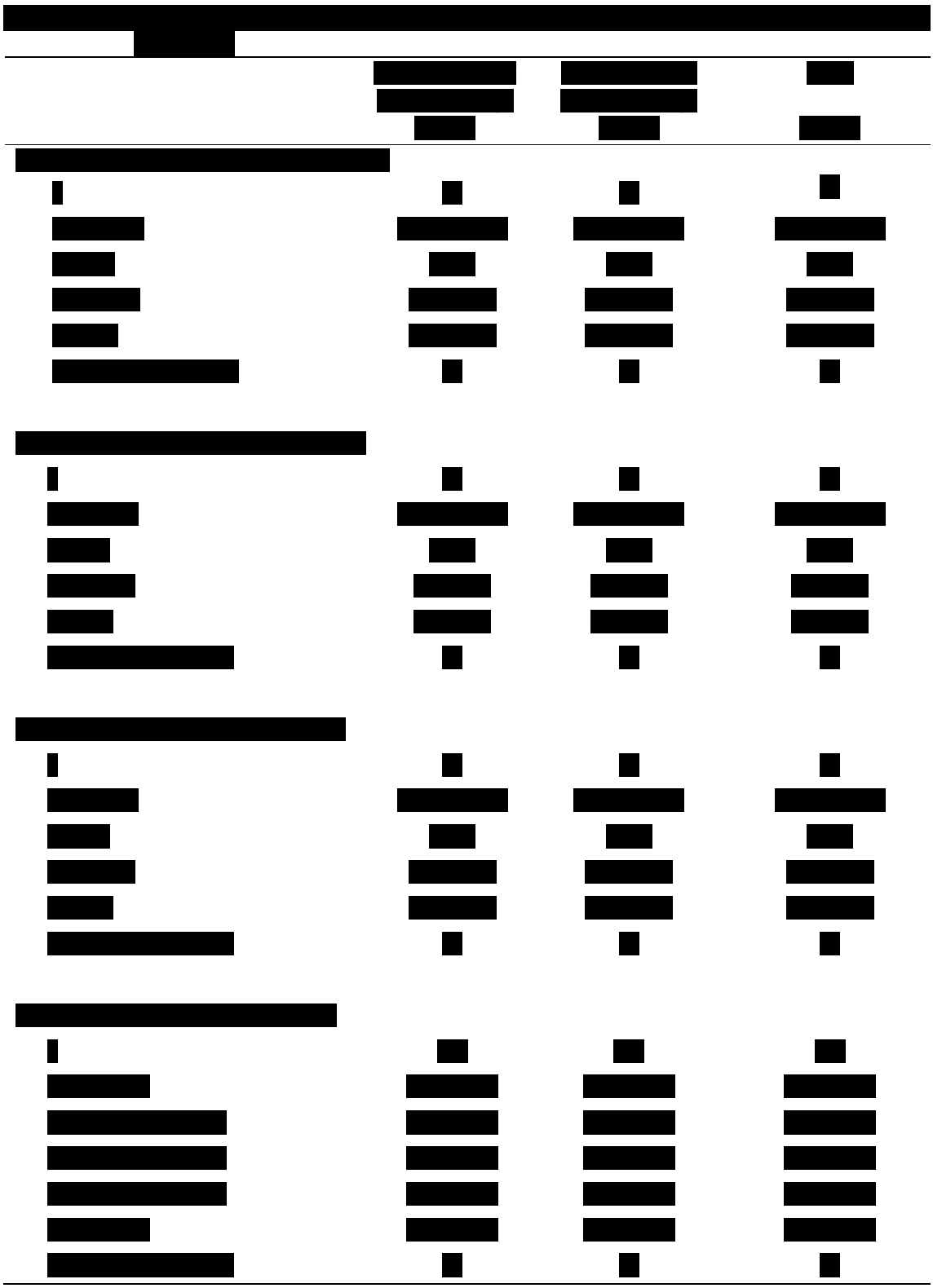

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8. REFERENCE LIST

9. APPENDICES

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